PiHKAL

A
CHEMICAL
LOVE STORY

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TRANSFORM
PRESS

BOOK II

THE
CHEMICAL
STORY

Penalties against possession of a drug should not be more damaging to an individual than the use of the drug itself.

President Jimmy Carter, October 2, 1977

A SHORT INDEX TO THE PHENETHYLAMINES

This short index to the phenethylamines lists the 179 entries that follow in alphebetical order. The abbreviation PEA is for phenethylamine, and A is for amphetamine. The long index includes all synonyms and is in Appendix A.

	Code	Compact chemical name	
1	AEM	α-Ethyl-3,4,5-trimethoxy-PEA	458
2	AL	4-Allyloxy-3,5-dimethoxy-PEA	460
3	ALEPH	4-Methylthio-2,5-dimethoxy-A	462
4	ALEPH-2	4-Ethylthio-2,5-dimethoxy-A	464
5	ALEPH-4	4-Isopropylthio-2,5-dimethoxy-A	468
6	ALEPH-6	4-Phenylthio-2,5-dimethoxy-A	469
7	ALEPH-7	4-Propylthio-2,5-dimethoxy-A	472
8	ARIADNE	2,5-Dimethoxy-α-ethyl-4-methyl-PEA	475
9	ASB	3,4-Diethoxy-5-methoxy-PEA	480
10	B	4-Butoxy-3,5-dimethoxy-PEA	484
11	BEATRICE	2,5-Dimethoxy-4,N-dimethyl-A	486
12	BIS-TOM	2,5-Bismethylthio-4-methyl-A	487
13	BOB	4-Bromo-2,5,ß-trimethoxy-PEA	490
14	BOD	2,5,ß-Trimethoxy-4-methyl-PEA	492
15	BOH	ß-Methoxy-3,4-methylenedioxy-PEA	496
16	BOHD	2,5-Dimethoxy-ß-hydroxy-4-methyl-PEA	498
17	BOM	3,4,5,ß-Tetramethoxy-PEA	500
18	4-Br-3,5-DMA	4-Bromo-3,5-dimethoxy-A	501
19	2-Br-4,5-MDA	2-Bromo-4,5-methylenedioxy-A	502
20	2C-B	4-Bromo-2,5-dimethoxy-PEA	503
21	3C-BZ	4-Benzyloxy-3,5-dimethoxy-A	507
22	2C-C	4-Chloro-2,5-dimethoxy-PEA	509

23	2C-D	4-Methyl-2,5-dimethoxy-PEA	511
24	2C-E	4-Ethyl-2,5-dimethoxy-PEA	515
25	3C-E	4-Ethoxy-3,5-dimethoxy-A	519
26	2C-F	4-Fluoro-2,5-dimethoxy-PEA	521
27	2C-G	3,4-Dimethyl-2,5-dimethoxy-PEA	522
28	2C-G-3	3,4-Trimethylene-2,5-dimethoxy-PEA	526
29	2C-G-4	3,4-Tetramethylene-2,5-dimethoxy-PEA	529
30	2C-G-5	3,4-Norbornyl-2,5-dimethoxy-PEA	532
31	2C-G-N	1,4-Dimethoxynaphthyl-2-ethylamine	535
32	2C-H	2,5-Dimethoxy-PEA	537
33	2C-I	4-Iodo-2,5-dimethoxy-PEA	539
34	2C-N	4-Nitro-2,5-dimethoxy-PEA	542
35	2C-O-4	4-Isopropoxy-2,5-dimethoxy-PEA	543
36	2C-P	4-Propyl-2,5-dimethoxy-PEA	545
37	CPM	4-Cyclopropylmethoxy-3,5-dimethoxy-PEA	548
38	2C-SE	4-Methylseleno-2,5-dimethoxy-PEA	551
39	2C-T	4-Methylthio-2,5-dimethoxy-PEA	554
40	2C-T-2	4-Ethylthio-2,5-dimethoxy-PEA	557
41	2C-T-4	4-Isopropylthio-2,5-dimethoxy-PEA	561
42	Ψ-2C-T-4	4-Isopropylthio-2,6-dimethoxy-PEA	564
43	2C-T-7	4-Propylthio-2,5-dimethoxy-PEA	567
44	2C-T-8	4-Cyclopropylmethylthio-2,5-dimethoxy-PEA	571
45	2C-T-9	4-(t)-Butylthio-2,5-dimethoxy-PEA	573
46	2C-T-13	4-(2-Methoxyethylthio)-2,5-dimethoxy-PEA	576
47	2C-T-15	4-Cyclopropylthio-2,5-dimethoxy-PEA	579
48	2C-T-17	4-(s)-Butylthio-2,5-dimethoxy-PEA	583
49	2C-T-21	4-(2-Fluoroethylthio)-2,5-dimethoxy-PEA	586
50	4-D	4-Trideuteromethoxy-3,5-dimethoxy-PEA	590
51	ß-D	ß,ß-Dideutero-3,4,5-trimethoxy-PEA	592
52	DESOXY	4-Me-3,5-dimethoxy-PEA	596
53	2,4-DMA	2,4-Dimethoxy-A	599
54	2,5-DMA	2,5-Dimethoxy-A	601
55	3,4-DMA	3,4-Dimethoxy-A	604
56	DMCPA	2-(2,5-Dimethoxy-4-methylphenyl)-cyclopropylamine	607
57	DME	3,4-Dimethoxy-ß-hydroxy-PEA	609
58	DMMDA	2,5-Dimethoxy-3,4-methylenedioxy-A	610
59	DMMDA-2	2,3-Dimethoxy-4,5-methylenedioxy-A	613
60	DMPEA	3,4-Dimethoxy-PEA	614
61	DOAM	4-Amyl-2,5-dimethoxy-A	617
62	DOB	4-Bromo-2,5-dimethoxy-A	620
63	DOBU	4-Butyl-2,5-dimethoxy-A	622
64	DOC	4-Chloro-2,5-dimethoxy-A	626

65	DOEF	4-(2-Fluoroethyl)-2,5-dimethoxy-A	628
66	DOET	4-Ethyl-2,5-dimethoxy-A	631
67	DOI	4-Iodo-2,5-dimethoxy-A	633
68	DOM	4-Methyl-2,5-dimethoxy-A	637
69	Ψ-DOM	4-Methyl-2,6-dimethoxy-A	643
70	DON	4-Nitro-2,5-dimethoxy-A	646
71	DOPR	4-Propyl-2,5-dimethoxy-A	647
72	E	4-Ethoxy-3,5-dimethoxy-PEA	650
73	EEE	2,4,5-Triethoxy-A	654
74	EEM	2,4-Diethoxy-5-methoxy-A	656
75	EME	2,5-Diethoxy-4-methoxy-A	658
76	EMM	2-Ethoxy-4,5-dimethoxy-A	659
77	ETHYL-J	N,α-diethyl-3,4-methylenedioxy-PEA	662
78	ETHYL-K	N-Ethyl-α-propyl-3,4-methylenedioxy-PEA	663
79	F-2	Benzofuran-2-methyl-5-methoxy-6-(2-aminopropane)	664
80	F-22	Benzofuran-2,2-dimethyl-5-methoxy-6-(2-aminopropane)	667
81	FLEA	N-Hydroxy-N-methyl-3,4-methylenedioxy-A	671
82	G-3	3,4-Trimethylene-2,5-dimethoxy-A	674
83	G-4	3,4-Tetramethylene-2,5-dimethoxy-A	676
84	G-5	3,4-Norbornyl-2,5-dimethoxy-A	676
85	GANESHA	3,4-Dimethyl-2,5-dimethoxy-A	678
86	G-N	1,4-Dimethoxynaphthyl-2-isopropylamine	681
87	HOT-2	2,5-Dimethoxy-N-hydroxy-4-ethylthio-PEA	682
88	HOT-7	2,5-Dimethoxy-N-hydroxy-4-(n)-propylthio-PEA	683
89	HOT-17	2,5-Dimethoxy-N-hydroxy-4-(s)-butylthio-PEA	685
90	IDNNA	2,5-Dimethoxy-N,N-dimethyl-4-iodo-A	687
91	IM	2,3,4-Trimethoxy-PEA	690
92	IP	3,5-Dimethoxy-4-isopropoxy-PEA	692
93	IRIS	5-Ethoxy-2-methoxy-4-methyl-A	694
94	J	α-Ethyl-3,4-methylenedioxy-PEA	698
95	LOPHOPHINE	3-Methoxy-4,5-methylenedioxy-PEA	701
96	M	3,4,5-Trimethoxy-PEA	702
97	4-MA	4-Methoxy-A	707
98	MADAM-6	2,N-Dimethyl-4,5-methylenedioxy-A	709
99	MAL	3,5-Dimethoxy-4-methallyloxy-PEA	712
100	MDA	3,4-Methylenedioxy-A	714
101	MDAL	N-Allyl-3,4-methylenedioxy-A	719
102	MDBU	N-Butyl-3,4-methylenedioxy-A	720
103	MDBZ	N-Benzyl-3,4-methylenedioxy-A	721
104	MDCPM	N-Cyclopropylmethyl-3,4-methylenedioxy-A	724
105	MDDM	N,N-Dimethyl-3,4-methylenedioxy-A	725

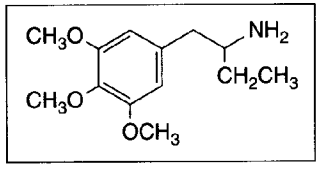
106	MDE	N-Ethyl-3,4-methylenedioxy-A	727
107	MDHOET	N-(2-Hydroxyethyl)-3,4-methylenedioxy-A	731
108	MDIP	N-Isopropyl-3,4-methylenedioxy-A	732
109	MDMA	N-Methyl-3,4-methylenedioxy-A	733
110	MDMC	N-Methyl-3,4-ethylenedioxy-A	739
111	MDMEO	N-Methoxy-3,4-methylenedioxy-A	741
112	MDMEOET	N-(2-Methoxyethyl)-3,4-methylenedioxy-A	742
113	MDMP	α,α,N–Trimethyl-3,4-methylenedioxy-PEA	743
114	MDOH	N-Hydroxy-3,4-methylenedioxy-A	744
115	MDPEA	3,4-Methylenedioxy-PEA	747
116	MDPH	α,α–Dimethyl-3,4-methylenedioxy-PEA	748
117	MDPL	N-Propargyl-3,4-methylenedioxy-A	752
118	MDPR	N-Propyl-3,4-methylenedioxy-A	753
119	ME	3,4-Dimethoxy-5-ethoxy-PEA	755
120	MEDA	3,4-Ethylenedioxy-5-methoxy-A	759
121	MEE	2-Methoxy-4,5-diethoxy-A	761
122	MEM	2,5-Dimethoxy-4-ethoxy-A	764
123	MEPEA	3-Methoxy-4-ethoxy-PEA	769
124	META-DOB	5-Bromo-2,4-dimethoxy-A	771
125	META-DOT	5-Methylthio-2,4-dimethoxy-A	772
126	METHYL-DMA	N-Methyl-2,5-dimethoxy-A	774
127	METHYL-DOB	4-Bromo-2,5-dimethoxy-N-methyl-A	776
128	METHYL-J	N-Methyl-α-ethyl-3,4-methylenedioxy-PEA	778
129	METHYL-K	N-Methyl-α-propyl-3,4-methylenedioxy-PEA	781
130	METHYL-MA	N-Methyl-4-methoxy-A	783
131	METHYL-MMDA-2	N-Methyl-2-methoxy-4,5-methylenedioxy-A	785
132	MMDA	3-Methoxy-4,5-methylenedioxy-A	787
133	MMDA-2	2-Methoxy-4,5-methylenedioxy-A	792
134	MMDA-3a	2-Methoxy-3,4-methylenedioxy-A	795
135	MMDA-3b	4-Methoxy-2,3-methylenedioxy-A	798
136	MME	2,4-Dimethoxy-5-ethoxy-A	800
137	MP	3,4-Dimethoxy-5-propoxy-PEA	803
138	MPM	2,5-Dimethoxy-4-propoxy-A	806
139	ORTHO-DOT	2-Methylthio-4,5-dimethoxy-A	809
140	P	3,5-Dimethoxy-4-propoxy-PEA	811
141	PE	3,5-Dimethoxy-4-phenethyloxy-PEA	813
142	PEA	PEA	815
143	PROPYNYL	4-Propynyloxy-3,5-dimethoxy-PEA	819
144	SB	3,5-Diethoxy-4-methoxy-PEA	820
145	TA	2,3,4,5-Tetramethoxy-A	822
146	3-TASB	4-Ethoxy-3-ethylthio-5-methoxy-PEA	826
147	4-TASB	3-Ethoxy-4-ethylthio-5-methoxy-PEA	829

148	5-TASB	3,4-Diethoxy-5-methylthio-PEA	832
149	TB	4-Thiobutoxy-3,5-dimethoxy-PEA	834
150	3-TE	4-Ethoxy-5-methoxy-3-methylthio-PEA	837
151	4-TE	3,5-Dimethoxy-4-ethylthio-PEA	840
152	2-TIM	2-Methylthio-3,4-dimethoxy-PEA	843
153	3-TIM	3-Methylthio-2,4-dimethoxy-PEA	846
154	4-TIM	4-Methylthio-2,3-dimethoxy-PEA	848
155	3-TM	3-Methylthio-4,5-dimethoxy-PEA	849
156	4-TM	4-Methylthio-3,5-dimethoxy-PEA	852
157	TMA	3,4,5-Trimethoxy-A	857
158	TMA-2	2,4,5-Trimethoxy-A	864
159	TMA-3	2,3,4-Trimethoxy-A	868
160	TMA-4	2,3,5-Trimethoxy-A	869
161	TMA-5	2,3,6-Trimethoxy-A	873
162	TMA-6	2,4,6-Trimethoxy-A	876
163	3-TME	4,5-Dimethoxy-3-ethylthio-PEA	880
164	4-TME	3-Ethoxy-5-methoxy-4-methylthio-PEA	882
165	5-TME	3-Ethoxy-4-methoxy-5-methylthio-PEA	884
166	2T-MMDA-3a	2-Methylthio-3,4-methylenedioxy-A	886
167	4T-MMDA-2	4,5-Thiomethyleneoxy-2-methoxy-A	888
168	TMPEA	2,4,5-Trimethoxy-PEA	891
169	2-TOET	4-Ethyl-5-methoxy-2-methylthio-A	893
170	5-TOET	4-Ethyl-2-methoxy-5-methylthio-A	896
171	2-TOM	5-Methoxy-4-methyl-2-methylthio-A	900
172	5-TOM	2-Methoxy-4-methyl-5-methylthio-A	904
173	TOMSO	2-Methoxy-4-methyl-5-methylsulfinyl-A	907
174	TP	4-Propylthio-3,5-dimethoxy-PEA	909
175	TRIS	3,4,5-Triethoxy-PEA	912
176	3-TSB	3-Ethoxy-5-ethylthio-4-methoxy-PEA	913
177	4-TSB	3,5-Diethoxy-4-methylthio-PEA	916
178	3-T-TRIS	4,5-Diethoxy-3-ethylthio-PEA	918
179	4-T-TRIS	3,5-Diethoxy-4-ethylthio-PEA	921

PHENETHYLAMINES

#1 AEM; α-ETHYLMESCALINE; 2-AMINO-1-(3,4,5-TRIMETHOXYPHENYL)BUTANE; 1-(3,4,5-TRIMETHOXY-PHENYL)-2-AMINOBUTANE

SYNTHESIS: To a solution of 45 g 3,4,5-trimethoxybenzaldehyde in 1.2 L IPA, there was added 125 g nitropropane and 67.5 g t-butylammonium acetate and the reaction mixture was held at reflux for 16 h. This was poured into 6 L H_2O, and extracted with 2x250 mL hexane. The pooled extracts were stripped of solvent under vacuum giving a residue that slowly set to a crystalline mass. On filtering, there was obtained 9.4 g of a crude yellow product which, on recrystallization from hexane provided 8.7 g of slightly sticky bright yellow crystals of 2-nitro-1-(3,4,5-trimethoxyphenyl)butene-1, with a mp of 71-73 °C. A second recrystallization from hexane gave fine yellow crystals with a mp of 72-73 °C. Attempts at the preparation of this nitrostyrene by the more conventional methods with ammonium acetate in acetic acid led either to the formation of a white product $C_{23}H_{30}N_2O_8$ which was composed of a molecule of the nitrostyrene, one of the benzaldehyde itself, and a molecule of ammonia, or to 3,4,5-trimethoxybenzonitrile, from reaction with the decomposition products of nitropropane.



A stirred suspension of 5.9 g LAH in 310 mL anhydrous Et_2O was held at a gentle reflux in an inert atmosphere. A solution of 8.5 g 2-nitro-1-(3,4,5-trimethoxyphenyl)butene-1 in 125 mL Et_2O is added drop-wise over the course of 0.5 h. The reaction was maintained at reflux for 6 h, then cooled, and the excess hydride destroyed by the cautious addition of 300 mL 1.8 N H_2SO_4. The phases were separated, and the aqueous phase brought to a pH of 6 by the addition of a saturated Na_2CO_3 solution. The neutral solution was brought to a boil, and clarified by

filtration through paper. To the hot filtrate there was added a solution of 8.9 g picric acid in 100 mL boiling EtOH. The mixture was stirred and cooled, with the formation of a heavy yellow crystalline mass. After standing in the ice tub for several hours the mixture was filtered, providing 8.0 g of the picrate salt with a mp of 176-181 °C from H_2O. A solution of this salt in 300 mL boiling H_2O was treated with 60 mL concentrated HCl. On cooling, there was a deposition of picric acid, which was removed by filtration. The aqueous filtrate was washed with 3x50 mL nitrobenzene, then with 3x50 mL Et_2O. The pH was brought above 9 by the addition of aqueous NaOH, and the filtrate was extracted with 3x100 mL CH_2Cl_2. Removal of the solvent from the pooled extracts gave a nearly colorless oil, which was dissolved in 300 mL anhydrous Et_2O and saturated with hydrogen chloride gas. The white crystals of 2-amino-1-(3,4,5-trimethoxyphenyl)butane hydrochloride (AEM) were removed by filtration, Et_2Owashed, and air dried. They weighed 4.72 g.

DOSAGE: greater than 220 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: The extension of the two-carbon chain of mescaline by alpha-methylation to the three carbon chain of TMA approximately doubled the potency of the compound. And it was felt to be a completely logical possibility that, by extending it one more carbon atom, to the four carbon chain of alpha-ethyl-mescaline, it might double again. And following that logical progression, the doubling of potency with each additional carbon atom, the factor would be 2 to the 7th power by the alpha-octyl (or 256x that of mescaline, or a milligram as active dose) and with a side chain of a 70-carbon alkyl group (alpha-heptacontylmescaline) it would take just a single molecule to be intoxicating. This was rich fantasy stuff. As an active compound, just where would it go in the brain? With an 80-carbon side-chain, would one-thousandth of a single molecule be enough for a person? Or might a single molecule intoxicate a thousand people? And how long a chain on the alpha-position might be sufficient that, by merely writing down the structure on a piece of paper, you would get high? Maybe just conceiving the structure in your mind would do it. That is, after all, the way of homeopathy.

Maybe it was just as well that this added two-carbon side-chain with lowered activity was already enough to disprove the doubling pattern. But by the time this non-activity had been learned, the alpha series had already been pushed out quite aways. The machinery of making the appropriate nitroalkane was straightforward, by reaction of the alkyl halide with nitrous acid, and separating the unwanted nitrite ester from the wanted nitroalkane by fractional distillation. The nitrostyrenes all formed reasonably although often in terrible yields, and reduced reasonably, and all formed crystalline picrates for isolation and crystalline hydrochloride salts for pharmacological manipulation. But since the first of these, AEM, was not active, there was no enthusiasm for tasting anything higher. This family was never

published; why publish presumably inactive and thus uninteresting material? The Table presents the properties of the precursor nitrostyrenes, and the product picrate and hydrochloride salts, at least whatever information I can still find after thirty years:

TABLE. Physical Properties of the α-Alkylmescaline Homologues and their Precursor Nitrostyrenes

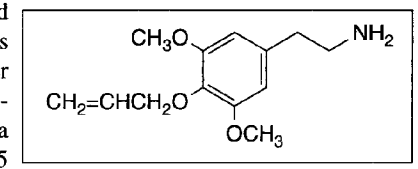
Code	Name	NS mp °C	picrate mp °C	HCl mp °C
APM	Alpha-propylmescaline	82-83		214-218
ABM	Alpha-butylmescaline	73-74	169-174	182-184
AAM	Alpha-amylmescaline	54-55	162-163	155-158
AHM	Alpha-hexylmescaline	51-52		
ASM*	Alpha-heptylmescaline	43-44		
AOM	Alpha-octylmescaline	**		
ANM	Alpha-nonylmescaline	46-47	***	
AUM	Alpha-undecylmescaline		***	

* S is for septyl, to distinguish heptyl from hexyl. **Never made, as no nonylbromide could be located to make the needed nitrononane. ***The synthesis got as far as the nitrostyrene stage when the inactivity of AEM was determined, and the project was dropped.

#2 AL; 4-ALLYLOXY-3,5-DIMETHOXYPHENETHYLAMINE; 3,5-DIMETHOXY-4-ALLYLOXYPHENETHYLAMINE

SYNTHESIS: A solution of 5.8 g of homosyringonitrile (see under E for its preparation), 100 mg decyltriethylammonium iodide, and 13.6 g allyl iodide in 50 mL anhydrous acetone was treated with 6.9 g finely powdered anhydrous K_2CO_3 and held at reflux for 16 h. The color changed from a near-black to a light yellow. The mixture was filtered, the solids washed with acetone, and the solvent from the combined filtrate and washes removed under vacuum. The residue was suspended in acidified H_2O, and extracted with 3x100 mL CH_2Cl_2. The pooled extracts were washed with 2x50 mL 5% NaOH, once with dilute HCl (which lightened the color of the extract) and then stripped of solvent under vacuum giving 12.4 g of an amber-colored oil. This was distilled at 125-137 °C at 0.1 mm/Hg to yield 5.7 g of 3,5-dimethoxy-4-allyloxyphenylacetonitrile as a yellow oil. Anal. ($C_{13}H_{15}NO_3S$) C,H.

A suspension of 4.0 g LAH in 150 mL anhydrous THF under N_2 was cooled to 0 °C and vigorously stirred. There was added, dropwise, 2.8 mL 100% H_2SO_4, followed by 5.5 g 3,5-dimethoxy-4-allyloxyphenylacetonitrile in 10 mL anhydrous THF. The reaction mixture was stirred at 0 °C for a few min, then brought to a reflux on the steam bath for 30 min. After cooling back to room temperature, there was added sufficient IPA to destroy the excess hydride, followed by sufficient 10% NaOH to form granular solids. These were removed by filtration, and washed with 20 mL IPA. The filtrate and washes were stripped of solvent under vacuum andthe residue added to 100 mL dilute H_2SO_4. This was washed with 2x50 mL CH_2Cl_2, made basic with aqueous NaOH, and extracted with 2x75 mL CH_2Cl_2. These extracts were pooled, the solvent removed under vacuum, and the residue distilled at 110-120 °C at 0.4 mm/Hg to give 4.9 g of a colorless oil. This was dissolved in 15 mL IPA, neutralized with concentrated HCl (55 drops required), and diluted with 50 mL Et_2O. The product was removed by filtration, washed with Et_2O, and air dried to give 4.9 g of 3,5-dimethoxy-4-allyloxyphenethylamine hydrochloride (AL) as white crystals.



DOSAGE: 20 - 35 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 24 mg) "I first became aware of something in about 10 minutes, a pleasant increase in energy. By 20 minutes it was getting pronounced and was a nice, smooth development. During the next hour positive and negative feelings developed simultaneously. Following a suggestion, I ate a bit of food even though I had not been hungry, and to my surprise all the negative feelings dropped away. I felt free to join the others wherever they were at. I moved into the creative, free-flowing kind of repertoire which I dearly love, and found everything enormously funny. Much of the laughter was so deep that I felt it working through buried depressions inside me and freeing me. From this point on, the experience was most enjoyable. The experience was characterized by clear-headedness and an abundance of energy which kept on throughout the day and evening. At one point I went out back and strolled along to find a place to worship. I had a profound sense of the Presence and great love and gratitude for the place, the people, and the activities taking place. The come-down from the experience was very gradual and smooth. Food tasted wonderful. I went to bed late, and quite ready for bed, although the energy was still running. However, sleep was not long in coming."

(with 24 mg) "The onset was extremely gradual and graceful, with the first alert that one could really sense at about 50 minutes. This was succeeded by a slow gentle climb to the peak at one hour and fifteen minutes. The experience itself left all of the sensory modalities functional; speech was cogent and rather fluid. In fact, there was an unusual ease of free association. All throughout the session, the talk was high in spirits and somehow indicative of an inner excitement. Affect was entirely pleasant, but not exalting nor conducive to insight or to problem solving. There were no requirements for withdrawal into the self. The material seemed wholly social in nature. No visual, auditory or olfactory sharpening was in

evidence. The plateau for this material seemed unusually long. I was unable to sleep for several hours, and took 25 mg Librium before sleep arrived. The next day was a lethargic and slow one, with the inner feeling that the effects had not worn off until the middle of the day following ingestion."

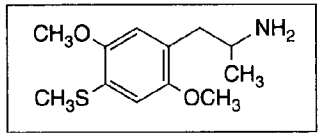
(with 35 mg) "I was a distinct +1 in 35 minutes and a +2 by the end of the hour. My head congestion in no way cleared up, absolving the material from having that particular virtue. The entire experience was somewhat dissociated — I could not connect with my feelings. Although my mind remained clear, there was a hangover feeling at the end of the experiment."

EXTENSIONS AND COMMENTARY: This compound was first explored in Prague by Leminger. He provided only the synthetic details and the statement that it was the most active compound that he had studied, with activity at 20 milligrams, with perceptual changes, color enhancement, and difficult dreams during sleep that night. Some effects persisted for more than 12 hours. Dosages above 35 milligrams remain unexplored.

As AL is one of the most potent 3,4,5-trisubstituted phenethylamines yet described, and since the corresponding amphetamines are of yet greater potency, it would be a good guess that 4-allyloxy-3,5-dimethoxyamphetamine (3C-AL) would be an interesting compound to explore. It could be made from syringaldehyde in reaction with allyl iodide, followed by the formation of a nitrostyrene with nitroethane, followed by reduction with aluminum hydride. It is, as of the present time, both unsynthesized and unexplored.

#3 ALEPH; DOT; PARA-DOT; 2,5-DIMETHOXY-4-METHYLTHIOAMPHETAMINE

SYNTHESIS: A solution of 2.3 g 2,5-dimethoxy-4-(methylthio)benzaldehyde (see under 2C-T for its synthesis) in 7.5 mL nitroethane was treated with 0.45 g anhydrous ammonium acetate and heated on the steam bath for 6 h. The excess solvent/reagent was removed under vacuum leaving a mass of orange crystals as residue. These were ground up under 10 mL MeOH, collected by filtration, washed with a little MeOH, and air dried to provide 2.6 g crude 1-(2,5-dimethoxy-4-methylthiophenyl)-2-nitropropene. After recrystallization from 140 mL boiling MeOH, filtering and drying there was in hand 1.8 g of bright orange crystals with a mp of 137-138 °C. Anal. ($C_{12}H_{15}NO_4S$) C,H,N,S.



A suspension of 1.4 g LAH in 10 mL anhydrous Et_2O and 40 mL anhydrous THF was put under an inert atmosphere and, with good stirring, brought up to a gentle reflux. A solution of 1.8 g 1-(2,5-dimethoxy-4-methylthiophenyl)-2-nitropropene in 30 mL anhydrous THF was added dropwise at a rate that maintained the reflux. Heating and stirring were maintained for an additional 7 h, then the reaction mixture was allowed to return to room temperature. There was added 1.6 mL H_2O (dissolved in a little THF), followed by 1.6 mL 15% NaOH, and finally another 4.8 mL H_2O. Stirring was continued until all the curdy solids had turned white. The reaction mixture was filtered, and the filter cake washed with THF. The filtrate and the washings were combined, and the solvent removed under vacuum. The residue was 1.3 g of a colorless oil that solidified. Its mp of 90-93 °C was improved slightly to 91-93 °C with recrystallization from hexane. The product was dissolved in 25 mL warm IPA, neutralized with concentrated HCl (0.57 mL required) and then diluted with 100 mL anhydrous Et_2O. After a moment's delay, the white crystalline product appeared. It was removed by filtration, washed with Et_2O, and air dried to provide 1.2 g 2,5-dimethoxy-4-methylthioamphetamine hydrochloride (ALEPH) with a mp of 200-201 °C. Recrystallization from IPA gave an analytical sample with a mp of 204-205 °C. Anal. ($C_{12}H_{20}ClNO_2S$) C,H; N: calcd, 5.04; found, 5.52.

DOSAGE: 5 - 10 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 5 mg) "The initial hints of action were physical — warming of first the legs, and then a comfortable warmth spread over the entire body. Intense intellectual stimulation, one that inspired the scribbling of some 14 pages of handwritten notes. Which is a pretty good record for an experience that is almost entirely non-verbal. The afterglow was benign and rich in empathy for everything. And by the sixth hour I was quite hungry."

(with 10 mg) "There was a rapid shift of frame of reference that made simple tasks such as reading and tuning the radio quite alien. I happened to catch the eyes of Pretty Baby, the cat, at the same moment she looked at me, and she turned and fled. I am able to interact with people on the telephone quite well but mechanical things, such as arranging flowers or alphabetizing names, are beyond me. Driving would be impossible."

EXTENSIONS AND COMMENTARY: This specific compound is probably the first sulfur-containing phenethylamine to have been evaluated as a potentially active CNS stimulant or psychedelic. It was a complete, total, absolute unknown. The first trials were made at the sub-microgram level, specifically at 0.25 micrograms, at 11:30 AM on September 3, 1975. Part of this extreme precaution was due to the uniqueness of a new heteroatom in a phenethylamine system. But part was due to the strange manic excitement that occurred at the time of the isolation and characterizing of the final product in the laboratory. Although it was certainly all placebo response, I was jumpy and unable to stay in the lab for more than a few minutes at a time. Maybe dust in the air? Maybe some skin contact with the free

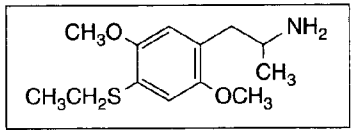
base? Now, I know there was nothing, but the possibility of extraordinary potency was real, and I did indeed wash everything down anyway. In fact, it took a total of 18 trials to work the experimental dosage up to as much as a single milligram. In retrospect, overly cautious. But retrospection, as they say, is cheap.

The 5 milligram experiment, briefly quoted from above, is the stuff of Chapter 14 of this book, important in that it gives an interesting example of some thought processes associated with psychedelic intoxication, ego-inflation, and what might be thought of as bits of mania. As is always the case with peak experiences that happen to be catalyzed by drugs, this extraordinary event could not be duplicated. At 7 milligrams there was an uneventful +1, and some 10 milligrams was needed to generate a full +3 experience. The first clue of the erratic nature of the Aleph family came from an independent assay by a colleague of mine, one who was very familiar with such states of consciousness, but for whom this was not a time for peak experiences. At 10 milligrams he told me that he had had only mild effects which he found relatively uninteresting.

As it stands, ALEPH remains relatively unexplored. Its two positional isomers are entered here as ORTHO-DOT and META-DOT. Three higher homologues have been more thoroughly looked at, and the generic name ALEPH (the first letter of the Hebrew alphabet) was given this group on the basis that they might have extraordinary properties in common. But the real treasure came in the exploring of the 2-carbon homologues, the compounds that make up the 2C-T family. Here, there proved to be much less uncertainty as to reasonable dosages, and much more richness in the subjective nature of the experience.

#4 ALEPH-2; 2,5-DIMETHOXY-4-ETHYLTHIOAMPHETAMINE

SYNTHESIS: A solution of 2.0 g 2,5-dimethoxy-4-(ethylthio)benzaldehyde (see under 2C-T-2 for its synthesis) in 12 mL nitroethane was treated with 0.4 g anhydrous ammonium acetate and heated on the steam bath for 3 h. All volatiles were removed under vacuum, leaving a residue that set up as brilliant red crystals. These were mechanically removed from the evaporation flask, blown free of nitroethane vapor, and recrystallized from boiling EtOH, producing 1.8 g pale orange crystals, with a mp of 110-112 °C. Recrystallization from 20 mL boiling IPA gave, after filtering and air drying, 1.70 g light orange crystals of 1-(2,5-dimethoxy-4-ethylthiophenyl)-2-nitropropene with a mp of 112-113 °C.



A suspension of 1.2 g LAH in 75 mL anhydrous THF was put under an inert atmosphere and, with good stirring, brought up to a gentle reflux. A solution of 1.5 g 1-(2,5-dimethoxy-4-ethylthiophenyl)-2-nitropropene in 20 mL anhydrous THF was added dropwise. Heating and stirring were maintained for an additional 24 h, and then the reaction mixture was allowed to come back to room temperature with stirring. There was added 1.4 mL H_2O (dissolved in a little THF), followed by 1.4 mL 15% NaOH and finally another 4.2 mL H_2O. Stirring was continued until all the curdy solids had turned white. The reaction mixture was filtered, and the filter cake washed with THF. The filtrate and the washings were combined, and the solvent removed under vacuum. The residue was 1.1 g of a pale amber oil. This was dissolved in 6 mL IPA, neutralized with concentrated HCl (about 8 drops were required) and then diluted with 150 mL anhydrous Et_2O. The slightly cloudy solution was stirred for a couple of min, then there was the formation of a heavy white crystalline mass. This was removed by filtration, washed with Et_2O, and air dried to provide 1.1 g 2,5-dimethoxy-4-ethylthioamphetamine hydrochloride (ALEPH-2) with a mp of 128-130 °C with decomposition.

DOSAGE: 4 - 8 mg

DURATION: 8 - 16 h.

QUALITATIVE COMMENTS: (with 4 mg) "There was a warm feeling in the total body and a light pressure in the head that changed with time into the feeling of a balloon without any anatomical definition. The usual color perception was not very much increased, and my vision was not sharpened as it was with DOM. Rather, I noticed waves of movement, very smooth and not too busy. Both my tactile perception and auditory acuity were enhanced. The main effect for me was, paradoxically, an easier handling of the outer world. None of the jitters of amphetamine. The body feeling is good, healthy, and I am at peace with the body-mind dualism. These are pretty much personal comments — I will write up the pharmacological points later."

(with 5 mg) "This turned out to be a day of extraordinary visuals and interpretations. About two hours into it, I felt that the effects were still climbing, but there was a marvelous onset of visual distortions and illusions, right at the edge of hallucination. The logs in the fireplace were in continuous motion. The notepaper I was writing on seemed to scrunch and deform under the pressure of the pen. Nothing would stay still; everything was always moving. There was a phase of unabated inflation. The intensity was noticeably dropping at the five hour point and I observed considerable residual shakes and a muscular tremor. Even towards midnight there was some tooth-rubbiness, but I was able to get a somewhat fretful though adequate sleep."

(with 5 mg) "I was exposed to a number of new environments and it was difficult to completely separate the experience into what was seen differently and what was seen for the first time. The Santa Cruz Mystery Spot should have been bizarre but it was simply hokey. And yet the boardwalk that should have been depressing was totally magical. The day was unworldly and I ended up with considerable muscular weakness. All in all, I handled it well, but I probably won't

do it again."

(with 7 mg) "An amazing unification of visual hallucination seen only in the very fine detail of something, and what must be considered retinal hallucination. There is no one-to-one correspondence between the many retinal cells of the high-resolution part of the eye. Thus, the mind can pick and choose, sometimes from the right eye, and sometimes from the left. And so a small curve or bump can become whatever you wish. For a moment. And then it chooses again, but differently. Is all of our perceived world as subjective as this?"

(with 8 mg) "Extreme intoxication, but almost no visual phenomena. Even well into the evening, I know I absolutely could not drive. Why? I don't know, since this experiment, at least, seemed to be quite free of strange colors and wiggly lines and streaks of light. It's that I don't trust that the reality I see is the same reality that the other driver might see. I am very much the center of the world about me, and I don't think I could trust anyone else to fully respect my reality."

EXTENSIONS AND COMMENTARY: As with ALEPH itself, and in most ways with the entire ALEPH family, there is no predictability of the dose/response relationship. One person had expressed his psychic isolation by taking and maintaining a fetal position in relative hibernation for several hours and with substantial amnesia; this at a four milligram dose. Yet another person, at fully twice this amount, was aware of a slight light-headedness that could in no way be measured as more than a bare threshold. But by the time this erratic nature had become apparent, the ALEPHS had been assigned and made, up to and including ALEPH-7.

ALEPH-3 was intended to be the methallylthio compound, 2,5-dimethoxy-4-(ß-methallylthio)amphetamine. The thioether (2,5-dimethoxyphenyl ß-methallyl sulfide) was easily made from 2,5-dimethoxythiophenol (see 2C-T-2 for its preparation) with 3.4 g dissolved in a solution of 1.7 g KOH in 25 mL boiling EtOH, and 2.72 g methallyl chloride, heated 1 h on the steam bath, poured into 250 mL H_2O, extracted with 3x100 mL CH_2Cl_2, and solvent removal yielding 4.4 g of the sulfide as an amber oil. An effort to convert this to 2,5-dimethoxy-4-(ß-methallylthio)-benzaldehyde (7.2 g $POCl_3$, 6.7 g N-methylformanilide, 4.2 g of the crude sulfide from above, 15 min heating on the steam bath, H_2O hydrolysis, hexane extraction of the residues from a CH_2Cl_2 extraction) produced 3.1 g of a peppermint-smelling oil that distilled at 140-160 °C at 0.3 mm/Hg and which did indeed have an aldehyde group present (by proton NMR) but the rest of the spectrum was a mess, and the project was abandoned.

Several years later, this entire project was reinitiated, and the aldehyde was obtained as a yellow crystal, but again it was not pursued. At that time, the earlier try had been totally forgotten, and a brand new ALEPH- (or 2C-T-) number had been assigned; i.e., 20. Thus, the corresponding phenethylamine (2,5-dimethoxy-4-(ß-methallylthio)phenethylamine), had it ever been made, which it was not, would have been called either 2C-T-3 or 2C-T-20, and the amphetamine homologue would

probably have been ALEPH-20.

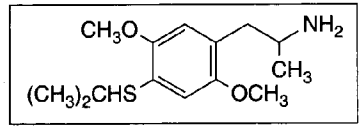
A closely related 2C-T-X compound was also started quite a while later — this was the allylthio homologue of the methallyl material 2C-T-3 or 2C-T-20. Its place in the flow of things is evident from its numbering, 2C-T-16. A mixture of 2,5-dimethoxythiophenol and KOH and allyl chloride in MeOH gave 2,5-dimethoxyphenyl allyl sulfide as a white oil which boiled at 110-125 °C at 0.25 mm/Hg. This, with $POCl_3$ and N-methylformanilide provided 2,5-dimethoxy-4-(allylthio)benzaldehyde which distilled at 140-160 °C at 0.4 mm/Hg and could be recrystallized from MeOH as a pale yellow solid. Reaction of this aldehyde in nitroethane in the presence of ammonium acetate (steam bath for 2.5 h) provided 2,5-dimethoxy-4-allylthio-ß-nitrostyrene as red crystals from acetonitrile. Its mp was 114-115 °C. Anal. ($C_{13}H_{15}NO_4S$) C,H. This has not yet been reduced to the final amine, 2,5-dimethoxy-4-allylthiophenethylamine, 2C-T-16. The corresponding amphetamine would be, of course, ALEPH-16.

ALEPH-5 was to be the cyclohexylthio analogue (2,5-dimethoxy-4-cyclohexylthioamphetamine). The thioether (2,5-dimethoxyphenyl cyclohexyl sulfide) was successfully made from 1.7 g 85% KOH pellets in 25 mL hot EtOH, 3.4 g 2,5-dimethoxythiophenol (again, see under 2C-T-2 for its preparation), and 4.9 g cyclohexyl bromide, 3 h on the steam bath, into 500 mL H_2O, extraction with 3x100 mL CH_2Cl_2, washing the extracts with 5% NaOH, and evaporation to yield 5.2 g of an amber oil. The aldehyde, (made from 6.1 g $POCl_3$ and 5.4 g N-methylformanilide, heated until claret colored, then treated with 5.0 g of the above crude thioether, heating for 20 min on the steam bath, into 300 mL H_2O, and overnight stirring) was obtained as 3.1 g of a flesh-colored solid that was clearly neither pure nor completely correct. Repeated partitioning with organic solvents and cooling and scratching the residues finally provided a pale orange crystal (1.3 g, mp 88-93 °C) which, after twice recrystallizing from MeOH, gave 0.4 g of pale yellow crystals with a mp 95-96 °C and a textbook perfect NMR in $CDCl_3$ (CHO, 1H (s) 10.41; ArH 2H (s) 6.93, 7.31; OCH_3, 6H, (2s) at 3.88 and 3.92; CH, 1H br. at 3.34; and $(CH_2)_5$ 10H br. at 1.20-2.34). The nitrostyrene was prepared from 200 mg of the above aldehyde in 1.2 mL nitroethane and 0.1 g ammonium acetate overnight on the steam bath, the solvent removed to give an orange oil that spontaneously crystallized after a few months' standing. This was never characterized, but sits there on the shelf to be reduced to ALEPH-5 some inspired day. The two-carbon homo-logue of this (2,5-dimethoxy-4-cyclohexylthiophenethylamine) will someday be called 2C-T-5 (if it is ever made).

The remaining members of this family, ALEPH-4, ALEPH-6, and ALEPH-7 have actually been prepared and they have all been entered here in Book II, under their own names.

#5 ALEPH-4; 2,5-DIMETHOXY-4-(i)-PROPYLTHIOAMPHETAMINE

SYNTHESIS: A solution of 2.0 g 2,5-dimethoxy-4-((i)-propylthio)benzaldehyde (see under 2C-T-4 for its synthesis) in 12 mL nitroethane was treated with 0.4 g anhydrous ammonium acetate and heated on the steam bath for 12 h, then allowed to stir for another 12 h at room temperature. The excess solvent/reagent was removed under vacuum leaving a residue as a heavy deep orange two-phase oily mass. This was brought into one phase with 2 mL MeOH and then, with continued stirring, everything spontaneously crystallized. This product was removed by filtration and, after washing sparingly with cold MeOH and air drying, yielded 2.0 g of 1-(2,5-dimethoxy-4-(i)-propylthiophenyl)-2-nitropropene as orange crystals with a mp of 96-98 °C. After recrystallization from 15 mL boiling 95% EtOH, filtering and air drying to constant weight, there was obtained 1.6 g of orange crystals with a mp of 99-100 °C.



A suspension of 1.0 g LAH in 100 mL warm THF was stirred under a N_2 atmosphere and heated to a gentle reflux. To this there was added, dropwise, a solution of 1.2 g 1-(2,5-dimethoxy-4-(i)-propylthiophenyl)-2-nitropropene in 20 mL anhydrous THF. This mixture was held at reflux for 1 day, then stirred at room temperature for 2 days. There was then added, slowly and with caution, 1 mL of H_2O, followed by 1 mL of 15% NaOH, and finally by another 3 mL of H_2O. Stirring was continued until the reaction mixture became white and granular, then all solids were removed by filtration and the filter cake was washed with additional THF. The filtrate and washings were combined, and the solvent removed under vacuum to give 1.1 g of residue which was an almost white oil. This was dissolved in 6 mL IPA, neutralized with concentrated HCl (10 drops were required) and then diluted with 200 mL anhydrous Et_2O. The resulting slightly turbid solution was clarified by filtration through a sintered glass filter, and the clear and slightly yellow filtrate was allowed to stand. A fine white crystalline product slowly separated over the next few h. This product, 2,5-dimethoxy-4-(i)-propylthioamphetamine hydrochloride (ALEPH-4) was removed by filtration, and after washing with Et_2O and air drying, weighed 0.5 g and had a mp of 146-147 °C, with prior sintering at 144 °C.

DOSAGE: 7 - 12 mg.

DURATION: 12 - 20 h

QUALITATIVE COMMENTS: (with 7 mg) "Things started off going downhill, initially negative with tension and depression, but as the momentum developed, so did the positive effect. My discomfort continued to develop, but I was struck by the visual beauty of the trees and the small stream that flowed off the mountain. My experience continued to grow, simultaneously, in both the negative and the positive

direction. Physically I was uncomfortable and found my breathing difficult, but I acknowledged a rapture in the very act of breathing. All moved over to the plus side with time, and the evening was gorgeous. I have never seen the sky so beautiful. The only flaw was when I choked on some lemonade and it seemed to me I almost drowned. I have been extremely conscious of eating, drinking and swallowing ever since. I barely slept the whole night and awoke extremely tired. I felt that the experience continued for many days, and I feel that it is one of the most profound and deep learning experiences I have had. I will try it again, but will block out more time for it."

(with 8 mg) "There was without question a plus two, but none of the edges of unreality that are part of LSD. The sounds that are just outside of my hearing are intriguing, and distract me from the eyes-closed imagery that is just barely possible with music while lying down. But, going outside, there were no obvious sources of the sounds that I heard. Could I drive? I suspect so. I took a shower and did just that — I drove to San Francisco without incident, and walked amongst the many strange faces on the downtown streets."

(with 12 mg) "The experience was very intense but completely under control except for a twenty minute period right in the middle of it. I had to get away from everything, from everyone. There was a sense of being surrounded and moved in upon that was suffocating. I was weighed down with everything — physical, psychic, emotional. My clothes had to come off, my hair had to be released, my shoes went, I needed to move away from where I was, to somewhere else, to some new place, any new place, with the hope that my other old place wouldn't follow me. Pretty soon I found I was myself, I could breathe again, and I was OK. Rather sheepishly, I dressed and rejoined the group. The rest of the day was spectacular, but those few minutes were scary. What if I couldn't have escaped?"

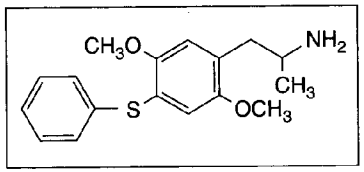
EXTENSIONS AND COMMENTARY: Again, there are hints and suggestions of complexities. These, and several other reports, suggest some sensory confusion, and interpretive aspects that are to some extent threatening. There is an underlying suggestion of body toxicity. I know of no experiment that exceeded 12 milligrams and I would not be able to predict what might come forth at higher dosages. I personally choose not to try them.

#6 ALEPH-6 2,5-DIMETHOXY-4-PHENYLTHIOAMPHETAMINE

SYNTHESIS: To a 300 mL three-neck round-bottom flask set up with a magnetic stirrer and protected with a N_2 atmosphere, there was added 75 mL hexane, 3.5 g tetramethylethylenediamine, and 4.2 g p-dimethoxybenzene. The reaction mixture was cooled to 0 °C with an external ice bath, and there was then added 19 mL of 1.6 M butyllithium in hexane. With stirring, the reaction was brought up to room temperature, and there were produced loose, creamy solids. There was then added,

as a solid and portionwise, 6.6 g diphenyldisulfide which resulted in an exothermic reaction and the production of a nearly clear solution. After stirring an additional 10 min, the reaction was quenched in 500 mL of dilute NaOH. The hexane phase was separated, and the aqueous phase extracted with 4x100 mL CH_2Cl_2 The organic extracts were combined, washed with dilute HCl and the solvents were removed under vacuum to provide 6.0 g of 2,5-dimethoxyphenyl phenyl sulfide as an impure amber oil. A small sample was saved for microanalysis and NMR, and the remainder converted to the corresponding benzaldehyde.

A mixture of 6.1 g $POCl_3$ and 5.4 g N-methylformanilide was heated for 3 min on the steam bath, and then added to the remainder of the above-described 2,5-dimethoxyphenyl phenyl sulfide. The reaction became immediately a deep red and, after heating on the steam bath for 0.5 h, was dumped into a large quantity of H_2O, producing a granular brown solid. This was removed by filtration, and washed sparingly with cold MeOH (the washes were saved). The resulting pale yellow solids were recrystallized from 20 mL boiling absolute EtOH providing, after cooling, filtration and air drying, 4.4 g of extremely pale yellow crystals of 2,5-dimethoxy-4-(phenylthio)benzaldehyde. This had a mp of 119-119.5 °C. All washes and mother liquors were combined, flooded with H_2O and extracted with CH_2Cl_2. This solvent was removed under vacuum, and the residue (a viscous oil) was dissolved in a little EtOH which, on cooling in dry ice, gave 1.2 g of a second crop of the aldehyde, mp 117-119 °C. Recrystallization from 5 mL 95% EtOH gave an additional 0.4 g product with a mp of 118-119 °C. This mp was not improved by recrystallization from cyclohexane. The NMR specrum was excellent, with OCH_3 singlets (3H) at 3.45 and 3.80 ppm; ArH singlets at 6.28 and 7.26 ppm, the C_6H_5 as a broad peak centered at 7.50, and the CHO proton at 10.37 ppm.



A solution of 4.4 g 2,5-dimethoxy-4-(phenylthio)benzaldehyde in 32 mL nitroethane was treated with 0.8 g anhydrous ammonium acetate and heated on the steam bath for 21 h. The excess solvent/reagent was removed under vacuum, leaving a dark red oil as residue. After much diddling and fiddling around, this set up as a crystalline mass. These solids were ground under 20 mL cold MeOH and filtered, providing 5.3 g of the crude nitrostyrene as an orange crystalline residue product after air-drying. This was ground up under 10 mL MeOH, the insolubles collected by filtration, washed with a little MeOH, and air dried to provide 5.3 g crude 1-(2,5-dimethoxy-4-phenylthiophenyl)-2-nitropropene as yellow crystals, with a mp of 100-102 °C (with prior sintering at about 98 °C). This was recrystallized from 50 mL boiling 95% EtOH. After cooling in an ice bath, it was filtered, washed with EtOH, and air drying provided gold-yellow crystals with a mp of 105-106 °C. The proton NMR was excellent (in $CDCl_3$).

A suspension of 2.0 g LAH in 100 mL refluxing THF, under an inert atmosphere and with good stirring, was treated with a solution of 3.5 g 1-(2,5-dimethoxy-4-phenylthiophenyl)-2-nitropropene in 20 mL anhydrous THF added dropwise at a rate that maintained the reflux. Heating and stirring were maintained for an additional 36 h, and then the reaction mixture was stirred at room temperature for an additional 24 h. There was added 2.0 mL H_2O (dissolved in a little THF), followed by 2.0 mL 15% NaOH, and finally another 6.0 mL H_2O. Stirring was continued until all formed solids had turned white. The reaction mixture was filtered, and the filter cake washed with THF. The filtrate and the washings were combined and the solvent removed under vacuum. The residue was 2.8 g of an oil that quite obviously contained some H_2O. This was dissolved in 400 mL CH_2Cl_2, washed first with dilute NaOH and then with 4x150 mL 1N HCl. The organic phase was stripped of solvent under vacuum, yielding a pale amber oil that crystallized. This was ground first under Et_2O, giving 3.4 g of a yellow solid. This was then ground under 10 mL of acetone, yielding 2.4 g of a white crystalline solid that darkened at 170 °C, sintered at 187 °C and had a mp of 191-193 °C. This was dissolved in 20 mL hot 95% EtOH, and diluted with 40 mL Et_2O to provide a clear solution which, after a minute's scratching with a glass rod, deposited 2,5-dimethoxy-4-phenylthioamphetamine hydrochloride (ALEPH-6) as white solids. After filtration and air drying, the weight was 1.8 g, with a mp of 194-195 °C. The dilute HCl washes, after being made basic with aqueous NaOH and extraction with CH_2Cl_2 gave a trivial quantity of additional product.

DOSAGE: greater than 40 mg.

DURATION: probably long.

QUALITATIVE COMMENTS: (with 30 mg) "I had an alert at the one hour point, and in another hour there was a clear 1+. There was a not well defined, gentle unworldliness. And it was still there quite unchanged twelve hours later. In a group I find that all voices about me are of equal intensity and equal importance. But this is not at all distracting. This will be a long lived thing for sure."

(with 40 mg) "I am into a subtle but real effect, no more than one plus, but real. I feel primed, but nothing more. It is not interfering with work, maybe even helping with it. After another hour of static one-plusness I decided to use it as a primer to LSD, using the usual 60 microgram quantity that is standard for primer studies. The combination showed definite synergism, with a rapid show of the LSD effects (within fifteen minutes) and an almost three plus effect. This is most unusual for the usual 60 microgram challenge amount. An absolutely delightful intoxication that had sufficiently descended towards baseline that I accepted a ride to a party that evening in Marin County to attend a poetry reading. There I felt myself at baseline and accepted (unusual for me) a little marijuana. And with the utmost quiet and delicacy, a rather incredible change of state took place. The most memorable event was the awareness of a clarinet playing somewhere, and the sneaky sounds from it actually coming along the carpet out of the dining room and into the hallway and

through the door and into the room where I was, and all of them gathering at my feet like docile kittens waiting for me to acknowledge them. I did, non-verbally, and I was amazed at the many additional follow-up sounds that came from the same clarinet along the same twisty path along the floor and through the door and into my space, over what seemed to be the next million hours. I ended up with a marvelous collection of notes and phrases at my feet, and I felt somehow honored. My speech sounded OK to me, but I knew that it would be odd to the ears of others, so I kept quiet. A final measure of the weirdness of the ALEPH-6/LSD/Pot combination was the viewing of the Larkspur ferry at its dock, abandoned for the evening and with no one aboard it, and with all that clean, dry sleeping space going to waste with so many people sleeping on the streets these days. Once home, I slept soundly and for a long while. Incredible experience."

EXTENSIONS AND COMMENTARY: In a sense, this compound was a disappointment. The beauty of putting a whole new ring into an active structure is that it provides a marvelous vehicle for introducing new substituents in new arrangements. Had Aleph-6 been a cleanly active and potent compound, then the new phenyl group could have been made electronegative to varying degrees (with methoxy substitution for example) or electropositive to varying degrees (with trifluoromethyls or nitros) and this fine-tuning could have been extremely rewarding.

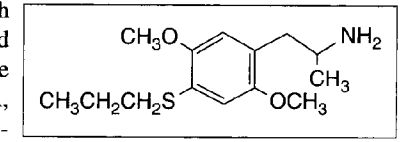
But this material had the earmarks of one of those forever threshold things. The 40 milligram experiment was hopelessly compromised, and nothing higher was ever scheduled or tried. The two-carbon homologue, 2,5-dimethoxy-4-phenylthiophenethylamine, or 2C-T-6, has never even been synthesized, let alone assayed.

#7 ALEPH-7; 2,5-DIMETHOXY-4-(n)-PROPYLTHIOAMPHETAMINE

SYNTHESIS: A solution of 2.6 g 2,5-dimethoxy-4-((n)-propylthio)benzaldehyde (see under 2C-T-7 for its synthesis) in 20 mL nitroethane and 0.5 g anhydrous ammonium acetate was heated on the steam bath overnight. The excess solvent/reagent was removed under vacuum leaving an orange oil as a residue that crystallized spontaneously. This crude product was recrystallized from 20 mL boiling MeOH to give, after cooling, filtering, and air drying, 2.4 g of 1-(2,5-dimethoxy-4-(n)-propylthiophenyl)-2-nitropropene as orange crystals. Its mp was 83-84 °C with prior sintering at 81 °C.

A suspension of 1.5 g LAH in 150 mL of warm anhydrous THF was stirred under an inert atmosphere and brought up to a gentle reflux. A solution of 2.3 g 1-(2,5-dimethoxy-4-(n)-propylthiophenyl)-2-nitropropene in 25 mL anhydrous THF was added dropwise at a rate that maintained the reflux. Heating and stirring were continued for 2 days, and then the reaction mixture was allowed to stir at room temperature for an additional 2 days. There was added 1.5 mL H_2O (dissolved in

10 mL THF), followed by 1.5 mL 15% NaOH, and finally another 4.5 mL H_2O. Stirring was continued until all the curdy solids had turned white. The reaction mixture was filtered, and the filter cake washed with slightly wet THF. The filtrate and the washings were combined, and the solvent removed under vacuum. The residue was about 2 mL of an amber colored oil that was dissolved in 200 mL CH_2Cl_2. This solution was washed with first dilute NaOH, and then with saturated brine. Removal of the solvent gave a pale amber oil that was dissolved in 10 mL IPA, neutralized with about 14 drops of concentrated HCl, and diluted with 200 mL anhydrous Et_2O. The clear solution was decanted from a little gritty material, and then set aside to allow the formation of 2,5-dimethoxy-4-(n)-propylthioamphetamine hydrochloride (ALEPH-7) as fine white crystals. After filtration and air drying, there was obtained 1.8 g of an off-white powder.



DOSAGE: 4 - 7 mg.

DURATION: 15 - 30 h.

QUALITATIVE COMMENTS: (with 4 mg) "At the second hour I had a paraesthetic twinge or two (all pins and needles), and then felt quite relaxed, quite willing to let this play itself out. In the evening my ears still feel 'popped' and there is a little bit of physical awareness. There is not much fun with this. The night following, I was unable to sleep and only dozed slightly, but I seemed to be OK the next day."

(with 6 mg) "The alert was felt within a half hour, and then nothing more. Then, over the next two hours, there was the evolution of an extremely neutral state. I danced wildly to a record of Keith Jarrett, but somehow didn't care for his style. I fell apart emotionally, with tears and a feeling of total loss of everything. Everything was visible to me only in some strange wide-angle lens viewing. I went for a walk, a waste of time. I tried classical music, but only jazz was acceptable. It was a couple of days before I lost the residual strangeness feeling. Never again."

(with 7 mg) "I did this alone, and in retrospect I wish I had not. Somewhere between the hours 2 and 3, I got to a full +++, and I was concerned that I saw the effects still developing. Where would it go now? There was no reality loss as with LSD, no shakes or shimmers, but an intense and profound +++ of something characterized only by the absence of extremes. And I am frightened because this is still deepening. A couple of calls to friends were not successful, but I found an ally in the Palo Alto area, and I told him I was coming to visit. My greater than one hour drive there was okay only because I had programmed every move ahead of time. In retrospect, to drive was completely stupid, and I certainly will never do it again, under any circumstances. But, there I was. I knew which lane I would be on, on the

S.F. Bay Bridge, at every moment of my travels. The middle lane through the tunnel. The second from the left when descending into San Francisco. The white lane-marker stripes were zipping up past my lateral field of vision as I drove, those that were to my right zipped past my right eye, those to the left past my left eye. Like disturbed fruit flies leaving an over-ripe peach. But, as everything had been preprogrammed, there were no surprises. I made it successfully, and my baby-sitting friend probed, with a blend of curiosity, love, and envy, my uncaring state. And in the course of the next couple of hours, this state evolved into a friendly, familiar place. I was still fully +++, but now for the first time I was at peace with it. A fruit salad tasted heavenly. By midnight I was able to doze lightly, and the next day I was sure that there were some residual effects. The second evening's sleep repaired everything. The neutralness was something new to me. I don't like not caring. Was this the "Beth" state of the strange twenty minutes seen by SL in the ALEPH-4 experience?"

(with 7 mg) "Strange, pleasant, unexciting, long-lasting. The induced state was characterized by: clear unintoxicated central field of vision, concentration but with the periphery sensed as being filled with a kind of strangeness, and also something sensed inside, at the back of the head. A feeling of something waiting to erupt, which never does. I had a faint touch of amusement, yet no part of the experience had the depth or richness of other compounds. No tremors. Slight visuals, but only when looked for. Hunger not present, but food tasted fine when eaten. Mildly pleasant but one would not take it again unless bored stiff."

EXTENSIONS AND COMMENTARY: This drug was the first definition of the term, Beth state.

There is something of the Fournier Transform in any and all drug experiments. A psychedelic drug experience is a complex combination of many signals going all at the same time. Something like the sound of an oboe playing the notes of the A-major scale. There are events that occur in sequence, such as the initial A, followed by B, followed by C-sharp and on and on. That is the chronology of the experience, and it can be written down as a series of perceived phenomena. The notes of the scale. Black quarter notes, with flags at the tops of their staffs, going up the page of music.

But within each of these single events, during the sounding of the note "A," for example, there is a complex combination of harmonics being produced at the same time, including all components from the fundamental oscillation on up through all harmonics into the inaudible. This mixture defines the played instrument as being an oboe. Each component may be shared by many instruments, but the particular combination is the unique signature of the oboe.

This analogy applies precisely to the study of psychedelic drugs and their actions. Each drug has a chronology of effect, like the notes of the A-major scale. But there are many components of a drug's action, like the harmonics from the fundamental to the inaudible which, taken in concert, defines the drug. With

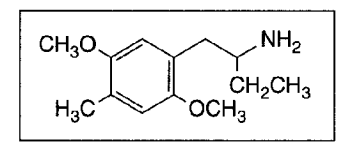
musical instruments, these components can be shown as sine waves on an oscilloscope. One component, 22%, was a sine wave at a frequency of 1205 cycles, and a phase angle of +55°. But in psychopharmacology? There is no psychic oscilloscope. There are no easily defined and measured harmonics or phase angles. Certainly, any eventual definition of a drug will require some such dissection into components each of which makes some contribution to the complex whole. The mental process may some day be defined by a particular combination of these components. And one of them is this Beth state. It is a state of uncaring, of anhedonia, and of emotionlessness.

Many drugs have a touch of this Beth state, ALEPH-7 more than most. If a sufficient alphabet of effects (I am using the Alephs, Beths, Gimels, and Daleths of the Hebrew as token starters only) were to be accumulated and defined, the actions of new materials might someday be more exactly documented. Could depression, euphoria, and disinhibition for example, all be eventually seen as being made up of their component parts, each contributing in some measured way to the sum, to the human experience? The psychologists of the world would be ecstatic. And drugs such as ALEPH-7 might be useful in helping to define one of these parts.

#8 ARIADNE; 4C-DOM; BL-3912; DIMOXAMINE; 1-(2,5-DIMETHOXY-4-METHYLPHENYL)-2-AMINOBUTANE; 2,5-DIMETHOXY-α-ETHYL-4-METHYLPHENETHYLAMINE

SYNTHESIS: In 50 mL of benzene there was dissolved 31.6 g 2,5-dimethoxy-4-methylbenzaldehyde (see recipe for 2C-D for its preparation), 20.2 mL 1-nitropropane, and 6 mL cyclohexylamine. This solution was held at reflux in a Dean Stark apparatus for 24 h, effectively removing the water of reaction. Upon cooling, there was deposited 19.6 g of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitro-1-butene as brilliant orange crystals. The mp, after recrystallization from MeOH, was 114-115 °C and a second recrystallization increased the mp another 2 °C. Anal. ($C_{13}H_{17}NO_4$) C,H,N.

A suspension of 12.5 g LAH in 600 mL anhydrous THF was stirred magnetically, and brought up to a reflux. To this there was added, dropwise, 15.0 g 1-(2,5-dimethoxy-4-methylphenyl)-2-nitro-1-butene dissolved in 150 mL THF. Refluxing was continued for 15 h and, after cooling, the excess hydride was decomposed by the addition of 12.5 mL H_2O. The inorganic salts were made loose and granular by the addition of 12.5 mL 15% NaOH followed by an additional 37.5 mL H_2O. These solids were removed by filtration, and the filter cake was washed with THF. The combined filtrate and washings were stripped of solvent under vacuum. The residue was dissolved in anhydrous Et_2O, and treated with hydrogen chloride gas, yielding 1-(2,5-dimethoxy-4-methylphenyl)-2-aminobutane



hydrochloride (ARIADNE) as white crystals which, after recrystallization from IPA, weighed 11.4 g and had a mp of 232.5-234.5 °C. Anal. ($C_{13}H_{22}ClNO_2$) C,H,N,Cl. The racemic mixture was resolved into its optical isomers by the formation of salts with (+)-2'-nitrotartranilic acid (to give the "S" isomer) or with (+)-2'-chlorotartranilic acid (to give the "R" isomer). The "R" isomer can also be prepared by the reductive amination of 1-(2,5-dimethoxy-4-methylphenyl)-2-butanone (from the above nitrostyrene and elemental iron) with (+)-α-methyl benzylamine followed by the hydrogenolysis of the benzyl group.

DOSAGE: as psychedelic, unknown.

DURATION: short.

QUALITATIVE COMMENTS: (with 12 mg) "I believe that my mood has distinctly improved, and my sleep that evening was excellent. This is physically benign."

(with 32 mg) "There was some sort of threshold that lasted for a couple of hours."

(with 25 mg of the "R" isomer) "There is the alert of a psychedelic, with none of the rest of the package. Perhaps a bit of paranoia. And by the fifth hour everything is largely gone."

EXTENSIONS AND COMMENTARY: How does one discover a new drug for a malady that does not exist in experimental animals? Drugs that interfere with sleep, or with appetite, or with some infecting bacterium, are naturals for animal screening, in that animals sleep, eat, and can be easily infected. But there are lots of syndromes that involve a state of mind, and these are uniquely human. Many of the psychopharmacological anti-this or anti-that agents address ailments such as anxiety, psychosis, paranoia, or depression, which are only known in man. So how does one discover a new drug in areas such as these? If one has in hand a drug that is known to be effective in one of these human ailments, an animal assay can be set up to give some measurable response to that specific drug, or a biochemical property can be rationalized as being related to a mechanism of action. And with the known drug as a calibration, and restricting your search to structurally related compounds, you can find structural relatives that give the same responses.

But how does one find a new class? One way is to kind of stumble into it as a side-line of human experimentation with new psychedelics. But it is really difficult to pick up the clues as to what will be a good anti-depressant if you are not depressed. This compound, to which I had given the name of ARIADNE as the first of my ten "classic ladies" (I'll say more about them later), was not really a stimulant of any kind, certainly it was not a psychedelic, and yet there was something there. It had been explored rather extensively as a potential psychotherapeutic ally by a friend of mine. He said that there seemed to be some value in a few of his patients

who had some underlying depression, but not much of anything with the others. So, I decided to call it an anti-depressant. I had mentioned some of this history one time when I was giving an address at a conference on the East Coast, and my host (who happened to be the research director at a large pharmaceutical house) asked if I would send him a sample. His company did many animal tests, one of which showed that it was not hallucinogenic (a cat whose tail erected dramatically with DOM did nothing with ARIADNE) and another that showed re-motivation (some old maze-running monkeys who had decided not to run any more mazes changed their minds with ARIADNE).

So patents were obtained for the "R" isomer, the more effective isomer, covering its use for such things as the restoring of motivation in senile geriatric patients. And a tradename of Dimoxamine was assigned it, despite several voices that held out for Ariadnamine. But it didn't have what was needed to make it all the way to the commercial market

Many, many analogues of ARIADNE have been made, and for a variety of reasons. In the industrial world there is research backup carried out, not only for the discovery of new things, but also for patent protection of old things. Several dozen analogues of ARIADNE have been made and pharmacologically evaluated, and some of them have been put into the published literature. The major points of variation have been two: keep the 4-position methyl group intact, and make the variations on the alpha-carbon (propyl, butyl, dimethyl, phenyl, benzyl, phenethyl, etc. — an extensive etc.) or: keep the alpha-position ethyl group intact and make the variations on the 4-position (chloro, iodo, methylthio, carboxy, etc. — again, an extensive etc.).

Some of these analogues I had made, and sent in for animal screening. The high potency of DOB suggested the bromo-counterpart of ARIADNE. The making of this entailed the proteo counterpart, 1-(2,5-dimethoxyphenyl)-2-aminobutane. Reaction of 2,5-dimethoxybenzaldehyde with nitropropane in benzene in a Dean Stark apparatus with cyclohexylamine as a catalyst produced 1-(2,5-dimethoxyphenyl)-2-nitrobutene, which crystallized as orange crystals from MeOH with a mp of 47-47.5 °C. Anal. ($C_{12}H_{15}NO_4$) C,H,N. This was reduced to the amine 1-(2,5-dimethoxyphenyl)-2-aminobutane with LAH in ether, and this gave a hydrochloride salt with a mp of 172-174 °C after recrystallization from acetonitrile. The free base of this compound was brominated in acetic acid to give 1-(2,5-dimethoxy-4-bromophenyl)-2-aminobutane which yielded a white hydrochloride salt with a mp of 204-206 °C following recrystallization from IPA. The isomeric non-brominated analogue, 1-(3,4-dimethoxyphenyl)-2-aminobutane was made and explored by the Chemical Warfare group at Edgewood Arsenal; its code number is EA-1322.

Several of the alpha-ethyl analogues of ARIADNE were N,N-dialkylated, and were target compounds for halogenation with radio-iodine or radio-fluorine, for evaluation as potential brain blood-flow indicators. In these studies. all examples followed a common flow diagram. The reaction of the appropriate benzaldehyde

and nitropropane, using N,N-dimethylethylenediamine as a catalyst and following recrystallization from MeOH, gave the corresponding 1-aromatic-2-nitro-1-butene (the nitrostyrene) which, by reduction with elemental iron, gave the corresponding 2-butanone (which was distilled at about 0.3 mm/Hg). This led, by reductive amination with dimethylamine hydrochloride and sodium cyanoborohydride, to the corresponding N,N-dimethyl product which was distilled at about 0.3 mm/Hg and which, in no case, either formed a solid HCl salt or reacted with carbon dioxide from the air. From 2,4-dimethoxybenzaldehyde, the nitrostyrene appeared as yellow crystals, the ketone as a white oil, and the product N,N-dimethyl-1-(2,4-dimethoxyphenyl)-2-aminobutane as a white oil. From 2,5-dimethoxybenzaldehyde, the nitrostyrene formed bright yellow crystal, the ketone was an off-white oil, and the product N,N-dimethyl-1-(2,5-dimethoxyphenyl)-2-aminobutane was a white oil. From 3,5-dimethoxybenzaldehyde, the nitrostyrene formed pale yellow crystals that discolored on exposure to the light, the ketone was an off-white clear oil, and the product N,N-dimethyl-1-(3,5-dimethoxyphenyl)-2-aminobutane was a white oil. From 2,6-dimethoxybenzaldehyde, the nitrostyrene was obtained as orange crystals, and was not pursued further.

A number of ARIADNE analogues have been made, or at least started, purely to serve as probes into whatever new areas of psychopharmacological activity might be uncovered. One of these is a HOT compound, and one is a TOM compound, and a couple of them are the pseudo (or near-pseudo) orientations. The HOT analogue was made from the nitrostyrene precursor to ARIADNE itself, reduced not with LAH or AH (which would give the primary amine), but rather with sodium borohydride and borane dimethylsulfide. The product, 1-(2,5-dimethoxy-4-methylphenyl)-N-hydroxy-2-aminobutane hydrochloride, was a white crystalline material. The 5-TOM analogue got as far as the nitrostyrene. This was made from 2-methoxy-4-methyl-5-(methylthio)benzaldehyde (see under the 5-TOM recipe for its preparation) and nitropropane in acetic acid, and gave bright yellow crystals. The true pseudo-analogue is the 2,4,6-trimethoxy material based on TMA-6, which is the "real" pseudo-TMA-2. The nitrostyrene from 2,4,6-trimethoxybenzaldehyde and nitropropane crystallized from MeOH/CH_3CN as fine yellow crystals, and this was reduced with AH in cold THF to 1-(2,4,6-trimethoxyphenyl)-2-aminobutane which was a bright, white powder.

And the near-pseudo analogue?

First, what is near-pseudo? I have explained already that the "normal" world of substitution patterns is the 2,4,5. Everyone knows that that is the most potent pattern. But, the 2,4,6 is in many ways equipotent, and has been named the pseudo-stuff. The "real," or "true" pseudo-stuff. So what is the "near" pseudo-stuff? I am willing to bet that the rather easily obtained 2,3,6-trisubstitution pattern, and the much more difficult to obtain 2,3,5-substitution pattern, will produce treasures every bit as unexpected and remarkable as either the 2,4,5- or the 2,4,6-counterparts. These are neither "real" nor "pseudo," but something else, and I will find a name for them when the time comes, something weird from the Greek

alphabet. And this will double again the range of possible exploration. The TMA-5 analogue mentioned came from 2,3,6-trimethoxybenzaldehyde and nitropropane using cyclohexylamine as a catalyst (yellow-orange solids) which was reduced to the amine with AH. This hydrochloride salt is an air-stable white powder. All of these materials remain unexplored.

Somewhere in the wealth of compounds implicit in the many structural variables possible (the normal versus the pseudo versus the near-pseudo patterns, coupled with the wide variety of promising substituents that can be placed on the 4-position, together with the availability of the the unexplored members of the Ten Classic Ladies harem), it would seem inescapable that interesting compounds will emerge.

Just what is this all about the ten "Classic Ladies?" In the chemical structure of DOM, there is a total of nineteen hydrogen atoms. Some of these are indistinguishable from others, such as the three hydrogen atoms on a methyl group. But there are exactly ten "types" of hydrogen atoms present. And, not having much, if any, intuition as to just why DOM was so powerful a psychedelic, I decided to systematically replace each of the ten unique hydrogens, one at a time of course, with a methyl group. And I planned to give the resulting materials the names of famous ladies, alphabetically, as you walk around the molecule.

ARIADNE was the first of these, the methyl for a hydrogen atom on the methyl group of the amphetamine chain. It was Ariadne who gave the long piece of thread to Theseus to guide him through the mazes of the Labyrinth so he could escape after killing the Minotaur. The record is fuzzy as to whether, after the successful killing, she went with him, or let him go on alone. A methyl group on the nitrogen atom produced BEATRICE. There is the legendary Beatrijs of the Dutch religious literature of the 14th century, and there is the Beatrice from *Beatrice and Benedict* (of Berlioz fame). But the one I had in mind was the lady from Florence whom Dante immortalized in the *Divina Commedia,* and she is entered under her own name in this footnote. Replacing the alpha-hydrogen of DOM with a methyl group would give the phentermine analogue which is named CHARMIAN. You may be thinking of Cleopatra's favorite attendant, but I was thinking of the sweet wife of a very dear friend of mine, a lady who has been in a state of gentle schizophrenia for some forty years now. The MDA analogue of CHARMIAN has been described in this foornote under the code name of MDPH. CHARMIAN, herself, has been synthesized and is of very much reduced potency in animals, as compared to DOM. It has not been tried in man as far as I know.

The two beta-hydrogen atoms of DOM are distinct in that, upon being replaced with methyl groups, one would produce a threo-isomer, and the other an erythro-isomer. I have named them DAPHNE (who escaped from Apollo by becoming a laurel tree which was, incidentally, named for her) and ELVIRA (who might not be too well known classically, but whose name has been attached to Mozart's 21st piano concerto as its slow movement was used as theme music for the movie *Elvira Madigan*). I don't know if either of this pair has been made—I started

and got as far as the cis-trans mixture of adducts between nitroethane and 2,5-dimethoxy-4-methylacetophenone. Whoever finally makes them gets to assign the names. I had made and tested the corresponding homologues of DMMDA that correspond to these two ladies.

And there are five positions (2,3,4,5 and 6) around the aromatic ring, each of which either carries a hydrogen atom or a methyl group that has a hydrogen atom. There is the 2-methoxy group which can become a 2-ethoxy group to produce a compound called FLORENCE. Her name is the English translation of the Italian Firenze, a city that, although having a female name, has always seemed thoroughly masculine to me. There is the 3-hydrogen atom which can become a 3-methyl group to produce a compound called GANESHA. This is a fine elephant-headed Indian God who is the symbol of worldly wisdom and also has been seen as the creator of obstacles. Here I really blew it; the Classic Lady turned out to be a Classic Gentleman; not even the name is feminine. There is the 4-methyl group which can become a 4-ethyl group to produce a compound called HECATE who presided over magic arts and spells. There is the 5-methoxy group which can become a 5-ethoxy group to produce a compound called IRIS, who is the Goddess of the rainbow. And there is the 6-hydrogen atom which can become a 6-methyl group to produce a compound called JUNO, who is pretty much a lady's lady, or should I say a woman's woman.

GANESHA, 2,5-dimethoxy-3,4-dimethylamphetamine has been made, and has proven to be an extraordinary starting point for a large series of potent phenethylamines and amphetamines which are described in this book. HECATE was given a synonym early in this process, and is now known as DOET (2,5-dimethoxy-4-ethylamphetamine). IRIS has also been entered under her name, and the other ethoxy homologue, FLORENCE, would be easily made based on the preparation of the phenethylamine analogue, 2CD-2ETO. Perhaps it has already been made somehow, somewhere, as I have noted that I have claimed its citrate salt as a new compound in a British patent. And, finally, JUNO (3,6-dimethoxy-2,4-dimethylamphetamine) has been made (from 2,5-dimethoxy-m-xylene, which was reacted with $POCl_3$ and N-methylformanilide to the benzaldehyde, mp 53-54 °C, and to the nitrostyrene with nitroethane, mp 73-74 °C from cyclohexane, and to the final amine hydrochloride with LAH in THF). Rather amazingly, I have had JUNO on the shelf for almost 14 years and have not yet gotten around to tasting it.

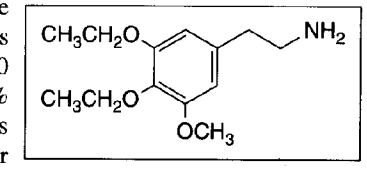
#9 ASB; ASYMBESCALINE; 3,4-DIETHOXY-5-METHOXY-PHENETHYLAMINE

SYNTHESIS: To a solution of 32 g of 5-bromobourbonal in 150 mL DMF there was added 31 g ethyl iodide and 32 g of finely ground 85% KOH pellets. There was the formation of a purple color and a heavy precipitate. On gradual heating to reflux, the color faded to a pale yellow and the precipitate dissolved over the course of 1

h. The heating was continued for an additional 1 h. The reaction mixture was added to 1 L H_2O, and extracted with 2x150 mL of petroleum ether. The extracts were pooled, washed with 2x200 mL 5% NaOH and finally with H_2O. After drying over anhydrous K_2CO_3 the solvents were removed under vacuum to yield 36 g of crude 3-bromo-4,5-diethoxybenzaldehyde as an amber liquid. This was used without purification for the following step. Distillation at 105-115 °C at 0.3 mm/Hg provided a white sample which did not crystallize. Anal. ($C_{11}H_{13}BrO_3$) C,H.

A mixture of 36 g 3-bromo-4,5-diethoxybenzaldehyde and 17 mL cyclohexylamine was heated with an open flame until it appeared to be free of H_2O. The residue was put under a vacuum (0.4 mm/Hg) and distilled at 135-145 °C, yielding 42 g 3-bromo-N-cyclohexyl-4,5-diethoxybenzylidenimine as a viscous light greenish oil. This slowly set to a crystalline glass with a mp of 60-61 °C. Recrystallization from hexane gave a white crystalline product without any improvement in the mp. Anal. ($C_{17}H_{24}BrNO_2$) C,H. This is a chemical intermediate to a number of active bases, taking advantage of the available bromine atom. This can be exchanged with a sulfur atom (leading to 5-TASB and 3-T-TRIS) or with an oxygen atom as described below.

A solution of 18 g 3-bromo-N-cyclohexyl-4,5-diethoxybenzylidenimine in 250 mL anhydrous Et_2O was placed in an atmosphere of He, stirred magnetically, and cooled with an external dry ice/acetone bath. Then 36 mL of a 1.5 M solution of butyllithium in hexane was added over 2 min, producing a clear yellow solution. This was stirred for 10 min. There was then added 30 mL of butyl borate at one time, the stirring continued for 5 min. The stirred solution was allowed to return to room temperature. There was added 150 mL of saturated aqueous ammonium sulfate. The Et_2O layer was separated, and the aqueous phase extracted with another 75 mL Et_2O. The combined organic phases were evaporated under vacuum. The residue was dissolved in 100 mL MeOH, diluted with 20 mL H_2O, and then treated with 15 mL 35% H_2O_2 added over the course of 2 min. This mildly exothermic reaction was allowed to stir for 15 min, then added to 500 mL H_2O. This was extracted with 2x100 mL CH_2Cl_2 and the solvent removed under vacuum. The residue was suspended in 150 mL dilute HCl and heated on the steam bath for 0.5 h. Stirring was continued until the reaction was again at room temperature, then it was extracted with 2x75 mL CH_2Cl_2. These extracts were pooled and extracted with 3x100 mL dilute aqueous KOH. The aqueous extracts were washed with CH_2Cl_2, reacidified with HCl, and reextracted with 2x75 mL CH_2Cl_2. These extracts were pooled, and the solvent removed under vacuum to yield a brown residue. This was distilled at 107-127 °C at 0.4 mm/Hg to yield 8.3 g of 3,4-diethoxy-5-hydroxybenzaldehyde as an oil that set to a tan solid. Recrystallization from cyclohexane gave a white product with a mp of 70.5-71.5 °C. Anal. ($C_{11}H_{14}O_4$) C,H.



A solution of 8.3 g of 3,4-diethoxy-5-hydroxybenzaldehyde and 3.0 g

KOH in 75 mL EtOH was treated with 5 mL methyl iodide and stirred at room temperature for 5 days. The reaction mixture was added to 400 mL H_2O and extracted with 2x50 mL CH_2Cl_2. The extracts were pooled, washed with 2x150 mL dilute NaOH, and the solvent removed under vacuum. The residual oil was distilled at 95-110 °C at 0.3 mm/Hg to yield 8.2 g of 3,4-diethoxy-5-methoxybenzaldehyde as a pale yellow liquid. This product was a crystalline solid below 20 °C but melted upon coming to room temperature. It was analyzed, and used in further reactions as an oil. Anal. ($C_{12}H_{16}O_4$) C,H.

To a solution of 6.4 g 3,4-diethoxy-5-methoxybenzaldehyde in 40 mL nitromethane there was added about 0.5 g anhydrous ammonium acetate, and this was held at reflux for 1 h. The excess solvent/reagent was removed under vacuum, producing a red oil which set up to crystals. These were recrystallized from 40 mL boiling MeOH to yield 3.0 g of 3,4-diethoxy-5-methoxy-ß-nitrostyrene as yellow plates, with a mp of 89-90 °C. Anal. ($C_{13}H_{17}NO_5$) C,H.

A solution of 3.0 g LAH in 150 mL anhydrous THF under He was cooled to 0 °C and vigorously stirred. There was added, dropwise, 2.1 mL of 100% H_2SO_4, followed by the dropwise addition of a solution of 3.5 g 3,4-diethoxy-5-methoxy-ß-nitrostyrene in 30 mL anhydrous THF, over the course of 10 min. The addition was exothermic. The mixture was held at reflux on the steam bath for 30 min. After cooling again, the excess hydride was destroyed with IPA, followed by the addition of 10% NaOH sufficient to covert the aluminum oxide to a white, granular form. This was removed by filtration, the filter cake washed with IPA, the mother liquor and filtrates combined, and the solvents removed under vacuum to provide a yellow oil. This residue was added to 100 mL dilute H_2SO_4 producing a cloudy suspension and some yellow insoluble gum. This was washed with 2x75 mL CH_2Cl_2. The aqueous phase was made basic with 25% NaOH, and extracted with 2x75 mL CH_2Cl_2. The solvent was removed from these pooled extracts and the residue distilled at 110-135 °C at 0.4 mm/Hg to provide 2.0 g of a colorless liquid. This was dissolved in 7 mL IPA, neutralized with about 40 drops of concentrated HCl, followed by 50 mL anhydrous Et_2O with stirring. The initially clear solution spontaneously deposited a white crystalline solid. This was diluted with an additional 30 mL Et_2O, let stand for 1 h, and the solids removed by filtration. After Et_2O washing, the product was air-dried to yield 1.25 g of 3,4-diethoxy-5-methoxyphenethylamine hydrochloride (ASB) with a mp of 142-143 °C. Anal. ($C_{13}H_{22}ClNO_3$) C,H.

DOSAGE: 200 - 280 mg.

DURATION: 10 - 15 h.

QUALITATIVE COMMENTS: (with 240 mg) "There was a pleasant and easy flow of day-dreaming thoughts, quite friendly and somewhat erotic. There was a gentle down-drift to my starting baseline mental status by about midnight (I started at 9:00 AM). I never quite made it to a +++, and rather regretted it."

(with 280 mg) "The plateau of effect was evident by hour two, but I found the experience lacking the visual and interpretive richness that I had hoped for. Sleep was very fitful after the effects had largely dropped — it was hard to simply lie back and relax my guard — and even while being up and about the next day I felt a residual plus one. Over all, there were few if any of the open interactions of 2C-B or LSD. Some negative side seemed to be present."

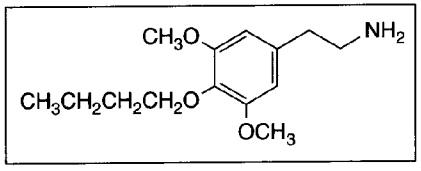
(with 280 mg) "The entire session was, in a sort of way, like being in a corridor outside the lighted halls where a beautiful mescaline experience is taking place, sensing the light from behind a grey door, and not being able to find my way in from the dusky underside passageways. This is sort of a gentle sister of mescaline, but with a tendency to emphasize (for me, at this time) the negative, the sad, the struggling. Sleep was impossible before the fifteenth hour. When I tried, I got visions of moonlight in the desert, with figures around me which were the vampire-werewolf aspect of the soul, green colored and evil. I had to sit quietly in the living room and wait patiently until they settled back to wherever they belonged and stopped trying to take over the scene. During the peak of the experience, my pulse was thready, somewhat slowed, and uneven. There was a faint feeling of physical weirdness."

EXTENSIONS AND COMMENTARY: This specific amine was a target for a single study in cats many years ago, in Holland, using material obtained from Hoffman La Roche in Basel. Their findings are hard to evaluate, in that 200 milligrams was injected into a 3.75 kilogram cat (53 mg/Kg), or about twice the dosage that they used in their studies with metaescaline. Within 5 minutes there were indications of catatonia, and within a half hour the animal was unable to walk. This condition persisted for two days, at which time the animal died. Although this dose was many times that used in man, perhaps hints of the physical unease and long action are there to be gleaned. The consensus from over a half dozen experiments is that there is not enough value to be had to offset the body load experienced.

A comment is needed on the strange name asymbescaline! In the marvelous world of chemical nomenclature, bi- (or di-) usually means two of something, and tri- and tetra- quite reasonably mean three and four of something. But occasionally there can be an ambiguity with bi (or tri or tetra) in that bi something-or-other might be two something-or-others hooked together or it might be two things hooked onto a something-or-other. So, the former is called bi- and the latter is called bis-. This compound is not two escalines hooked together (bi-escaline) but is only one of them with two ethyl groups attached (bis-escaline or bescaline). And since there are two ways that this can be done (either symmetrically or asymmetrically) the symmetric one is called symbescaline (or SB for short) and this one is called asymbescaline (or ASB for short). To complete the terminology lecture, the term tri- becomes tris- (the name given for the drug with all three ethoxy groups present in place of the methoxys of mescaline) and the term tetra- mutates into the rather incredible tetrakis-!

#10 B; BUSCALINE; 4-(n)-BUTOXY-3,5-DIMETHOXY-PHENETHYLAMINE

SYNTHESIS: A solution of 5.8 g of homosyringonitrile (see under E for preparation), 100 mg decyltriethylammonium iodide, and 11 g n-butyl bromide in 50 mL anhydrous acetone was treated with 6.9 g finely powdered anhydrous K_2CO_3 and held at reflux for 10 h. An additional 6 g of n-butyl bromide was added to the mixture, and the refluxing continued for another 48 h. The mixture was filtered, the solids washed with acetone, and the solvent from the combined filtrate and washes removed under vacuum. The residue was suspended in acidified H_2O, and extracted with 3x175 mL CH_2Cl_2. The pooled extracts were washed with 2x50 mL 5% NaOH, once with dilute HCl, and then stripped of solvent under vacuum giving 13.2 g of a deep yellow oil. This was distilled at 132-145 °C at 0.2 mm/Hg to yield 5.0 g of 4-(n)-butyloxy-3,5-dimethoxyphenylacetonitrile as a pale yellow oil which set up to crystals spontaneously. The mp was 42-43 °C. Anal. ($C_{14}H_{19}NO_3$) C H N.



A solution of AH was prepared by the cautious addition of 0.67 mL of 100% H_2SO_4 to 25 mL of 1.0 M LAH in THF, which was being vigorously stirred under He at ice bath temperature. A total of 4.9 g of 4-(n)-butyloxy-3,5-dimethoxyphenylacetonitrile was added as a solid over the course of 10 min. Stirring was continued for another 5 min, then the reaction mixture was brought to reflux on the steam bath for another 45 min. After cooling again to room temperature, IPA was added to destroy the excess hydride (about 5 mL) followed by 10 mL of 15% NaOH which was sufficient to make the aluminum salts loose, white, and filterable. The reaction mixture was filtered, the filter cake washed with IPA, and the mother liquor and washes combined and the solvent removed under vacuum to yield an amber oil. This residue was treated with dilute H_2SO_4 which generated copious solids. Heating this suspension effected solution, and after cooling, all was washed with 3x50 mL CH_2Cl_2. The aqueous phase was made basic with aqueous NaOH, and the product extracted with 2x100 mL CH_2Cl_2. The extracts were evaporated to a residue under vacuum, and this was distilled at 128-138 °C at 0.5 mm/Hg yielding 3.8 g of a colorless oil. This was dissolved in 40 mL IPA, neutralized with concentrated HCl (about 55 drops required) and, with vigorous stirring, 80 mL of anhydrous Et_2O was added which produced fine white plates. After standing for several h, the product was filtered, washed with 20% IPA in Et_2O, and finally with Et_2O. Air drying yielded 3.9 g of 4-(n)-butyloxy-3,5-dimethoxyphenethylamine hydrochloride (B) with a mp of 152-153 °C. An analytical sample melted at 155-157 °C. Anal. ($C_{14}H_{24}ClNO_3$) C,H,N.

DOSAGE: greater than 150 mg.

DURATION: several hours.

QUALITATIVE COMMENTS: (with 120 mg) "There is a strange taste, not really bitter, it does not linger. The slight change of baseline has certainly disappeared by the eighth hour. No noticeable changes in either the visual or the auditory area.

(with 150 mg) "Throughout the experiment it was my impression that whatever effects were being felt, they were more in body than mind. The body load never mellowed out, as it would have with mescaline, after the first hour or two. Mental effects didn't develop in any interesting way. I was aware of brief heart arrhythmia. Tummy was uncomfortable, off and on, and there was light diarrhea. Even as late as the fifth hour, my feet were cold, and the whole thing left me with a slightly uncomfortable, 'Why did I bother?' feeling."

EXTENSIONS AND COMMENTARY: There is a jingle heard occasionally in chemical circles, concerning the homologues of methyl. It goes, "There's ethyl and propyl, but butyl is futile." And to a large measure this is true with the 4-position homologues of mescaline. This butyl compound, B or Buscaline, had originally been patented in England in 1930 without any physical or pharmacological description, and the few physical studies that had involved it (lipophilic this and serotonin that) suggested that it was less active than mescaline.

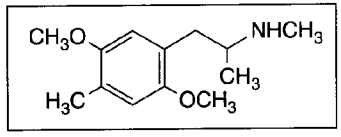
In principle, the 5-, the 6-, the 7- and the on-up homologues might be called amylescaline (possibly pentescaline?), hexescaline, heptescaline (possibly septescaline), and God-knows-what-scaline. They would certainly be easily makeable, but there would be little value that could be anticipated from nibbling them. In keeping with the name B (for butoxy), these would be known as A (for amyloxy, as the use of a P could confuse pentoxy with propoxy), as H (for hexyloxy, but careful; this letter has been used occasionally for DMPEA, which is Homopiperonylamine), and as S (the H for heptyloxy has been consumed by the hexyloxy, so let's shift from the Greek *hepta* to the Latin *septum* for the number seven). It seems most likely that the toxic symptoms that might well come along with these phenethylamines would discourage the use of the dosage needed to affect the higher centers of the brain. The same generally negative feeling applies to the amphetamine counterparts 3C-B, 3C-A, 3C-H and 3C-S.

A brief reiteration of the 2C-3C nomenclature, to avoid a possible misunderstanding. The drug 2C-B is so named in that it is the two-carbon chain analogue of the three-carbon chain compound DOB. The drug 3C-B is so named because it is the three-carbon chain analogue of the two-carbon chain compound Buscaline, or more simply, B. There is no logical connection whatsoever, either structural or pharmacological, between 2C-B and 3C-B.

#11 BEATRICE; N-METHYL-DOM; 2,5-DIMETHOXY-4,N-DIMETHYLAMPHETAMINE

SYNTHESIS: A fused sample of 5.0 g of white, crystalline free base 2,5-dimethoxy-4-methylamphetamine, DOM, was treated with 10 mL ethyl formate, and held at reflux on the steam bath for several h. Removal of the solvent gave 5.5 g of a white solid, which could be recrystallized from 15 mL MeOH to give 3.8 g of fine white crystals of 2,5-dimethoxy-N-formyl-4-methylamphetamine. An analytical sample from ethyl formate gave granular white crystals.

To a stirred suspension of 4.0 g LAH in 250 mL anhydrous Et_2O at reflux and under an inert atmosphere, there was added, by the shunted Soxhlet technique, 4.2 g of 2,5-dimethoxy-N-formyl-4-methylamphetamine as rapidly as its solubility in hot Et_2O would allow. The mixture was held at reflux for 24 h and then stirred at room temperature for several additional days. The excess hydride was destroyed with the addition of dilute H_2SO_4 (20 g in 500 mL water) followed by the additional dilute H_2SO_4 needed to effect a clear solution. The Et_2O was separated, and the aqueous phase extracted with 100 mL Et_2O and then with 2x250 mL CH_2Cl_2. Following the addition of 100 g potassium sodium tartrate, the mixture was made basic with 25% NaOH. The clear aqueous phase was extracted with 3x250 mL CH_2Cl_2 These extracts were pooled, and the solvent removed under vacuum. The residual amber oil was dissolved in 400 mL anhydrous Et_2O, and saturated with hydrogen chloride gas. The white crystals that formed were removed by filtration, washed with Et_2O, and air dried to constant weight. There was obtained 4.2 g of product with a mp of 131.5-133.5 °C. This product was recrystallized from 175 mL boiling ethyl acetate to give 3.5 g 2,5-dimethoxy-4,N-dimethylamphetamine hydrochloride (BEATRICE) as pale pink crystals with a mp of 136-137 °C. A sample obtained from a preparation that employed the methyl sulfate methylation of the benzaldehyde adduct of DOM had a mp of 125-126 °C and presented a different infra-red spectrum. It was, following recrystallization from ethyl acetate, identical to the higher melting form in all respects.



DOSAGE: above 30 mg.

DURATION: 6 - 10 h.

QUALITATIVE COMMENTS: (with 20 mg) "There was a gentle and demanding rise from the one to the three hour point that put me into an extremely open, erotic, and responsive place. I had to find a familiar spot to orient myself, and the kitchen served that need. As the experience went on, it showed more and more of a stimulant response, with tremor, restlessness, and a bit of trouble sleeping. But there was no anorexia! An OK experience."

(with 30 mg) "There is a real physical aspect to this, and I am not completely happy with it. There is diarrhea, and I am restless, and continuously aware of the fact that my body has had an impact from something. The last few hours were spent in talking, and I found myself still awake some 24 hours after the start of the experiment. The mental was not up there to a +++, and yet the physical disruption was all that I might care to weather, and exceeds any mental reward. When I did sleep, my dreams were OK, but not rich. Why go higher?"

EXTENSIONS AND COMMENTARY: This is another example of the N-methyl homologues of the psychedelics. None of them seem to produce stuff of elegance. It is clear that the adding of an N-methyl group onto DOM certainly cuts down the activity by a factor of ten-fold, and even then results in something that is not completely good. Three milligrams of DOM is a winner, but even ten times this, thirty milligrams of N-methyl-DOM, is somewhat fuzzy. In the rabbit hyperthermia studies, this compound was some 25 times less active than DOM, so even animal tests say this is way down there in value. This particular measure suggests that the active level in man might be 75 milligrams. Well, maybe, but I am not at all comfortable in trying it at that level. In fact I do not intend to explore this any further whatsoever, unless there is a compelling reason, and I see no such reason. For the moment, let us leave this one to others, who might be more adventurous but less discriminating.

In browsing through my notes I discovered that I had made another N-substitution product of DOM. Efforts to fuse free-base DOM with the ethyl cyclopropane carboxylate failed, but the reaction between it and the acid chloride in pyridine gave the corresponding amide, with a mp of 156-157 °C from MeOH. Anal. ($C_{16}H_{23}NO_3$) C,H,N. This reduced smoothly to the corresponding amine, N-cyclopropyl-2,5-dimethoxy-4-methylamphetamine which formed a hydrochloride salt melting at 153-156 °C. I can't remember the reasoning that led to this line of synthesis, but it must not have been too exciting, as I never tasted the stuff.

#12 BIS-TOM; 4-METHYL-2,5-bis-(METHYLTHIO)-AMPHETAMINE

SYNTHESIS: A solution of 9.0 g 2,5-dibromotoluene in 50 mL petroleum ether was magnetically stirred under a He atmosphere. To this there was added 50 mL of a 1.6 M hexane solution of butyllithium, and the exothermic reaction, which produced a granular precipitate, was allowed to stir for 12 h. The mixture was cooled to 0 °C and there was then added 7.5 g dimethyldisulfide. There was a heavy precipitate formed, which tended to become lighter as the addition of the disulfide neared completion. After 20 min additional stirring, the reaction mixture was poured into H_2O that contained some HCl. The phases were separated and the

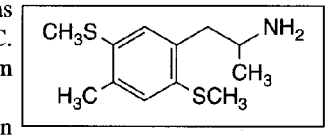
aqueous phase extracted with 50 mL Et_2O. The organic phase and extract were combined, washed with dilute NaOH, and then with H_2O. After drying over anhydrous K_2CO_3, the solvent was removed under vacuum and the residue distilled to give a fraction that boiled at 75-85 °C at 0.3 mm/Hg and weighed 5.3 g. This was about 80% pure 2,5-bis-(methylthio)toluene, with the remainder appearing to be the monothiomethyl analogues. A completely pure product was best obtained by a different, but considerably longer, procedure. This is given here only in outline. The phenolic OH group of 3-methyl-4-(methylthio)phenol was converted to an SH group by the thermal rearrangement of the N,N-dimethylthioncarbamate. The impure thiophenol was liberated from the product N,N-dimethylthiolcarbamate with NaOH treatment. The separation of the phenol/thiophenol mixture was achieved by a H_2O_2 oxidation to produce the intermediate 3-methyl-4-methylthiophenyldisulfide. This was isolated as a white crystalline solid from MeOH, with a mp of 78-79 °C. Anal. ($C_{16}H_{18}S_4$) C,H. It was reduced with zinc in acetic acid, and the resulting thiophenol (a water-white liquid which was both spectroscopically and microanalytically correct) was methylated with methyl iodide and KOH in MeOH to give the desired product, 2,5-bis-(methylthio)toluene, free of any contaminating mono-sulfur analogues.

A solution of 3.9 g of 2,5-bis-(methylthio)toluene in 20 mL acetic acid was treated with a crystal of iodine followed by the addition of 3.5 g elemental bromine. This mixture was heated on the steam bath for 1 h, which largely discharged the color and produced a copious evolution of HBr. Cooling in an ice bath produced solids that were removed by filtration. Recrystallization from IPA gave 1.9 g of 2,5-bis-(methylthio)-4-bromotoluene as a white crystalline solid with a mp of 133-134 °C. Anal. ($C_9H_{11}BrS_2$) C,H. An alternate synthesis of this intermediate was achieved from 1,4-dibromobenzene which was converted to the 1,4-bis-(methylthio)benzene (white crystals with a mp of 83.5-84.5 °C) with sodium methylmercaptide in hexamethylphosphoramide. This was dibrominated to 2,5-dibromo-1,4-bis-(methylthio)benzene in acetic acid (white platelets from hexane melting at 195-199 °C). This, in Et_2O solution, reacted with BuLi to replace one of the bromine atoms with lithium, and subsequent treatment with methyl iodide gave 2,5-bis-(methylthio)-4-bromotoluene as an off-white solid identical to the above material (by TLC and IR) but with a broader mp range.

A solution of 2.4 g 2,5-bis-(methylthio)-4-bromotoluene in 100 mL anhydrous Et_2O, stirred magnetically and under a He atmosphere, was treated with 10 mL of a 1.6 M solution of butyllithium in hexane. After stirring for 10 min there was added 2.5 mL N-methylformanilide which led to an exothermic reaction. After another 10 min stirring, the reaction mixture was added to 100 mL dilute HCl, the phases were separated, and the aqueous phase extracted with 2x50 mL Et_2O. The combined organic phase and extracts were dried over anhydrous K_2CO_3, and the solvent removed under vacuum. The partially solid residue was distilled at 140-150 °C at 0.2 mm/Hg to give a crystalline fraction that, after recrystallization from 15 mL boiling IPA gave 2,5-bis-(methylthio)-4-methylbenzaldehyde as a yellow-

brown solid which weighed 1.1 g and had a mp of 107-109 °C. An analytical sample from MeOH melted at 110-111 °C with an excellent IR and NMR. Anal. ($C_{10}H_{12}OS_2$) C,H. An alternate synthesis of this aldehyde employs the 2,5-bis-(methylthio)toluene described above. A CH_2Cl_2 solution of this substituted toluene containing dichloromethyl methyl ether was treated with anhydrous $AlCl_3$, and the usual workup gave a distilled fraction that spontaneously crystallized to the desired aldehyde but in an overall yield of only 11% of theory.

To a solution of 0.5 g 2,5-bis-(methylthio)-4-methylbenzaldehyde in 15 mL nitroethane there was added 0.15 g anhydrous ammonium acetate and the mixture was heated on the steam bath for 1 h. The excess solvent was removed under vacuum and the residue was dissolved in 10 mL boiling MeOH. This solution was decanted from a little insoluble residue, and allowed to cool to ice bath temperature yielding, after filtering and drying to constant weight, 0.55 g of 1-[2,5-bis-(thiomethyl)-4-methylphenyl]-2-nitropropene as pumpkin-colored crystals with a mp of 90-91 °C. This was not improved by recrystallization from EtOH. Anal. ($C_{12}H_{15}NO_2S_2$) C,H.



A cooled, stirred solution of 0.5 g LAH in 40 mL THF was put under an inert atmosphere, cooled to 0 °C with an external ice bath, and treated with 0.42 mL 100% H_2SO_4, added dropwise. A solution of 0.5 g 1-[2,5-bis-(thiomethyl)-4-methylphenyl]-2-nitropropene in 20 mL anhydrous THF was added over the course of 5 min, and the reaction mixture held at reflux for 30 min on the steam bath. After cooling again to ice temperature, the excess hydride was destroyed by the addition of IPA and the inorganics were converted to a loose, white filterable form by the addition of 1.5 mL 5% NaOH. These solids were removed by filtration and the filter cake was washed with 2x50 mL IPA. The combined filtrate and washings were stripped of solvent under vacuum to give a residue that was a flocculant solid. This was suspended in dilute H_2SO_4 and extracted with 2x50 mL CH_2Cl_2, and the combined organics extracted with 2x50 mL dilute H_3PO_4. The aqueous extracts were made basic, and the product removed by extraction with 2x75 mL CH_2Cl_2. After removal of the solvent under vacuum, the residue was distilled at 126-142 °C at 0.2 mm/Hg to give 0.2 g of product which crystallized in the receiver. This was dissolved in 1.5 mL hot IPA, neutralized with 4 drops of concentrated HCl, and diluted with 3 mL anhydrous Et_2O to give, after filtering and air drying, 0.2 g. of 2,5-bis-(methylthio)-4-methylamphetamine hydrochloride (BIS-TOM) as white crystals with a mp of 228-229 °C. Anal. ($C_{12}H_{20}ClNS_2$) C,H.

DOSAGE: greater than 160 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 160 mg) "I was vaguely aware of something

in the latter part of the afternoon. A suggestion of darting, physically (when going to sleep), but nothing at the mental level. This is as high as I will go."

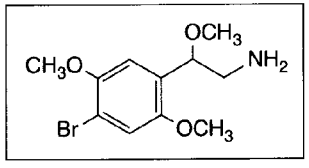
EXTENSIONS AND COMMENTARY: It is reasonable, in retrospect, to accept that BIS-TOM is not an active compound. The replacement of the 2-position oxygen of DOM with a sulfur atom (to give 2-TOM) dropped the potency by a factor of 15x, and the replacement of the 5-position oxygen with a sulfur atom (to give 5-TOM) dropped the potency by a factor of about 10x. It would be a logical calculation that the replacement of both oxygen atoms with sulfur might drop the potency by a factor of 150x. So, with DOM being active at maybe 5 milligrams, a logical prediction of the active level of BIS-TOM would be 750 milligrams. And maybe this would be the right level, but with the hints of neurological disturbance that seemed to be there at 160 mg, there was no desire to go up by a factor of five again. The rewards would simply not be worth the risks.

The 2-carbon analogue, 2C-BIS-TOM, was prepared from the intermediate aldehyde above, first by reaction with nitromethane to give the nitrostyrene as tomato-colored crystals from EtOAc, mp 145-146 °C. Anal. ($C_{11}H_{13}NO_2S_2$) C,H. This was reduced with AH to give 2,5-bis-(methylthio)-4-methylphenethylamine hydrochloride as ivory-colored crystals with a mp of 273-277 °C.

Although there are many interesting psychedelic drugs with sulfur atoms in them (the TOM's, the TOET's, the ALEPH's and all of the 2C-T's), there just aren't many that contain two sulfur atoms. BIS-TOM bombed out, and 2C-BIS-TOM remains untried, but will probably also fail, as the phenethylamines are rarely more potent than the corresponding amphetamines. This leaves 2C-T-14 as the remaining hope, and its synthesis is still underway.

#13 BOB; ß-METHOXY-2C-B; 4-BROMO-2,5-ß-TRIMETHOXY-PHENETHYLAMINE

SYNTHESIS: To a vigorously stirred suspension of 2.1 g 4-bromo-2,5-dimethoxy-ß-nitrostyrene [from 4-bromo-2,5-dimethoxybenzaldehyde and nitromethane in acetic acid with ammonium acetate as a catalyst, mp 157-158 °C, anal. ($C_{10}H_{10}BrNO_4$) C,H] in 20 mL anhydrous MeOH, there was added a solution of sodium methoxide in MeOH (generated from 0.5 g metallic sodium in 20 mL anhydrous MeOH). After a few min there was added 10 mL acetic acid (no solids formed) followed by the slow addition of 50 mL of H_2O. A cream-colored solid was produced, which was removed by filtration and washed well with H_2O. After air drying the product, 1-(4-bromo-2,5-dimethoxyphenyl)-1-methoxy-2-nitroethane, weighed 2.0 g. An analytical sample from MeOH was off-white in



color and had a mp of 119-120 °C. Anal. ($C_{11}H_{14}BrNO_5$) C,H.

A solution of LAH (15 mL of 1 M solution in THF) was diluted with an equal volume of anhydrous THF, and cooled (under He) to 0 °C with an external ice bath. With good stirring there was added 0.38 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 1.0 g 1-(4-bromo-2,5-dimethoxyphenyl)-1-methoxy-2-nitroethane as a solid over the course of 5 min. After an hour of stirring at 0 °C, the temperature was brought up to a gentle reflux on the steam bath for 30 min. There was no vigorous exothermic reaction seen, unlike that with the syntheses of BOD, BOH and BOM. The reaction mixture was cooled again to 0 °C, and the excess hydride was destroyed by the cautious addition of IPA. This was followed by sufficent dilute aqueous NaOH to give a white granular character to the oxides, and to assure that the reaction mixture was basic. The reaction mixture was filtered, and the filter cake washed first with THF followed by IPA. The combined filtrate and washings were stripped of solvent under vacuum and dissolved in dilute H_2SO_4, with the apparent generation of yellow solids. This was washed with 2x50 mL CH_2Cl_2, and the aqueous phase made basic with NaOH. This was extracted with 2x50 mL CH_2Cl_2, and the pooled extracts were stripped of solvent under vacuum. The residue was distilled at 130-150 °C at 0.2 mm/Hg to give 0.2 g of product as a clear white oil. This fraction was dissolved in 10 mL IPA, and neutralized with 4 drops concentrated HCl. The addition of 30 mL anhydrous Et_2O allowed the formation of 4-bromo-2,5,ß-trimethoxyphenethylamine hydrochloride (BOB) as a fine white crystalline product. This was removed by filtration, washed with Et_2O, and air dried. There was obtained 0.1 g white crystals with a mp of 187-188 °C. Anal. ($C_{11}H_{17}BrClNO_3$) C,H.

DOSAGE: 10 - 20 mg.

DURATION: 10 - 20 h.

QUALITATIVE COMMENTS: (with 10 mg) "I don't know if it was me this day, or if it was the chemical, but I got into a granddaddy of a paranoid, sociopathic snit, without feeling and without emotion. I was indifferent to everything. Later on, there was some improvement, with body tingling (good, I'm pretty sure) and a sense of awareness (good, I guess) but I still canceled my evening dinner company. All in all, pretty negative."

(with 10 mg) "I had to get away and into myself, so I weeded in the vegetable garden for almost an hour. Then I lay down in the bedroom, and enjoyed a magnificent vegetable garden, in Southern France, in my mind's eye. An extraordinary zucchini. And the weeds had all been magically pulled. In another couple of hours a neurological over-stimulation became apparent, and I spent the rest of the day defending myself. In the evening, I took 100 milligrams phenobarbital which seemed to smooth things just enough. Too bad. Nice material, otherwise."

(with 15 mg) "The erotic was lustful, but at the critical moment of orgasm,

the question of neurological stability became quite apparent. Does one really let go? Everything seemed a bit irritable. The tinnitus was quite bad, but the excitement of the rich altered place I was in was certainly worth it all. Through the rest of the day, I became aware of how tired I was, and how much I wanted to sleep, and yet how scared I was to give myself over to sleep. Could I trust the body to its own devices without me as an overseeing caretaker? Let's risk it. I slept. The next day there was a memory of this turmoil. Clearly the first part of the experience might have been hard to define, but it was quite positive. But the last part makes it not really worth while."

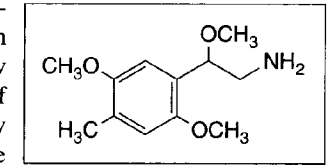
EXTENSIONS AND COMMENTARY: This compound, BOB, is the most potent of the BOX series. And yet, as with all of the members of this family, there are overtones of physical concern, and of some worry as to the integrity of the body. There may well be a separation of activity with the two optical isomers, but there is not a tremendous push to explore this particular family much further. They can't all be winners, I guess. What would be the activities of compounds with a sulfur instead of an oxygen at the beta-oxygen position? What would be the nature of action if there were an alpha-methyl group, making all of these into amphetamine derivatives? Or what about both a sulfur and a methyl group? And what about the isomers that are intrinsic to all of this, the threo- and the erythro- and the "D's" and the "L's"? All this is *terra incognita*, and must someday be looked into. It is chemically simple, and pharmacologically provocative. Someone, somewhere, someday, answer these questions!

#14 BOD; ß-METHOXY-2C-D; 4-METHYL-2,5,ß-TRIMETHOXYPHENETHYLAMINE

SYNTHESIS: A solution of 39.6 g 1-(2,5-dimethoxy-4-methylphenyl)-2-nitrostyrene (see recipe for 2C-D for its preparation) in 300 mL warm MeOH was prepared. Separately, a solution of 9 g elemental sodium in 150 mL MeOH was also prepared. This sodium methoxide solution was added to the well-stirred nitrostyrene solution, which resulted in a dramatic loss of color. There was then added 75 mL acetic acid, and all was poured into 2 L H_2O. This was extracted with 3x100 mL CH_2Cl_2. The pooled extracts were stripped of solvent, and the 35 g of residue was treated with 5 mL MeOH, allowed to stand for a short while, decanted from some insoluble residue, and the separated clear solution kept at 0 °C overnight. There was the deposition of a yellow crystalline product which, after removal by filtration and air drying, weighed 9.7 g. Recrystallization from 25 mL MeOH gave, after filtering and drying, 8.4 g of canary-yellow crystals of 1-(2,5-dimethoxy-4-methylphenyl)-1-methoxy-2-nitroethane with a mp of 78-79 °C. Evaporation of the mother liquors from the filtration of the first crop yielded 3.8 g of additional product which, upon

recrystallization from 11 mL MeOH, provided another 2.7 g with a mp of 77-78 °C. Further workup of the mother liquors yielded only impure starting nitrostyrene.

A solution of LAH (96 mL of 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 2.4 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 10.8 g 1-(2,5-dimethoxy-4-methylphenyl)-1-methoxy-2-nitroethane. There was immediate discoloration. After the addition was complete, the reaction mixture was held at reflux on the steam bath for 2 h. After cooling again, the excess hydride was destroyed with 4 mL IPA and the reaction mixture made basic with 15% NaOH. The insoluble inorganic salts were removed by filtration, and the filter cake was washed first with THF, and then with IPA. The bright yellow filtrate and washes were pooled and stripped of solvent under vacuum, yielding 14 g of a yellow oil. This was suspended in 1 L dilute H_2SO_4 to give an ugly, cloudy, yellow-orange mess. Extraction with 3x75 mL CH_2Cl_2 removed much of the color, and the remaining aqueous phase was made basic with 25% NaOH, and extracted with 3x75 mL CH_2Cl_2. Evaporation of the solvent under vacuum gave 9 g of a pale amber oil which was distilled at 115-130 °C at 0.4 mm/Hg. The water-white distillate was dissolved in 15 mL IPA, neutralized with concentrated HCl, and then diluted with 70 mL anhydrous Et_2O. After a few min, white crystals formed, and these were removed by filtration and Et_2O washed. When air-dried to constant weight, 4.49 g brilliant white crystals of 4-methyl-2,5,ß-trimethoxyphenethylamine hydrochloride (BOD) with a mp of 171-172 °C with decomposition, were obtained. The mother liquors on standing deposited 0.66 g additional crystals which were impure and were discarded. Anal. ($C_{12}H_{20}ClNO_3$) C,H.



DOSAGE: 15 - 25 mg.

DURATION: 8 - 16 h.

QUALITATIVE COMMENTS: (with 20 mg) "There were some very pleasant visuals starting at 2-2.5 hours and continuing to 4-5 hours after the beginning of the experiment. Open eye visuals seem to come on after staring at particular areas, such as the living room ceiling or at trees. The surroundings tended to move slightly. There was no flowing of the images at all. When looking at the pine trees, the needles appeared crystal clear and sharply defined, with strong contrasts. Though the mental effect is difficult to define, I am not sure it was all that great. I did become tired of the effect (along with the confusion) after 8 hours, and was quite happy to note that it did taper off in the early evening. I am not particularly sure I would want to try this material again."

(with 20 mg) "For the first three or so hours, the beauty of the experience was marred by a strange discomfort. There was some queasiness, and I felt a

sluggishness of mind. Then I began moving in and out of a pleasant place, and finally the discomfort completely dissolved and the experience turned full on. Height of beauty, visual perception. Lights below are amazing. Outside, marvelous sense of Presence. There is not an elation, as often with other materials, but a strong, even powerful sense of goodness, inner strength, solidity."

(with 25 mg) "This was quite quick. The onset of the experience was apparent within a half hour, and we were both at +++ within the hour. Body load minimal. There was very little visual, compared with some materials. Very interesting eyes-closed, but not continually — just now and then an intense vision might flash. Very benign and friendly and pleasant and good-humored feeling. Superb for conversation and conceptualization."

(with 25 mg) "The body load was quite noticeable for everyone. But the general state of mind was excellent; everyone was extremely relaxed and funny. Puns, insults, delightful amusement. Not very much insight work possible. Juices were needed and tolerated well, but no one was particularly hungry. Sleep was difficult for most people, not deep and not too refreshing. Excellent material, but body price a bit too much for the mental effects. Pleasant, and I wouldn't hesitate to take it again, but nothing very memorable except the tremendous humor and laughter, which was truly delightful."

EXTENSIONS AND COMMENTARY: This compound, BOD, was the first exploratory member of a new family of phenethylamines. This family is called the BOX series because an oxygen atom has been put on the benzylic carbon (the "benzyl-oxy" or "BO") of each of several well studied drugs with recognized substituent patterns on the aromatic ring. The "X" would be "D," as used here with BOD, making reference to 2C-D, it would be a "B" in BOB making reference to 2C-B, etc. Actually the original thought was to make the "O" into an "OM" for methoxy, as this would allow more versatility in the naming of things such as ethoxys ("OE") or hydroxys ("OH"), but the methoxylated 2C-B analogue would have come out as BOMB, so the idea was dropped.

Actually, the concept of naming of drugs with some acronym that is pronounceable has led into some interesting byways. Some examples have been unintended. I have heard DOM pronounced "dome" and DOET pronounced as "do it." And elsewhere I have mentioned the embarrassing occasions where the TOM and TOET families were pronounced "the toms and twats." Some examples have had names that have been contractions of popular names, such as XTC for ecstasy. And there are instances where a name might be proposed simply to irritate the newspaper people. An early street suggestion for PCP was FUK, and a current name for free-base methamphetamine is SNOT. And marijuana is fondly called SHIT by its aficionados. The final "A" on government groups such as the CIA or the DEA or the FDA is strongly reminscent of the final "A" which stands for amphetamine in things such as TMA and MDMA. Might there someday be a drug such as 4-cyclopropylmethyl-N-isopropylamphetamine (CIA), or 3,5-dimethoxy-4-

ethylamphetamine (DEA)? It has just occurred to me that there is already a 4-fluoro-2,5-dimethoxyamphetamine (FDA), but I have already named it DOF. If all drugs were known only by publicly embarrassing names, there might be less publicity given them by the press.

Back to the commentary on BOD. The rationale for this inclusion of a beta-oxygen atom into the structure of a phenethylamine is based directly on the chemistry that occurs naturally in the brain. The phenethylamine neurotransmitter, dopamine, is converted both in the brain and in the body to the equally important transmitter norepinephrine by just this sort of transformation. There is the enzymatic addition of an oxygen atom to the "benzylic" position of dopamine. And identical chemistry goes on with tyramine in a number of plants and animals, with a similar addition of oxygen to form octopamine, so-named for its discovered presence in the salivary glands of *Octopus vulgaris*. In the first explorations in the BOX series, this oxygen was intentionally blocked with a methyl group, to ease its entry into the brain, and increase the possibilities of its being active as a psychedelic. As mentioned above, the "D" in BOD follows from its ring orientation pattern being the same as that of 2C-D (and this, originally from the mimicking of the pattern of DOM). All of these D- compounds have the 2,5-dimethoxy-4-methyl ring-substitution pattern.

An interesting complication is also part of this structure package. The added methoxy group (or hydroxy group, see recipe for BOHD) also adds a new asymmetric center, allowing for the eventual separation of the material into two optical isomers. And at such time as the corresponding amphetamine homologues might be made and studied, the presence of yet another chiral center (under the alpha-methyl group) will demand that there be actually two racemic compounds synthesized, and a total of four isomers to contend with, if really careful and thorough work is to be done.

A parallel chemistry to all of this follows the addition of sodium ethoxide (rather than sodium methoxide) to the nitrostyrene. The final product, then, is the ethoxy homologue 2,5-dimethoxy-ß-ethoxy-4-methylphenethylamine, or BOED. It is down in human potency by a factor of three, with a normal dosage being 70-75 milligrams. It has a ten hour duration, and is both anorexic and diuretic. There have been no visual effects or insights reported, but rather simply a highly intoxicated state.

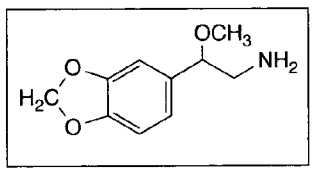
Two synonyms, two definitions, and an expression of admiration. The word norepinephrine is synonymous with noradrenalin, and the word epinephrine is synonymous with adrenalin. The distinctions are that the first in each case is American and the second British. And the term "chiral" indicates a potential asymmetry in a molecule that would allow eventual separation into two optical isomers. The term "racemic" refers to a mixture of these two isomers which has not yet been separated into the individual components. A racemic mixture is called a racemate and, from the point of view of the human animal (which is completely asymmetric), must be considered as a mixture of two structurally identical but

optically mirror-image isomers, which can be potentially separated and which will certainly have different pharmacologies. And the admiration? This is directed to the explorer who ventured close enough to an octopus to locate its salivary glands and to discover a phenethylamine there!

#15 BOH; ß-METHOXY-3,4-METHYLENEDIOXY-PHENETHYLAMINE

SYNTHESIS: To a solution of 30 g piperonal in 100 mL acetic acid there was added 20 mL nitromethane and 10 mL cyclohexylamine. After heating on the steam bath for 1.5 h, the reaction mixture started to crystallize. The mixture was cooled in an ice bath, and the heavy mass of deposited crystals removed by filtration and washed with 20 mL acetic acid. All was supended in 100 mL warm MeOH, cooled again, and filtered to give 24.5 g of 3,4-methylenedioxy-ß-nitrostyrene as canary-yellow crystals, with a mp of 158-160 °C. Reduction of this compound with LAH gives rise to MDPEA, which is a separate entry with a recipe of its own.

To a vigorously stirred suspension of 20 g 3,4-methylenedioxy-ß-nitro - styrene in 100 mL anhydrous MeOH there was added a freshly prepared solution of 5.5 g elemental sodium in 100 mL MeOH. The nitrostyrene goes into solution over the course of 5 min. There was then added, first, 50 mL acetic acid with the stirring continued for an additional 1 min. There was then added 300 mL H_2O. An oil separated and was extracted into 200 mL CH_2Cl_2. The organic extract was washed with 500 mL dilute aqueous $NaHCO_3$, followed by 500 mL H_2O. Removal of the solvent gave a residue that was distilled at 128-145 °C at 0.4 mm/Hg, providing 16.6 g of a yellow viscous liquid which slowly crystallized. An analytical sample was recrystallized from four volumes of MeOH to give 1-methoxy-1-(3,4-methylenedioxyphenyl)-2-nitroethane as bright yellow crystals with a mp of 58-59 °C. Anal. ($C_{10}H_{11}NO_5$) C,H.



A solution of LAH (100 mL of 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 2.5 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 12 g 1-methoxy-1-(3,4-methylenedioxyphenyl)-2-nitroethane over the course of 2 min. There was an immediate loss of color. After a few minutes further stirring, the temperature was brought up to a reflux with a heating mantle. There was a gentle gas evolution for a few min, followed by an exothermic reaction that exceeded the capacity of the condenser. Once the reaction had subsided, the unreacted hydride was destroyed with a minimum of IPA, and 15% NaOH was added to convert the inorganics to a loose white filterable mass. The reaction mixture was filtered, and the filter cake washed thoroughly with THF. The combined filtrate and washes were

stripped of solvent under vacuum, providing an orange oil. This was dissolved in 400 mL dilute H_2SO_4, which was washed with 3x75 mL CH_2Cl_2. After making the aqueous phase basic, it was extracted with 2x100 mL CH_2Cl_2. The pooled extracts were stripped of solvent under vacuum, and the residue distilled at 103-112 °C at 0.5 mm/Hg. There was obtained 2.5 g of a colorless, viscous oil which was dissolved in 25 mL IPA, neutralized with 45 drops of concentrated HCl, and finally diluted with 30 mL anhydrous Et_2O. There was thus formed ß-methoxy-3,4-methylenedioxyphenethylamine hydrochloride (BOH) as a fine white crystalline product. The mp was 105-106.5 °C, with bubbling and darkening. The mp properties proved to be inconsistent, as the salt was a hydrate. Recrystallization from CH_3CN, or simply heating to 100 °C in toluene, converted the salt to an anhydrous form, with mp of 152-153 °C. Anal. ($C_{10}H_{14}ClNO_3$) C,H.

DOSAGE: 80 - 120 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 90 mg) "Distinct body awareness in an hour. The threshold is mostly physical. Faint sense of inside warmth, skin prickling, cold feet, loose bowels, anorexia. By the fifth hour, I was on the downslope, and in retrospect I found it good humored but not insightful."

(with 100 mg) "There was a vague nausea, and a chilling of the feet. It reached a real plus two, with dilated pupils and quite a thirst. How can one describe the state? There were no visuals, and I was not even stoned. I was just very turned on. And I was completely back to baseline by hour number six."

EXTENSIONS AND COMMENTARY: There are several reports of a nice, mild mood enhancement in the 20-40 milligram dosage area, but searches for psychedelic effects at higher levels gave a strange mix of some sort of an altered state along with bodily discomfort. The BOH name for this member of the BOX family follows the convention discussed in the BOD recipe — with "H" for homopiperonylamine, the simplest of the muni-metro family, q.v. The demethylated homologue of BOH is BOHH, and is the methylenedioxy analogue of norepinephrine. It might well hydrolytically open up in the body to provide this neurotransmitter, and serve as some sort of transmitter in its own right. It is discussed under DME.

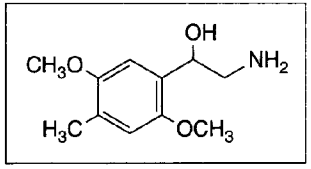
Maybe there is something to the concept that when you imitate a neurotransmitter too closely, you get a hybrid *gemisch* of activity. The term "pro-drug" is used to identify a compound that may not be intrinsically active, but one which metabolizes in the body to provide an active drug. I feel the term should have been pre-drug, but pro-drug was the word that caught on. BOH may well act in the body as a pro-drug to norepinephrine, but with the temporary blocking of the polar functions with ether groups, it can gain access to the brain. And once there, it can be stripped of these shields and play a direct neurological role. I uncovered a very

similar analogy in the tryptamine world some years ago. Just as norepinephrine is a neurotransmitter, so is serotonin. And I found that by putting an O-ether on the indolic phenol (to hide its polarity) and an alpha-methyl group next to the primary amine (to protect it from metabolic deaminase), it became an extremely potent, and most complex, psychedelic. This was the compound alpha,O-dimethylserotonin, or α,O-DMS. There is an uncanny analogy between this tryptamine and the phenethylamine BOH.

Somehow the quiet voice deep inside me says, don't use too much, too quickly. Maybe one of the optical isomers is the body thing, and the other isomer is the mind thing. So far, only the racemic mixture has been tasted, to the best of my knowledge.

#16 BOHD; 2,5-DIMETHOXY-ß-HYDROXY-4-METHYL-PHENETHYLAMINE

SYNTHESIS: A solution of 0.4 g 1-(2,5-dimethoxy-4-methylphenyl)-1-methoxy-2-nitroethane (see preparation in the recipe for BOD) in 3.0 mL acetic acid was heated to 100 °C on a steam bath. There was added 1.0 g powdered zinc, followed by additional acetic acid as needed to maintain smooth stirring. After 0.5 h there was added 1.0 mL concentrated HCl and, following an additional few minutes heating, the reaction mixture was poured into 300 mL H_2O. After washing the aqueous phase with 3x75 mL CH_2Cl_2, the mixture was made basic with 25% NaOH, and extracted with 3x50 mL CH_2Cl_2. Removal of the solvent and distillation of the residue at 130-140 °C 0.25 mm/Hg gave an oil that, on dissolving in IPA, neutralization with concentrated HCl, and the addition of anhydrous Et_2O, gave beautiful white crystals of 2,5-dimethoxy-ß-hydroxy-4-methylphenethylamine hydrochloride (BOHD). The yield was 0.2 g, and the mp was 180-181 °C. The infrared spectrum was that of an amine salt with a strong OH group present. Anal. ($C_{11}H_{18}ClNO_3$) C,H.



DOSAGE: greater than 50 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 50 mg) "At about the two hour point, there was a precipitous drop of blood pressure (from 120/72 to 84/68) although the pulse stayed steady at 60. This trend had been apparent in earlier trials, and was being watched carefully. No further tests are planned."

EXTENSIONS AND COMMENTARY: The usual method of making beta-

ethanolamine such as this is through the reduction of the cyanohydrin of the corresponding benzaldehyde and, in fact, that method is described in the recipe for DME. This above procedure was actually part of an exploration of different agents that might be used in the reduction of the intermediate nitroalkane. This product was the unexpected result of trying zinc.

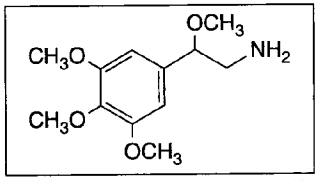
Why the potent cardiovascular effect seen by this compound? There are a couple of points that might argue for some adrenolytic toxicity. This material is a beta-ethanolamine and, with maybe one or two exceptions, clinically used beta-receptor blockers are beta-ethanolamines. In fact, a few of these so-called beta-blockers actually have two methoxy groups on the aromatic rings, also a property of BOHD. The antidiabetic drug Butaxamine (BW 64-9 in the code of Burroughs Wellcome) is identical to BOHD except that the 4-methyl group is on the alpha-carbon instead, and there is a tertiary butyl group on the nitrogen atom. Another point involves the proximity of the beta-hydroxy group and the methoxyl oxygen atom in the 2-position of the ring. There is going to be a strong hydrogen-bonding with this orientation, with the formation of a stable six-membered ring. This might help obscure the hydrophilic nature of the free hydroxyl group and allow the compound to pass into the brain easily. If this group is masked by an easily removed group such as an acetate ester, one gets the compound beta-acetoxy-3,4-dimethoxy-4-methylphenethylamine (BOAD) which is similar to BOHD as a hypotensive.

The code-naming procedure used here (and elsewhere here in Book II) is: (1) to use "BO" as the alert to there being an oxygen on the benzyl carbon of a phenethylamine (it is a benzyl alcohol); (2) if there is just one more letter (a third and last letter) it will identify the 2C-X parent from which it has been derived ["B" comes from 2C-B, "D" comes from 2C-D, "H" comes from homopiperonylamine (MDPEA) rather than from 2C-H, "M" comes from mescaline, and in every case the beta-substituent is a methoxy group]; and (3) if there are four letters, then the fourth letter is as above, and the third letter (the next to last letter) is the substituent on that benzylic oxygen. With a three letter code, the substituent is a methyl group, an "H" for a third letter of four makes it a hydroxyl group, and an "A" for the third letter is an acetyl group, and an "E" is for an ethyl group. A similar sort of cryptographic music was composed by Du Pont in their three-number codes for the Freons. The first number was one less than the number of carbons in the molecule, the second number was one more than the number of hydrogens in the molecule, the third number was the exact number of fluorines in the molecule, and the rest of the bonds were filled with chlorines, Thus Freon 11 (really Freon 011) was trichlorofluoromethane and Freon 116 was hexafluoroethane.

Complex, yes. But both systems are completely straightforward, and flexible for future creations. A few additional examples of similar beta-ethanolamines are scattered throughout Book II and they have, in general, proved to be uninteresting, at least as potential psychedelic compounds.

#17 BOM; ß-METHOXYMESCALINE; 3,4,5,ß-TETRA-METHOXYPHENETHYLAMINE

SYNTHESIS: To a vigorously stirred suspension of 9.0 g ß-nitro-3,4,5-trimethoxystyrene (see under the recipe for M for the preparation of this intermediate) in 50 mL anhydrous MeOH there was added a solution obtained from the addition of 2.0 g metallic sodium to 50 mL anhydrous MeOH. The bright orange color faded to a light cream as the nitrostyrene went into solution. After 3 min there was added 30 mL acetic acid, which produced white solids, and this was followed by further dilution with 150 mL H_2O. The formed solids were removed by filtration, washed well with H_2O, and recrystallized from 150 mL boiling MeOH. After removal of the product by filtration and air drying to constant weight, there was obtained 6.9 g of 1-methoxy-2-nitro-1-(3,4,5-trimethoxyphenyl)ethane as fine, cream-colored crystals. The mp was 143-144 °C, and the Rf by TLC (silica-gel plates and CH_2Cl_2 as moving phase) was identical to that of the starting aldehyde. Anal. ($C_{12}H_{17}NO_6$) C,H.



A solution of LAH (50 mL of 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.25 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 6 g of solid 1-methoxy-2-nitro-1-(3,4,5-trimethoxyphenyl)ethane over the course of 2 min. There was some gas evolution. After 5 min additional stirring, the temperature was brought up to a reflux with a heating mantle. There was a gentle gas evolution for a few minutes, followed by an exothermic reaction with vigorous gas evolution. Once everything had settled down, the reaction mixture was held at reflux temperature for an additional 2 h. The excess hydride was destroyed by the addition of IPA and 15% NaOH was added to convert the inorganic salts to a loose white filterable mass. The reaction mixture was filtered, and the filter cake washed thoroughly with THF. The combined filtrate and washes were stripped of solvent under vacuum which provided a red-brown liquid. This was dissolved in dilute H_2SO_4 and washed with 3x75 mL CH_2Cl_2. After making the aqueous phase basic with NaOH, it was extracted with 2x100 mL CH_2Cl_2. The pooled extracts were stripped of solvent under vacuum, and the colorless residue distilled at 120-150 °C at 0.3 mm/Hg. There was obtained 2.8 g of a colorless oil which was dissolved in 30 mL IPA and neutralized with concentrated HCl, allowing the spontaneous formation of the hydrochloride salt. This was diluted with 75 mL anhydrous Et_2O, yielding 2.8 g 3,4,5,ß-tetramethoxyphenethylamine hydrochloride (BOM) as a white crystalline product. This had a mp of 198.5-199.5 °C. Anal. ($C_{12}H_{20}ClNO_4$) C,H.

DOSAGE: greater than 200 mg.

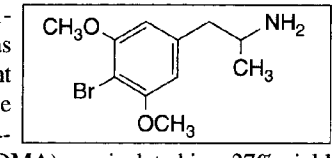
DURATION: unknown.

EXTENSIONS AND COMMENTARY: There are some indicators of central activity with assays involving both the 120 milligram and the 180 milligram levels, but nothing that can be rated as over a plus one. It can be seen with the two active members of the BOX series (BOD and BOB) that the potency is about equal to, or a little more (up to a factor of maybe x2), than the analogue without the methoxyl group on the aliphatic chain. If this formula were to hold in the relationship between mescaline and BOM, the active level might well be in the 200-400 milligram range. But at the moment, it remains unknown.

Again, the name of the compound (BOM) is from the "BO-" prefix of this family (from benzyl + oxy), plus the "M" of mescaline (which has provided the ring substitution pattern).

#18 4-BR-3,5-DMA; 3,5-DIMETHOXY-4-BROMOAMPHETAMINE

SYNTHESIS: The starting material 3,5-dimethoxy-4-bromobenzoic acid (made from the commercially available resorcinol by the action of methyl sulfate) was a white crystalline solid from aqueous EtOH with a mp of 248-250 °C. Reaction with thionyl chloride produced 3,5-dimethoxy-4-bromobenzoyl chloride which was used as the crude solid product, mp 124-128 °C. This was reduced with tri-O-(t)-butoxy lithium aluminum hydride to produce 3,5-dimethoxy-4-bromobenzaldehyde which was recrystallized from aqueous MeOH and had a mp of 112-114 °C. Anal. ($C_9H_9BrO_3$) C,H. This aldehyde, with nitroethane and anhydrous ammonium acetate in acetic acid, was converted to the nitrostyrene 1-(3,5-dimethoxy-4-bromophenyl)-2-nitropropene, with a mp of 121-121.5 °C. Anal. ($C_{11}H_{12}BrNO_4$) C,H,N. This was reduced at low temperature with just one equivalent of LAH, to minimize reductive removal of the bromine atom. The product 3,5-dimethoxy-4-bromoamphetamine hydrochloride (4-BR-3,5-DMA) was isolated in a 37% yield and had a mp of 221-222 °C. Anal. ($C_{11}H_{17}BrClNO_2$) C,H,N.



DOSAGE: 4 - 10 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 3 mg) "This is certainly no placebo. At about 2 hours I felt some analgesia and numbing in my extremities, but if there were any sensory distortions, they were barely perceptible."

(with 6 mg) "There is a very shallow threshold, no more."

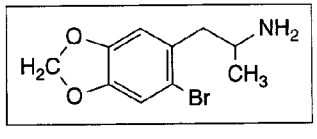
(with 10 mg) "I can certainly confirm the indications of anesthesia that were hinted at. It was for me central in nature, however. I could (this at three hours)

pierce a skin pinch on my left arm with no bother except for the emerging of the needle due to skin resistance. There was little bleeding. And multiple needle prickings into the thumb abductor were not felt. A quick plunge of the tip of my little finger into boiling water elicited reflex response, but no residual pain. Judgment was OK, so I stayed out of physical trouble, luckily! The perhaps ++ was dropping in the fourth or fifth hour, and by the tenth hour there were few effects still noted, except for some teeth-rubbiness and a burning irritation at the pin-prick area, so feeling is back. No sleep problems at just past midnight."

EXTENSIONS AND COMMENTARY: Here is a complex and, at the moment, totally undefined drug. There were two independent reports of analgesia, yet a thorough screen in experimental animals, conducted by a major pharmaceutical house, failed to confirm any of it. A ++ report does not necessarily reflect a psychedelic effect, since this quantitative measure of the level of activity represents the extent of impairment of function, regardless of the nature of the drug producing it. In other words, if you were experiencing the effects of a drug that would in your judgment interfere with safe and good driving, this would be a ++ whether your performance was being limited by a psychedelic, a stimulant, a hypnotic or a narcotic. None of the quantitative reports ever mentioned any sensory distortion (analgesia is a loss, not a distortion) or visual effect. Perhaps 4-BR-3,5-DMA showed its ++ as a narcotic. But then, the rats had said no.

#19 2-BR-4,5-MDA; 6-BR-MDA; 2-BROMO-4,5-METHYLENEDIOXYAMPHETAMINE

SYNTHESIS: A solution of 3,4-methylenedioxyamphetamine (MDA) in acetic acid was treated with elemental bromine, generating the hydrobromide salt of 2-bromo-4,5-methylenedioxyamphetamine in a yield of 61% of theory. The mp was 221-222 °C. Anal. ($C_{10}H_{13}Br_2NO_2$) C,H,Br.



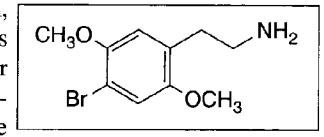
DOSAGE: 350 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: Both the synthetic and the pharmacological details for this compound are sparse. There has been only a single report of the human activity of this drug in the literature, and the statement has been offered that the effects are amphetamine-like. No other qualitative comments have been made available, and neither I nor anyone in my circle has tried it, personally. Someday, perhaps. But at that high level, perhaps not.

#20 2C-B; 4-BROMO-2,5-DIMETHOXYPHENETHYLAMINE

SYNTHESIS: A solution of 100 g of 2,5-dimethoxybenzaldehyde in 220 g nitromethane was treated with 10 g anhydrous ammonium acetate, and heated on a steam bath for 2.5 h with occasional swirling. The deep-red reaction mixture was stripped of the excess nitromethane under vacuum, and the residue crystallized spontaneously. This crude nitrostyrene was purified by grinding under IPA, filtering, and air-drying, to yield 85 g of 2,5-dimethoxy-ß-nitrostyrene as a yellow-orange product of adequate purity for the next step. Further purification can be achieved by recrystallization from boiling IPA.



In a round-bottomed 2 L flask equipped with a magnetic stirrer and placed under an inert atmosphere, there was added 750 mL anhydrous THF, containing 30 g LAH. There was then added, in THF solution, 60 g 2,5-dimethoxy-ß-nitrostyrene. The final solution was a dirty yellow-brown color, and it was kept at reflux temperature for 24 h. After cooling, the excess hydride was destroyed by the dropwise addition of IPA. Then 30 mL 15% NaOH was added to convert the inorganic solids to a filterable mass. The reaction mixture was filtered and the filter cake washed first with THF and then with MeOH. The combined mother liquors and washings were freed of solvent under vacuum and the residue suspended in 1.5 L H_2O. This was acidified with HCl, washed with with 3x100 mL CH_2Cl_2, made strongly basic with 25% NaOH, and reextracted with 4x100 mL CH_2Cl_2. The pooled extracts were stripped of solvent under vacuum, yielding 26 g of oily residue, which was distilled at 120-130 °C at 0.5 mm/Hg to give 21 g of a white oil, 2,5-dimethoxyphenethylamine (2C-H) which picks up carbon dioxide from the air very quickly.

To a well-stirred solution of 24.8 g 2,5-dimethoxyphenethylamine in 40 mL glacial acetic acid, there was added 22 g elemental bromine dissolved in 40 mL acetic acid. After a couple of min, there was the formation of solids and the simultaneous evolution of considerable heat. The reaction mixture was allowed to return to room temperature, filtered, and the solids washed sparingly with cold acetic acid. This was the hydrobromide salt. There are many complicated salt forms, both polymorphs and hydrates, that can make the isolation and characterization of 2C-B treacherous. The happiest route is to form the insoluble hydrochloride salt by way of the free base. The entire mass of acetic acid-wet salt was dissolved in warm H_2O, made basic to at least pH 11 with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent gave 33.7 g of residue which was distilled at 115-130 °C at 0.4 mm/Hg. The white oil, 27.6 g, was dissolved in 50 mL H_2O containing 7.0 g acetic acid. This clear solution was vigorous stirred, and treated with 20 mL concentrated HCl. There was an immediate formation of the anhydrous salt of 2,5-dimethoxy-4-bromophenethylamine hydrochloride (2C-B). This mass of crystals was removed by filtration (it can be loosened considerably by the addition of another 60 mL H_2O), washed with a little H_2O, and then with several 50

mL portions of Et_2O. When completely air-dry, there was obtained 31.05 g of fine white needles, with a mp of 237-239 °C with decomposition. When there is too much H_2O present at the time of adding the final concentrated HCl, a hydrated form of 2C-B is obtained. The hydrobromide salt melts at 214.5-215 °C. The acetate salt was reported to have a mp of 208-209 °C.

DOSAGE: 12 - 24 mg.

DURATION: 4 - 8 h.

QUALITATIVE COMMENTS: (with 16 mg) "A day at the Stanford museum. Things were visually rich, yet I felt that I was reasonably inconspicuous. The Rodin sculptures were very personal and not terribly subtle. I saw Escher things in the ceiling design, when I decided to sit in a foyer somewhere and simply pretend to rest. Walking back, the displays seen in the bark of the eucalyptus trees, and the torment and fear (of others? of themselves?) in the faces of those who were walking towards us, were as dramatic as anything I had seen in the art galleries. Our appetites were enormous, and we went to a smorgasbord that evening. A rich experience in every possible way."

(with 20 mg) "The drug effect first became known to me as a shift of colors toward golden and rose tones. Pigments in the room became intensified. Shapes became rounder, more organic. A sensation of lightness and rivulets of warmth began seeping through my body. Bright lights began pulsing and flashing behind my closed lids. I began to perceive waves of energy flowing through all of us in unison. I saw all of us as a gridwork of electrical energy beings, nodes on a bright, pulsating network of light. Then the interior landscape shifted into broader scenes. Daliesque vistas were patterned with eyes of Horus, brocades of geometric design began shifting and changing through radiant patterns of light. It was an artist's paradise — representing virtually the full pantheon of the history of art."

(with 20 mg) "The room was cool, and for the first hour I felt cold and chilled. That was the only mildly unpleasant part. We had been hanging crystals earlier that day, and the visions I had were dominated by prismatic light patterns. It was almost as if I became the light. I saw kaleidoscopic forms — similar to, but less intense than, when on acid — and organic forms like Georgia O'Keefe flowers, blossoming and undulating. My body was flooded with orgasms — practically from just breathing. The lovemaking was phenomenal, passionate, ecstatic, lyric, animal, loving, tender, sublime. The music was voluptuous, almost three-dimensional. Sometimes the sound seemed distorted to me, underwater like. This was especially so for the less good recordings — but I could choose to concentrate on the beauty of the music or the inadequacy of the sound's quality, and mostly chose to concentrate on the beauty."

(with 24 mg) "I am totally into my body. I am aware of every muscle and nerve in my body. The night is extraordinary — moon full. Unbelievably erotic, quiet and exquisite, almost unbearable. I cannot begin to unravel the imagery that imposes itself during the finding of an orgasm. Trying to understand physical/spiritual merging in nature — ."

EXTENSIONS AND COMMENTARY: Four quotations were chosen arbitrarily from literally hundreds that have worked their ways into the files. The vast majority are positive, ranging from the colorful to the ecstatic. But not all are. There are people who choose not to go into the corporeal but, rather, prefer the out-of-body experience. They express discomfort with 2C-B, and seem to lean more to the Ketamine form of altered state, one which dissociates body from mind.

There have been reports of several overdoses that prove the intrinsic safety of this compound. Prove is used here in the classic British sense; i.e., to challenge. "The proof of the pudding is in the eating," is not a verification of quality, but an inquiry into the quality itself. (The French simplify all this by using two separate verbs for prove.) One overdose was intentional, the other accidental.

(with 64 mg) "I found only mild visual and emotional effects at the 20 milligram dose, so I took the remaining 44 milligrams. I was propelled into something not of my choosing. Everything that was alive was completely fearsome. I could look at a picture of a bush, and it was just that, a picture, and it posed no threat to me. Then my gaze moved to the right, and caught a bush growing outside the window, and I was petrified. A life-form I could not understand, and thus could not control. And I felt that my own life-form was not a bit more controllable." This was from the comments of a physician who assured me that he saw no neurological concerns during this dramatic and frightening experience.

(with 100 mg) "I had weighed correctly. I had simply picked up the wrong vial. And my death was to be a consequence of a totally stupid mistake. I wanted to walk outside, but there was a swimming pool there and I didn't dare fall into it. A person may believe that he has prepared himself for his own death, but when the moment comes, he is completely alone, and totally unprepared. Why now? Why me? Two hours later, I knew that I would live after all, and the experience became really marvelous. But the moment of facing death is a unique experience. In my case, I will some day meet it again, and I fear that I will be no more comfortable with it then than I was just now." This was from the comments of a psychologist who will, without doubt, use psychedelics again in the future, as a probe into the unknown.

Many of the reports that have come in over the years have mentioned the combination of MDMA and 2C-B. The most successful reports have followed a program in which the two drugs are not used at the same time, nor even too closely spaced. It appears that the optimum time for the 2C-B is at, or just before, the final baseline recovery of the MDMA. It is as if the mental and emotional discoveries can be mobilized, and something done about them. This combination has several enthusiastic advocates in the psychotherapy world, and should be the basis of careful research when these materials become legal, and accepted by the medical

community.

A generalized spectrum of 2C-B action can be gleaned from the many reports that have been written describing its effects. (1) There is a steep dose response curve. Over the 12 to 24 milligram range, every 2 milligrams can make a profound increase or change of response. Initially, one should go lightly, and increase the dosage in subsequent trials by small increments. A commonly used term for a level that produces a just perceptible effect is "museum level." This is a slightly-over-threshold [illegible] which allows public activities (such as viewing paintings in a museum or [illegible] ry watching as a passenger in a car) to be entered into without attracting attention. There can be considerable discomfort associated with being in the public eye, with higher doses. (2) The 2C-B experience is one of the shortest of any major psychedelic drug. Wherever you might be, hang on. In an hour or so you will be approaching familiar territory again. (3) If there is anything ever found to be an effective aphrodisiac, it will probably be patterned after 2C-B in structure.

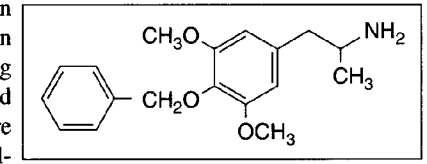
There are two "Tweetios" known that are related to 2C-B. (See recipe #23 for the origin of this phrase.) The 2-EtO- homologue of 2C-B is 4-bromo-2-ethoxy-5-methoxyphenethylamine, or 2CB-2ETO. The unbrominated benzaldehyde (2-ethoxy-5-methoxybenzaldehyde) had a melting point of 47.5-48.5 °C, the unbrominated nitrostyrene intermediate a melting point of 76-77 °C, and the final hydrochloride a melting point of 185-186 °C. The hydrobromide salt had a melting point of 168.5-169.5 °C. It seems that one gets about as much effect as can be had, with a dosage of about 15 milligrams, and increases above this, to 30 and to 50 milligrams merely prolong the activity (from about 3 hours to perhaps 6 hours). At no dose was there an intensity that in any way resembled that of 2C-B.

The 2,5-DiEtO- homologue of 2C-B is 4-bromo-2,5-diethoxyphenethylamine, or 2CB-2,5-DIETO. The unbrominated impure benzaldehyde (2,5-diethoxybenzaldehyde) had a melting point of about 57 °C, the unbrominated impure nitrostyrene intermediate a melting point of about 60 °C, and the final hydrochloride a melting point of 230-231 °C. The hydrobromide salt had a melting point of 192-193 °C. At levels of 55 milligrams, there was only a restless sleep, and strange dreams. The active level is not yet known.

I have been told of some studies that have involved a positional rearrangement analogue of 2C-B. This is 2-bromo-4,5-dimethoxyphenethylamine (or 6-BR-DMPEA). This would be the product of the elemental bromination of DMPEA, and it has been assayed as the hydrobromide salt. Apparently, the intravenous injection of 60 milligrams gave a rapid rush, with intense visual effects reported, largely yellow and black. Orally, there may be some activity at the 400 to 500 milligram area, but the reports described mainly sleep disturbance. This would suggest a stimulant component. The N-methyl homologue of this rearranged compound was even less active.

#21 3C-BZ; 4-BENZYLOXY-3,5-DIMETHOXYAMPHETAMINE

SYNTHESIS: A solution of 268 g 2,6-dimethoxyphenol and 212 g allyl bromide in 700 mL dry acetone was treated with 315 g anhydrous K_2CO_3 and held at reflux for 16 h. The solvent was removed under vacuum, and the residue dissolved in H_2O and extracted with 3x100 mL CH_2Cl_2. The pooled extracts were washed with 5% NaOH, then with H_2O, and the solvent removed under vacuum. The residue, which weighed 245 g, was stirred and heated in an oil bath to 230 °C at which point an exothermic reaction set in. The heating was maintained at 230 °C for 0.5 h, and then the reaction mixture distilled. There was obtained a total of 127 g of 5-allyl-1,3-dimethoxy-2-hydroxybenzene as a colorless distillate, that was identical in all respects to natural 5-methoxyeugenol obtained from Oil of Nutmeg.



A solution containing 40.4 g 5-methoxyeugenol and 26.6 g benzyl chloride in 65 mL EtOH was added, all at once, to a hot and well stirred solution of 11.7 g KOH in 500 mL EtOH. The potassium salt of the phenol crystallized out immediately. By maintaining reflux conditions, this slowly redissolved, and was replaced by the steady deposition of KCl. After 6 h, the reaction mixture was cooled, and the solids removed by filtration. The filtrate was stripped of solvent under vacuum to give 57 g of crude 5-allyl-2-benzyloxy-1,3-dimethoxybenzene. This was dissolved in a solution of 60 g KOH in 80 mL EtOH and heated on the steam bath for 16 h. The reaction mixture was quenched in 500 mL H_2O, and extracted with 2x200 mL CH_2Cl_2. Removal of the solvent under vacuum gave 35.6 g of crude 2-benzyloxy-1,3-dimethoxy-5-propenylbenzene.

To a stirred, ice-cold solution of 33.6 g of the above impure 2-benzyloxy-1,3-dimethoxy-5-propenylbenzene and 13.6 g pyridine in 142 mL acetone, there was added 24.6 g tetranitromethane. After stirring for 3 min, there was added a solution of 7.9 g KOH in 132 mL H_2O, followed by additional H_2O. The oily phase that remained was H_2O washed, and then diluted with an equal volume of MeOH. This slowly set up to yellow crystals, which were removed by filtration and washed sparingly with MeOH. There was obtained 9.2 g 1-(4-benzyloxy-3,5-dimethoxyphenyl)-2-nitropropene with a mp of 84-85 °C. An analytical sample, from EtOH, had a mp of 86-87 °C.

To a refluxing suspension of 5.5 g LAH in 360 mL anhydrous Et_2O under an inert atmosphere, there was added 8.6 g 1-(4-benzyloxy-3,5-dimethoxyphenyl)-2-nitropropene by letting the condensing Et_2O leach out a saturated solution from a modified Soxhlet condenser. The addition took 1.5 h and the refluxing was maintained for an additional 4 h. After cooling, the excess hydride was destroyed by the cautious addition of 330 mL of 1.5 N H_2SO_4. The aqueous phase was heated up to 80 °C, filtered through paper to remove a small amount of insoluble material, and treated with a solution of 8 g picric acid in 150 mL boiling EtOH. Cooling in

the ice chest overnight gave globs of the amine picrate, but no clear signs of crystallization. These were washed with cold H_2O, then dissolved in 5% NaOH to give a bright yellow solution. This was extracted with 3x150 mL CH_2Cl_2, the solvent removed under vacuum, the residue dissolved in 300 mL anhydrous Et_2O, freed from a little particulate material by filtration through paper, and then saturated with hydrogen chloride gas. There was thus obtained, after filtering, Et_2O washing and air drying, 2.5 g 4-benzyloxy-3,5-dimethoxyamphetamine hydrochloride (3C-BZ) as a white solid with a mp of 161-164 °C.

DOSAGE: 25 - 200 mg.

DURATION: 18 - 24 h.

QUANTITATIVE COMMENTS: (with 25 mg) "I went into an emotionally brittle place, and for a while I was uncomfortable with childhood reminiscences. The seeing of my family's Christmas tree in my mind was almost too much. I cried."

(with 50 mg) "The action is distinct — wakeful — alerting and wound up. Hypnogogic imagery, and I could not sleep at night with my mind doing many uncontrolled, tangential, busy things. I had fleeting nausea early in the process."

(with 100 mg) "I took this in two portions. Following 50 milligrams I was aware of a slight light-headedness at a half-hour, but there was little else. At 1 1/2 hours, I took the second 50 milligrams and the augmentation of effects was noted in another half hour. The experience quietly built up to about the fifth hour, with some erotic fantasy and suggestions of changes in the visual field. I could not sleep until the twelfth hour, and my dreams were wild and not too friendly. There was no body threat from this, but I was not completely baseline until the next day. I am not too keen to do this again — it lasts too long."

(with 100 mg) "No effects."

(with 150 mg) "This is in every way identical to 100 micrograms of LSD."

(with 180 mg) "I can compare this directly to TMA which was the material I took last week. Many similarities, but this is unquestionably more intense than the TMA was at 200 milligrams. It is hard to separate the degree of impact that this drug has, from the simple fact that it lasts forever, and I was getting physically tired but I couldn't sleep. There is some amphetamine-like component, more than with TMA."

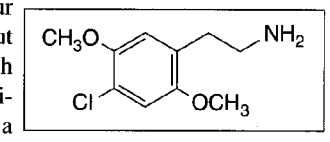
EXTENSIONS AND COMMENTARY: Two points are worthy of commentary; the potency and the promise of 3C-BZ.

As to potency, there is such uncertainty as to the effective dose, that it is for all intents and purposes impossible to predict just what dose should be considered for a person's first time with this. The choice of quotations was made with the intention of giving a picture of this scatter. A total of ten subjects have explored this compound, and the very broad range given above, 25 to 200 milligrams, reflects the degree of variation that has been encountered.

Which is a shame, because the concept of a new ring such as is found here on the 4-position would have allowed an extremely wide array of substituents. Electron-rich things, electron-poor things, heavy things, light things, and on and on. This could have been a location of much variation, but it is a possibility that the uncertainties of dosage might extrapolate to these novel ring substitutions as well. Only a single variation was made, the 4-fluorobenzyl analogue. This was prepared following exactly the procedure given here for 3C-BZ, except for the replacement of benzyl chloride with 4-fluorobenzyl chloride. The allyl intermediate was an oil, but the propenyl isomer gave solids with a melting point of 59-60 °C from hexane. The nitrostyrene was a yellow crystalline solid from methanol with a melting point of 98-99 °C. The end product, 3,5-dimethoxy-4-(4-fluorobenzyloxy)amphetamine hydrochloride (3C-FBZ) was a white solid with a melting point of 149-150 °C. It has been assayed only up to 4 milligrams and there was absolutely no activity of any kind observed at that level.

#22 2C-C; 2,5-DIMETHOXY-4-CHLOROPHENETHYLAMINE

SYNTHESIS: (from 2C-H) The free base of 2,5-dimethoxyphenethylamine was generated from its salt (see recipe for 2C-H for the preparation of this compound) by treating a solution of 16.2 g of the hydrochloride salt in 300 mL H_2O with aqueous NaOH, extraction with 3x75 mL CH_2Cl_2, and removal of the solvent from the pooled extracts under vacuum. The colorless residue was dissolved in 75 mL glacial acetic acid (the solids that initially formed redissolved completely) and this was cooled to 0 °C with an external ice bath. With vigorous stirring, there was added 4.0 mL of liquid chlorine, a little bit at a time with a Pasteur pipette. The theoretical volume was 3.4 mL, but some was lost in pipetting, some on contact with the 0 °C acetic acid, and some was lost by chlorination of the acetic acid. The reaction turned a dark amber color, was allowed to stir for an additional 10 min, then quenched with 400 mL H_2O. This was washed with 3x100 mL CH_2Cl_2 (which removed some of the color) then brought to neutrality with dilute aqueous NaOH and treated with a small amount of sodium dithionite which discharged most of the color (from deep brown to pale yellow). The reaction was made strongly basic with aqueous KOH, and extracted with 3x75 mL CH_2Cl_2. The pooled extracts were washed once with H_2O and the solvent was removed under vacuum leaving about 10 mL of a deep amber oil as residue. This was dissolved in 75 mL IPA and neutralized with concentrated HCl which allowed spontaneous crystallization. These crystals were removed by filtration, washed with an additional 20 mL IPA, and air-dried to constant weight. There was thus obtained 4.2 g 2,5-dimethoxy-4-chlorophenethylamine hydrochloride (2C-C) with a mp of 218-221 °C. Recrystallization from



IPA increased this to 220-222 °C. The position of chlorination on the aromatic ring was verified by the presence of two para-protons in the NMR, at 7.12 and 7.20 ppm from external TMS, in a D_2O solution of the hydrochloride salt.

Synthesis from 2C-B. To a solution of 7.24 g 2,5-dimethoxy-4-bromophenethylamine (2C-B) and 4.5 g phthalic anhydride in 100 mL anhydrous DMF there was added molecular sieves. After 16 h reflux, the reaction mixture was cooled and the sieves removed by filtration. The addition of a little CH_2Cl_2 prompted the deposition of yellow crystals which were recrystallized from EtOH. The resulting 1-(2,5-dimethoxy-4-bromophenyl)-2-(phthalimido)ethane weighed 7.57 g and had a mp of 141-142 °C. Anal. ($C_{18}H_{16}BrNO_4$) C,H,N,Br.

A solution of 14.94 g of 1-(2,5-dimethoxy-4-bromophenyl)-2-(phthalimido)ethane and 4.5 g cuprous chloride in 300 mL anhydrous DMF was heated for 5 h at reflux. The cooled mixture was poured into 20 mL H_2O that contained 13 g hydrated ferric chloride and 3 mL concentrated HCl. The mixture was maintained at about 70 °C for 20 min, and then extracted with CH_2Cl_2. After washing the pooled organic extracts with dilute HCl and drying with anhydrous $MgSO_4$, the volatiles were removed under vacuum to provide a solid residue. This was recrystallized from EtOH to provide 12.18 g of 1-(2,5-dimethoxy-4-chlorophenyl)-2-(phthalimido)ethane as yellow needles that had a mp of 138-140 °C. Anal. ($C_{18}H_{16}ClNO_4$) C,H,N,Cl.

To 60 mL absolute EtOH there was added 12.2 g 1-(2,5-dimethoxy-4-chlorophenyl)-2-(phthalimido)ethane and 2.9 mL of 100% hydrazine. The solution was held at reflux for 15 min. After cooling, the cyclic hydrazone by-product was removed by filtration, and the alcoholic mother liquors taken to dryness under vacuum. The residue was distilled at 145-155 °C at 0.05 mm/Hg to give 5.16 g of a clear, colorless oil. This was dissolved in anhydrous Et_2O and treated with hydrogen chloride gas, producing 2,5-dimethoxy-4-chlorophenethylamine hydrochloride (2C-C) as white crystals with a mp of 220-221 °C. Anal. ($C_{10}H_{15}Cl_2NO_2$) C,H,N.

DOSAGE: 20 - 40 mg.

DURATION: 4 - 8 h.

QUALITATIVE COMMENTS: (with 20 mg) "This is longer lived than 2C-B, and there is a longer latency in coming on. It took an hour and a half, or even two hours to get there. It had a slight metallic overtone."

(with 24 mg) "I was at a moderately high and thoroughly favorable place, for several hours. It seemed to be a very sensual place, but without too much in the way of visual distraction.

(with 40 mg) "There were a lot of visuals — something that I had noted at lower levels. There seems to be less stimulation than with 2C-B, and in some ways it is actually sedating. And yet I was up all night. It was like a very intense form of relaxation."

EXTENSIONS AND COMMENTARY: Other reports mention usage of up to 50 milligrams which seems to increase yet further the intensity and the duration. I have one report of an intravenous administration of 20 milligrams, and the response was described as overwhelming. The effects peaked at about 5 minutes and lasted for perhaps 15 minutes.

The halogens represent a small group of atoms that are unique for a couple of reasons. They are all located in a single column of the periodic table, being monovalent and negative. That means that they can be reasonably stable things when attached to an aromatic nucleus. But, being monovalent, they cannot be modified or extended in any way. Thus, they are kind of a dead end, at least as far as the 2C-X series is considered. The heaviest, iodine, was explored as the phenethylamine, as 2C-I, and as the amphetamine as DOI. These are the most potent. The next lighter is bromine, where the phenethylamine is 2C-B and the amphetamine is DOB. These two are a bit less potent, and are by far the most broadly explored of all the halides. Here, in the above recipe, we have the chlorine counterpart, 2C-C. There is also the corresponding amphetamine DOC. These are less potent still, and much less explored. Why? Perhaps because chlorine is a gas and troublesome to handle (bromine is a liquid, and iodine is a solid). The fluorine analogue is yet harder to make, and requires procedures that are indirect, because fluorine (the lightest of all the halides) is not only a gas, but is dangerous to handle and does not react in the usual halogen way. There will be mention made of 2C-F, but DOF is still unexplored.

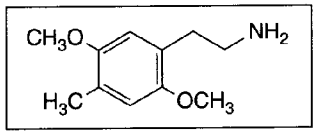
The treatment of the 2C-B phthalimide described above, with cuprous cyanide rather than cuprous chloride, gave rise to the cyano analog which, on hydrolysis with hydrazine, yielded 2,5-dimethoxy-4-cyanophenethylamine (2C-CN). Hydrolysis of this with hot, strong base gave the corresponding acid, 2,5-dimethoxy-4-carboxyphenethylamine, 2C-COOH. No evaluation of either of these compounds has been made in the human animal, as far as I know.

#23 2C-D; LE-25; 2,5-DIMETHOXY-4-METHYL-PHENETHYLAMINE

SYNTHESIS: Into 1 L H_2O that was being stirred magnetically, there was added, in sequence, 62 g toluhydroquinone, 160 mL 25% NaOH, and 126 g dimethyl sulfate. After about 2 h, the reaction mixture was no longer basic, and another 40 mL of the 25% NaOH was added. Even with stirring for a few additional days, the reaction mixture remained basic. It was quenched in 2.5 L H_2O, extracted with 3x100 mL CH_2Cl_2 and the pooled extracts stripped of solvent under vacuum. The remaining 56.4 g of amber oil was distilled at about 70 °C at 0.5 mm/Hg to yield 49.0 g of 2,5-dimethoxytoluene as a white liquid. The aqueous residues, on acidification,

provided a phenolic fraction that distilled at 75-100 °C at 0.4 mm/Hg to give 5.8 g of a pale yellow distillate that partially crystallized. These solids (with mp of 54-62 °C) were removed by filtration, and yielded 3.1 g of a solid which was recrystallized from 50 mL hexane containing 5 mL toluene. This gave 2.53 g of a white crystalline product with a mp of 66-68 °C. A second recrystallization (from hexane) raised this mp to 71-72 °C. The literature value given for the mp of 2-methyl-4-methoxyphenol is 70-71 °C. The literature value given for the mp of the isomeric 3-methyl-4-methoxyphenol is 44-46 °C. This phenol, on ethylation, gives 2-ethoxy-5-methoxytoluene, which leads directly to the 2-carbon 2CD-5ETO (one of the Tweetios) and the 3-carbon Classic Lady IRIS.

A mixture of 34.5 g $POCl_3$ and 31.1 g N-methylformanilide was heated for 10 min on the steam bath, and then there was added 30.4 g of 2,5-dimethoxytoluene.



Heating was continued for 2.5 h, and the viscous, black, ugly mess was poured into 600 mL of warm H_2O and stirred overnight. The resulting rubbery miniature-rabbit-droppings product was removed by filtration and sucked as free of H_2O as possible. The 37.2 g of wet product was extracted on the steam-bath with 4x100 mL portions of boiling hexane which, after decantation and cooling, yielded a total of 15.3 g of yellow crystalline product. This, upon recrystallization from 150 mL boiling hexane, gave pale yellow crystals which, when air dried to constant weight, represented 8.7 g of 2,5-dimethoxy-4-methylbenzaldehyde, and had a mp of 83-84 °C. Anal. ($C_8H_{12}O_3$) C,H,N. The Gattermann aldehyde synthesis gave a better yield (60% of theory) but required the use of hydrogen cyanide gas. The malononitrile derivative, from 5.7 g of the aldehyde and 2.3 g malononitrile in absolute EtOH, treated with a drop of triethylamine, was an orange crystalline product. A sample recrystallized from EtOH gave a mp of 138.5-139 °C.

A solution of 8.65 g 2,5-dimethoxy-4-methylbenzaldehyde in 30 g nitromethane was treated with 1.1 g anhydrous ammonium acetate and heated for 50 min on the steam bath. Stripping off the excess nitromethane under vacuum yielded orange crystals which weighed 12.2 g. These were recrystallized from 100 mL IPA providing yellow crystals of 2,5-dimethoxy-4-methyl-ß-nitrostyrene which weighed, when dry, 7.70 g. The mp was 117-118 °C, and this was increased to 118-119 °C upon recrystallization from benzene/heptane 1:2.

To a well stirred suspension of 7.0 g LAH in 300 mL of warm THF under an inert atmosphere, there was added 7.7 g 2,5-dimethoxy-4-methyl-ß-nitrostyrene in 35 mL THF over the course of 0.5 h. This reaction mixture was held at reflux for 24 h, cooled to room temperature, and the excess hydride destroyed with 25 mL IPA. There was then added 7 mL 15% NaOH, followed by 21 mL H_2O. The granular gray mass was filtered, and the filter cake washed with 2x50 mL THF. The combined filtrate and washes were stripped of their volatiles under vacuum to give a residue weighing 7.7 g which was distilled at 90-115 °C at 0.3 mm/Hg to provide 4.90 g of a clear, white oil, which crystallized in the receiver. This was dissolved

in 25 mL IPA, and neutralized with concentrated HCl which produced immediate crystals of the salt. These were dispersed with 80 mL anhydrous Et_2O, filtered, and washed with Et_2O to give, after air drying to constant weight, 4.9 g of fluffy white crystals of 2,5-dimethoxy-4-methylphenethylamine hydrochloride (2C-D). The mp was 213-214 °C which was not improved by recrystallization from CH_3CN/IPA mixture, or from EtOH. The hydrobromide salt had a mp of 183-184 °C. The acetamide, from the free base in pyridine treated with acetic anhydride, was a white crystalline solid which, when recrystallized from aqueous MeOH, had a mp of 116-117 °C.

DOSAGE: 20 - 60 mg.

DURATION: 4 - 6 h.

QUALITATIVE COMMENTS: (with 10 mg) "There is something going on, but it is subtle. I find that I can just slightly redirect my attention so that it applies more exactly to what I am doing. I feel that I can learn faster. This is a 'smart' pill!"

(with 20 mg) "Butterflies in stomach whole time. OK. This is about the right level. In retrospect, not too interesting. Primarily a stimulant, not entirely physically pleasant. The visual is not too exciting. I am easily distracted. One line of thought to another. I feel that more would be too stimulating."

(with 30 mg) "I was into it quite quickly (not much over three-quarters of an hour) and got up to a ++ by the end of an hour. There is something unsatisfactory about trying to classify this level. I had said that I was willing to increase the dose to a higher level, to break out of this not-quite-defined level into something psychedelic. But I may not want to go higher. Under different circumstances I would not mind trying it at a considerably lower dosage, perhaps at the 10 or 15 milligrams. I do not have a comfortable label on this material, yet."

(with 45 mg) "There was a rocket from the half-hour to the one and a half hour, from nothing up to a +++. Somehow the intimacy and the erotic never quite knit, and I feel that I am always waiting for the experience to come home. Talking is extremely easy, but something is missing. Appetite is good. I am down by the fifth hour, and sleep is comfortable. This compound will take some learning."

(with 75 mg) "This is a +++, but the emphasis is on talking, not on personal interacting. I am putting out, but my boundaries are intact. I was able to sleep at the sixth hour. Communication was excellent. This is fast on, but not too long lived. Maybe a therapy tool?"

(with 150 mg) "A truly remarkable psychedelic, one which could compare favorably with 2C-B. There are intense colors, and I feel that more would be too much."

EXTENSIONS AND COMMENTARY: Wow! This particular compound is what I call a pharmacological tofu. It doesn't seem to do too much by itself, always

teasing, until you get to heroic levels. But a goodly number of experimental therapists have said that it is excellent in extending the action of some other materials. It seems to boost the waning action of another drug, without adding its own color to the experience. Yet, the comment above, on the high level of 150 milligrams, is a direct quote from the use of this compound in Germany (where it is called LE-25) in therapeutic research.

This is probably the most dramatic example of the loss of potency from an amphetamine (DOM, active at maybe 3 milligrams) to a phenethylamine (only one tenth as active). It is so often the case that the first of a series is not the most interesting nor the most potent member. As intriguing and as difficult-to-define as the 2C-D story might be, the next higher homologue of this set, 2C-E, is maximally active at the 15 to 20 milligram level, and is, without any question, a complete psychedelic.

The N-monomethyl and the N,N-dimethyl homologues of 2C-D have been synthesized from 2C-D. The N-monomethyl compound was obtained by the quaternization of the Schiff's base formed between 2C-D and benzaldehyde with methyl sulfate, followed by hydrolysis; the hydrochloride salt had a melting point of 150-151 °C, from EtOH. The N,N-dimethyl compound resulted from the action of formaldehyde-formic acid on 2C-D; the hydrochloride salt had a melting point of 168-169 °C from EtOH/ether. These two compounds were some ten times less effective in interfering with conditioned responses in experimental rats. There is no report of their having been explored in man.

I have learned of an extensive study of ethoxy homologues of a number of the phenethylamines in the 2C-X series; they have been collectively called the "Tweetios." This Sylvester and Tweety-bird allusion came directly from the compulsive habit of trying to alleviate the boredom of driving long distances (not under the influence of anything) by the attempt to pronounce the license plates of cars as they passed. The first of this series of compounds had a name that indicated that there was an ethoxy group at the 2-position, or 2-EtO, or Tweetio, and the rest is history. In every compound to be found in the 2C-X family, there are two methoxy groups, one at the 2-position and one at the 5-position. There are thus three possible tweetio compounds, a 2-EtO-, a 5-EtO- and a 2,5-di-EtO-. Those that have been evaluated in man are included after each of the 2C-X's that has served as the prototype. In general, the 2-EtO- compounds have a shorter duration and a lower potency, the 5-EtO- compounds have a relatively unchanged potency and a longer time duration; the 2,5-di-EtO- homologues are very weak, if active at all.

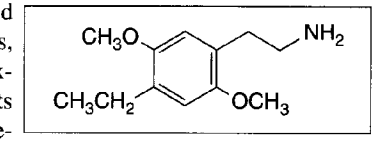
The 2-EtO-homologue of 2C-D is 2-ethoxy-5-methoxy-4-methylphenethylamine, or 2CD-2ETO. The benzaldehyde (2-ethoxy-5-methoxy-4-tolualdehyde) had a melting point of 60.5-61 °C, the nitrostyrene intermediate a melting point of 110.5-111.5 °C, and the final hydrochloride a melting point of 207-208 °C. The hydrobromide salt had a melting point of 171-173 °C. At levels of 60 milligrams, there was the feeling of closeness between couples, without an appreciable state of intoxication. The duration was about 4 hours.

The 5-EtO- homologue of 2C-D is 5-ethoxy-2-methoxy-4-methylphenethylamine, or 2CD-5ETO. The benzaldehyde (5-ethoxy-2-ethoxy-4-tolualdehyde) had a melting point of 81-82 °C, and the details of this synthesis are given in the recipe for IRIS. The nitrostyrene intermediate had a melting point of 112.5-113.5 °C and the final hydrochloride salt had a melting point of 197-198 °C. The hydrobromide salt had a melting point of 158-159 °C. At dosage levels of 40 to 50 milligrams, there was a slow, gradual climb to the full effects that were noted in about 2 hours. The experience was largely free from excitement, but with a friendly openness and outgoingness that allowed easy talk, interaction, humor, and a healthy appetite. The duration of effects was 12 hours.

The 2,5-di-EtO- homologue of 2C-D is 2,5-diethoxy-4-methylphenethylamine, or 2CD-2,5-DIETO. The benzaldehyde (2,5-diethoxy-4-tolualdehyde) had a melting point of 102-103 °C, the nitrostyrene intermediate a melting point of 108-109 °C, and the final hydrochloride salt a melting point of 251-252 °C. At a level of 55 milligrams, a plus one was reached, and what effects there were, were gone after four hours.

#24 2C-E; 2,5-DIMETHOXY-4-ETHYLPHENETHYLAMINE

SYNTHESIS: A suspension of 140 g anhydrous $AlCl_3$ in 400 mL CH_2Cl_2 was treated with 100 g acetyl chloride. This slurry was added to a vigorously stirred solution of 110 g p-dimethoxybenzene in 300 mL CH_2Cl_2. Stirring was continued at ambient temperature for an additional 40 min, then all was poured into 1 L water and the phases separated. The aqueous phase was extracted with 2x100 mL CH_2Cl_2 and the combined organic phases washed with 3x150 mL 5% NaOH. These washes, after combination and acidification, were extracted with 3x75 mL CH_2Cl_2 and the extracts washed once with saturated $NaHCO_3$. Removal of the solvent under vacuum provided 28.3 g of 2-hydroxy-5-methoxyacetophenone as yellow crystals which, on recrystallization from 2 volumes of boiling MeOH and air drying, provided 21.3 g of product with a mp of 49-49.5 °C. Ethylation of this material serves as the starting point for the synthesis of 2CE-5ETO. The CH_2Cl_2 fraction from the base wash, above, was stripped of solvent on the rotary evaporator to give a residual oil that, on distillation at 147-150 °C at the water pump, provided 111.6 g of 2,5-dimethoxyacetophenone as an almost white oil.



In a round bottom flask equipped with a reflux condenser, a take-off adapter, an immersion thermometer, and a magnetic stirrer, there was placed 100 g 2,5-dimethoxyacetophenone, 71 g 85% KOH pellets, 500 mL of triethylene glycol, and 125 mL 65% hydrazine. The mixture was brought up to a boil by heating with an electric mantle, and the distillate was removed, allowing the temperature of the pot contents to continuously increase. When the pot temperature had reached 210

°C, reflux was established and maintained for an additional 3 h. After cooling, the reaction mixture and the distillate were combined, poured into 3 L water, and extracted with 3x100 mL hexane. After washing the pooled extracts with water, the solvent was removed yielding 22.0 g of a pale straw-colored liquid that was free of both hydroxy and carbonyl groups by infrared. This was distilled at 120-140 °C at the water pump to give 2,5-dimethoxy-1-ethylbenzene as a white fluid product. Acidification of the spent aqueous phase with concentrated HCl produced a heavy black oil which was extracted with 3x100 mL CH_2Cl_2. Removal of the solvent on the rotary evaporator yielded 78 g.of a black residue that was distilled at 90-105 °C at 0.5 mm/Hg to provide 67.4 g of an orange-amber oil that was largely 2-ethyl-4-methoxyphenol. This material could eventually be used as a starting material for ethoxy homologues. However, remethylation (with CH_3I and KOH in methanol) provided some 28 g additional 2,5-dimethoxyethylbenzene.

A solution of 8.16 g of 2,5-dimethoxy-1-ethylbenzene in 30 mL CH_2Cl_2 was cooled to 0 °C with good stirring and under an inert atmosphere of He. There was then added 11.7 mL anhydrous stannic chloride, followed by 3.95 mL dichloromethyl methyl ether dropwise over the course of 0.5 h. The stirred reaction mixture was allowed to come up to room temperature, then held on the steam bath for 1 h. The reaction mixture was poured into 1 L water, extracted with 3x75 mL CH_2Cl_2, and the pooled extracts washed with dilute HCl. The organic phase was stripped under vacuum yielding 10.8 g of a dark viscous oil. This was distilled at 90-110 °C at 0.2 mm/Hg to yield a colorless oil that, on cooling, set to white crystals. The yield of 2,5-dimethoxy-4-ethylbenzaldehyde was 5.9 g of material that had a mp of 46-47 °C. After purification through the bisulfite complex, the mp increased to 47-48 °C. The use of the Vilsmeier aldehyde synthesis (with $POCl_3$ and N-methylformanilide) gave results that were totally unpredictable. The malononitrile derivative (from 0.3 g of this aldehyde and 0.3 g malononitrile in 5 mL EtOH and a drop of triethylamine) formed red crystals which, on recrystallization from toluene, had a mp of 123-124 °C.

A solution of 21.0 g of the unrecrystallized 2,5-dimethoxy-4-ethylbenzaldehyde in 75 g nitromethane was treated with 4 g of anhydrous ammonium acetate and heated on the steam bath for about 2 h. The progress of the reaction was best followed by TLC analysis of the crude reaction mixture on silica gel plates with CH_2Cl_2 as the developing solvent. The excess solvent/reagent was removed under vacuum yielding granular orange solids that were recrystallized from seven volumes of boiling MeOH. After cooling in external ice-water for 1 h, the yellow crystalline product was removed by filtration, washed with cold MeOH and air dried to give 13.4 g of 2,5-dimethoxy-4-ethyl-ß-nitrostyrene. The mp was 96-98 °C which improved to 99-100 °C after a second recrystallization from MeOH.

A total of 120 mL of 1.0 M solution of LAH in THF (120 mL of 1.0 M) was transferred to a 3 neck 500 mL flask, under an inert atmosphere with good magnetic stirring. This solution was cooled to 0 °C with an external ice-water bath, and there was then added 3.0 mL of 100% H_2SO_4 over the course of 0.5 h. This was followed

by a solution of 5.85 g of 2,5-dimethoxy-4-ethyl-ß-nitrostyrene, in 40 mL of warm THF. The reaction mixture was stirred for 0.5 h, brought to room temperature, heated on the steam bath for 0.5 h, and then returned to room temperature. The addition of IPA dropwise destroyed the excess hydride, and some 4.5 mL of 5% NaOH produce a white cottage cheese, in a basic organic medium. This mixture was filtered, washed with THF, and the filtrate evaporated to produce 2.8 g of an almost white oil. The filter cake was resuspended in THF, made more basic with additional 15 mL of 5% NaOH, again filtered, and the filtrate removed to provide an additional 2.8 g of crude product. These residues were combined and distilled at 90-100 °C at 0.25 mm/Hg to give a colorless oil. This was dissolved in 30 mL IPA, neutralized with concentrated HCl, and diluted with 50 mL anhydrous Et_2O to provide, after spontaneous crystallization, filtration, washing with Et_2O, and air drying, 3.87 g of 2,5-dimethoxy-4-ethylphenethylamine hydrochloride (2C-E) as magnificent white crystals. A similar yield can be obtained from the reduction of the nitrostyrene in a suspension of LAH in THF, without the use of H_2SO_4. With 11.3 g of LAH in 300 mL dry THF, there was added, dropwise, a solution of 13.4 g of 2,5-dimethoxy-4-ethyl-ß-nitrostyrene in 75 mL THF over the course of 2 h. The mixture was kept at reflux for an additional 8 h, and killed by the careful addition of 11 mL H_2O, followed with 11 mL 15% NaOH, and finally another 33 mL of H_2O. This mass was filtered, washed with THF, and the combined filtrates and washes evaporated to a residue under vacuum The approximately 15 mL of residue was dissolved in 300 mL CH_2Cl_2 and treated with 200 mL H_2O containing 20 mL concentrated HCl. On shaking the mixture, there was deposited a mass of the hydrochloride salt which was diluted with a quantity of additional H_2O. The organic phase was extracted with additional dilute HCL, and these aqueous phases were combined. After being made basic with 25% NaOH, this phase was again extracted with 3x75 mL CH_2Cl_2 and after the removal of the solvent, yielded 12.6 g of a colorless oil. This was dissolved in 75 mL of IPA and neutralized with concentrated HCl. The solidified mass that formed was loosened with another 50 mL IPA, and then filtered. After Et_2O washing and air drying there was obtained 7.7 g of 2,5-dimethoxy-4-ethylphenethylamine hydrochloride (2C-E) as lustrous white crystals. Anal. ($C_{12}H_{20}ClNO_2$) C,H.

DOSAGE: 10 - 25 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 16 mg) "There was a strange devil-angel pairing. As I was being told of the ecstatic white-light ascent of my partner into the God-space of an out-of-body experience, I was fighting my way out of a brown ooze. She saw the young Jesus at the bottom of a ladder drifting upwards step by step to some taking-off place, and I saw all the funny gargoyles around the base of the ladder surrounded by picnic bunting. For me it was the 4th of July, rather than Easter!"

(with 20 mg) "The view out of the window was unreal. The garden was painted on the window, and every petal of flower and tuft of grass and leaf of tree was carefully sculptured in fine strokes of oil paint on the surface of the glass. It was not out there; it was right here in front of me. The woman who was watering the plants was completely frozen, immobilized by Vermeer. And when I looked again, she was in a different place, but again frozen. I was destined to become the eternal museum viewer."

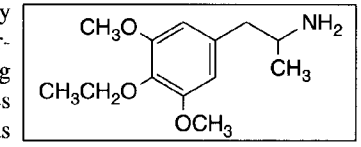
(with 25 mg) "I have a picture in my living room that is a stylized German scene with a man on horseback riding through the woods, and a young girl coming out to meet him from the nearby trees. But she was not just 'coming out.' He was not just riding through the woods. The wind was blowing, and his horse was at full gallop, and his cape was flapping in the storm, and she was bearing down upon him at full bore. The action never ceased. I became exhausted."

(with 25 mg) "Within minutes I was anxious and sweaty. Each person has his own brand of toxic psychosis — mine always starts with the voices in my head talking to me, about all my worst fears, a jumble of warnings and deep fears spinning faster. Twenty minutes later this complex chaos passed as quickly as it had come. At lower dosages 2C-E has been a truly enjoyable esthetic enhancer. But it really has a steep dose/response curve."

EXTENSIONS AND COMMENTARY: Here is another of the magical half-dozen. The range is purposefully broad. At 10 milligrams there have been some pretty rich +++ experiences, and yet I have had the report from one young lady of a 30 milligram trial that was very frightening. My first experience with 2C-E was really profound, and it is the substance of a chapter within the story. The amphetamine homologue is DOET, which is not only much longer in action, but considerably more potent. Several people have said, about 2C-E, "I don't think I like it, since it isn't that much fun. But I intend to explore it again." There is something here that will reward the experimenter. Someday, the full character of 2C-E will be understood, but for the moment, let it rest as being a difficult and worth-while material. A very much worth-while material. One Tweetio of 2C-E is known. The 5-EtO-homologue of 2C-E is 5-ethoxy-4-ethyl-2-methoxyphenethylamine, or 2CE-5ETO. The nitrostyrene intermediate had a melting point of 110-110.5 °C, and the final hydrochloride a melting point of 184-185 °C. The effective level of 2CE-5ETO is in the 10 to 15 milligram range. It is gentle, forgiving, and extremely long lived. Some 3 to 4 hours were needed to achieve plateau, and on occasion experiments were interrupted with Valium or Halcion at the 16 hour point. After a night's sleep, there were still some effects evident the next day. Thus, the dose is comparable to the parent compound 2C-E, but the duration is 2 to 3 times longer. It was given the nickname "Eternity" by one subject.

#25 3C-E; 3,5-DIMETHOXY-4-ETHOXYAMPHETAMINE

SYNTHESIS: A solution of 3.6 g syringaldehyde (3,5-dimethoxy-4-hydroxybenzaldehyde) in 50 mL MeOH was combined with a solution of 3.7 g 85% KOH in 75 mL warm MeOH. This clear solution suddenly set up to crystals of the potassium salt, too thick to stir satisfactorily. To this suspension there was added 7.4 g ethyl iodide (a large excess) and the mixture was held at reflux temperature with a heating mantle. The solids eventually loosened and redissolved, giving a clear amber-colored smooth-boiling solution. Refluxing was maintained for 2 days, then all volatiles were removed under vacuum. The residue was dissolved in 400 mL H_2O, made strongly basic with 25% NaOH, and extracted with 4x100 mL CH_2Cl_2. The pooled extracts were washed with saturated brine, and the solvent removed under vacuum to give 3.3 g of a pale amber oil which set up as crystals of 3,5-dimethoxy-4-ethoxybenzaldehyde with a mp of 47-48 °C. A small sample recrystallized from methanol had a mp of 48-49 °C.



A solution of 3.3 g 3,5-dimethoxy-4-ethoxybenzaldehyde in 25 mL nitroethane was treated with 0.5 g anhydrous ammonium acetate and heated on the steam bath for 36 h. The solvent/reagent was removed under vacuum giving a thick yellow-orange oil that was dissolved in two volumes hot MeOH. As this cooled, crystals appeared spontaneously, and after cooling in ice for a short time, these were removed by filtration and washed sparingly with cold MeOH, Air drying to constant weight provided 2.2 g 1-(3,5-dimethoxy-4-ethoxyphenyl)-2-nitropropene with a mp of 84-85 °C. The mother liquors, on standing overnight, deposited large chunks of crystalline material which was isolated by decantation, ground up under a small amount of methanol, then recrystallized from 60% EtOH. A second crop of 0.7 g of the nitrostyrene was thus obtained, as canary-yellow crystals with a mp of 83-85 °C.

A solution of 2.7 g 1-(3,5-dimethoxy-4-ethoxyphenyl)-2-nitropropene in 20 mL anhydrous THF was added to a suspension of 2.0 g LAH in 150 mL warm THF. The mixture was held at reflux for 48 h. After stirring at room temperature for another 48 h, the excess hydride was destroyed by the addition of 2.0 mL H_2O in 10 mL THF, followed by 2.0 mL 15% NaOH and then an additional 6.0 mL H_2O. The inorganic salts were removed by filtration, and the filter cake washed with THF. The combined mother liquor and washings were stripped of solvent under vacuum leaving a yellow oil with some inorganic salts still in it. This was dissolved in 300 mL CH_2Cl_2, washed with dilute NaOH, and extracted with 3x150 mL 1 N HCl. The pooled extracts were washed once with CH_2Cl_2 made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. The combined organics were washed with saturated brine, and the solvent removed under vacuum to yield about 2 mL of a colorless oil. This was dissolved in 10 mL IPA, neutralized with concentrated HCl (10 drops were required), and diluted with 125 mL anhydrous Et_2O. The slight

cloudiness gradually became the formation of fine white crystals. After standing at room temperature for 2 h, these were removed, Et_2O washed, and air dried. There was thus obtained 1.9 g of 3,5-dimethoxy-4-ethoxyamphetamine hydrochloride (3C-E) as brilliant white crystals.

DOSAGE: 30 - 60 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 40 mg) "It developed into a strange and indefinable something. It is unworldly. I am very much in control, but with an undertone of unreality that is a little reminiscent of high doses of LSD. If there were a great deal of sensory input, I might not see it. And if I were in complete sensory quiet I would miss it, too. But just where I am, I can see it. Eerie state of awareness. And by the 8th hour I am sober, with no residue except for some slight teeth clenching, and pretty much disbelieving the whole thing."

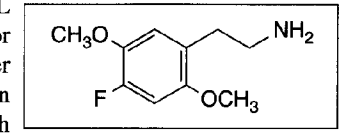
(with 60 mg) "Visuals very strong, insistent. Body discomfort remained very heavy for first hour. Sense of implacable imposition of something toxic for a while. I felt at the mercy of uncomfortable physical effects — faint or pre-nausea, heavy feeling of tremor (although tremor actually relatively light) and general disease, un-ease, non-ease. Kept lying down so as to be as comfortable as possible. Fantasy began to be quite strong. At first, no eyes closed images, and certainly anti-erotic. 2nd hour on, bright colors, distinct shapes — jewel-like — with eyes closed. Suddenly it became clearly not anti-erotic. That was the end of my bad place, and I shot immediately up to a +++. Complex fantasy which takes over — hard to know what is real, what is fantasy. Continual erotic. Image of glass-walled apartment building in mid-desert. Exquisite sensitivity. Down by ? midnight. Next morning, faint flickering lights on looking out windows."

EXTENSIONS AND COMMENTARY: This is an interesting closing of the circle. Although mescaline launched the entire show, the first half could be called the amphetamine period, with variations made on all aspects of the molecule except for that three-carbon chain. And it was found that the 4-substitution position was of paramount importance in both the potency and the quality of action of a compound. Then, looking at the long-ignored chain, lengthening it by the addition of a carbon atom eliminated all psychedelic effects and gave materials with reduced action. The action present was that of an antidepressant. But removing a carbon atom? This returned the search to the world of mescaline, but with the knowledge of the strong influence of the 4-position substituent. The two-carbon side-chain world was rediscovered, principally with 2C-B and 2C-D, and the 4-ethoxy-analogue of mescaline, E. This second half of the show could be called the phenethylamine period. And with compounds such as 3C-E which is, quite simply, Escaline (or E) reextended again to a 3-carbon chain amphetamine, there is a kind of satisfying closure. A fascinating compound, but for most subjects a little too heavy on the body.

#26 2C-F; 2,5-DIMETHOXY-4-FLUOROPHENETHYLAMINE

SYNTHESIS: A solution of 76.6 g 2,5-dimethoxyaniline in 210 mL H_2O containing 205 mL fluoroboric acid was cooled to 0 °C. with an external ice bath. There was then added, slowly, a solution of 35 g sodium nitrite in 70 mL H_2O. After an additional 0.5 h stirring, the precipitated solids were removed by filtration, washed first with cold H_2O, then with MeOH and finally Et_2O. Air drying yielded about 100 g of the fluoroborate salt of the aniline as dark purple-brown solids. This salt was pyrolyzed with the cautious application of a flame, with the needed attention paid to both an explosion risk, and the evolution of the very corrosive boron trifluoride. The liquid that accumulated in the receiver was distilled at about 120 °C at 20 mm/Hg, and was subsequently washed with dilute NaOH to remove dissolved boron trifluoride. The product, 2,5-dimethoxyfluorobenzene, was a fluid, straw-colored oil that weighed 7.0 g.

To a vigorously stirred solution of 40.7 g 2,5-dimethoxyfluorobenzene in 215 mL CH_2Cl_2 cooled with an external ice bath, there was added 135 g of anhydrous stannic chloride. There was then added, dropwise, 26 g of dichloromethyl methyl ether at a rate that precluded excessive heating. The reaction mixture was allowed to come to room temperature over the course of 0.5 h, and then quenched by dumping into 500 g shaved ice containing 75 mL concentrated HCl. This mixture was stirred for an additional 1.5 h. The separated organic layer was washed with 2x100 mL dilute HCl, then with dilute NaOH, then with H_2O and finally with saturated brine. Removal of the solvent under vacuum yielded a solid residue that was recrystallized from aqueous EtOH yielding 41.8 g 2,5-dimethoxy-4-fluorobenzaldehyde with a mp of 99-100 °C.



A solution of 2.5 g 2,5-dimethoxy-4-fluorobenzaldehyde in 15 mL acetic acid containing 1 g nitromethane was treated with 0.2 g anhydrous ammonium acetate, and heated on the steam bath for 4 h. After cooling, and following the judicious addition of H_2O, crystals separated, and additional H_2O was added with good stirring until the first signs of oiling out appeared. The solids were removed by filtration, and recrystallized from acetone to give 2.0 g of 2,5-dimethoxy-4-fluoro-ß-nitrostyrene with a mp of 159-162 °C.

To a suspension of 2.0 g LAH in 200 mL cool anhydrous Et_2O under an inert atmosphere, there was added a THF solution of 2.0 g 2,5-dimethoxy-4-fluoro-ß-nitrostyrene. The reaction mixture was stirred at room temperature for 2 h and then heated briefly at reflux. After cooling, the excess hydride was destroyed by the

cautious addition of H_2O, and when the reaction was finally quiet, there was added 2 mL of 15% NaOH, followed by another 6 mL of H_2O. The basic insolubles were removed by filtration, and washed with THF. The combined filtrate and washes were stripped of solvent, yielding a residual oil that was taken up in 10 mL of IPA, neutralized with concentrated HCl, and the generated solids diluted with anhydrous Et_2O. The white crystalline 2,5-dimethoxy-4-fluorophenethylamine hydrochloride (2C-F) was recrystallized from IPA to give an air-dried product of 0.5 g with a mp of 182-185 °C.

DOSAGE: greater than 250 mg.

DURATION: unknown

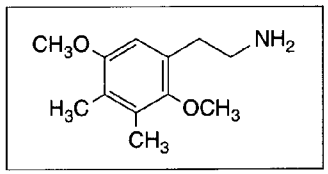
QUALITATIVE COMMENTS: (with 250 mg) "Even at 250 milligrams, the effects were slight and uncertain. There may have been some eyes-closed imagery above normal, but certainly not profound. At several hours there was a pleasant lethargy; sleep was completely normal that night."

EXTENSIONS AND COMMENTARY: A number of graded acute dosages were tried, and it was only with amounts in excess of 100 milligrams that there were any baseline disturbances at all. And at no dose that was tried was there any convincing indication of believable central effects.

The three-carbon amphetamine analogue of 2C-F would quite logically be called DOF (2,5-dimethoxy-4-fluoroamphetamine). It has been prepared by reaction of the above benzaldehyde with nitroethane (giving 1-(2,5-dimethoxy-4-fluorophenyl)-2-nitropropene, with a melting point of 128-129 °C from ethanol) followed by LAH reduction to DOF (the hydrochloride salt has a melting point of 166-167 °C, after recrystallization from ether/ethyl acetate/ethanol). Animal studies that have compared DOF to the highly potent DOI and DOB imply that the human activity will be some four to six times less than these two heavier halide analogues. As of the present time, no human trials of DOF have been made.

#27 2C-G; 2,5-DIMETHOXY-3,4-DIMETHYLPHENETHYLAMINE

SYNTHESIS: To a clear solution of 40.4 g flake KOH in 400 mL warm EtOH there was added 86.5 g 2,3-xylenol followed by 51.4 g methyl iodide. This mixture was held at reflux for 2 days, stripped of volatiles under vacuum, the residues dissolved in 1 L of H_2O, and extracted with 4x200 mL CH_2Cl_2. The pooled extracts were washed with 5% NaOH until the washes remained basic. Following a single washing with dilute HCl, the solvent



was removed under vacuum, and the residue, 41.5 g of a pungent smelling amber oil, spontaneously crystallized. The mp of 2,3-dimethylanisole was 25-26 °C and it was used without further purification in the next step. From the aqueous basic washes, following acidification, extraction, and solvent removal, there was obtained 46.5 g crude unreacted xylenol which could be recycled.

A mixture of 205 g $POCl_3$ and 228 g N-methylformanilide was allowed to incubate at room temperature until there was the development of a deep claret color with some spontaneous heating. To this, there was added 70.8 g 2,3-dimethylanisole, and the dark reaction mixture heated on the steam bath for 2.5 h. The product was then poured into 1.7 L H_2O, and stirred until there was a spontaneous crystallization. These solids were removed by filtration, H_2O washed and air dried to give 77.7 g of crude benzaldehyde as brown crystals. This was distilled at 70-90 °C at 0.4 mm/Hg to give 64.8 g of 2,3-dimethyl-4-methoxybenzaldehyde as a white crystalline product with a mp of 51-52 °C. Recrystallization from MeOH produced an analytical sample with a mp of 55-55.5 °C. Anal. ($C_{10}H_{12}O_2$) C,H. The malononitrile derivative (from the aldehyde and malononitrile in EtOH with a drop of triethylamine) had a mp of 133-133.5 °C from EtOH. Anal. ($C_{13}H_{12}N_2O$) C,H,N. Recently, this aldehyde has become commercially available.

A solution of 32.4 g 2,3-dimethyl-4-methoxybenzaldehyde in 800 mL CH_2Cl_2 was treated with 58.6 g 85% m-chloroperoxybenzoic acid and held at reflux for 3 days. After cooling to room temperature, the white solids (m-chlorobenzoic acid) were removed by filtration (about 40 g when dry). The filtrate was extracted with several portions of saturated $NaHCO_3$ (on acidification, this aqueous wash yielded additional m-chlorobenzoic acid) and the organic solvent removed under vacuum. The crystalline residue (weighing 32 g and deeply colored) was dissolved in 150 mL boiling MeOH to which there was added 18 g of solid NaOH and the solution heated on the steam bath for a few min. The mixture was added to 800 mL H_2O, and a little surface scum mechanically removed with a piece of filter paper. The solution was acidified with concentrated HCl, depositing 30.9 g of a tan solid. Recrystallization from H_2O gave 2,3-dimethyl-4-methoxyphenol as white needles, with a mp of 95-96 °C. Anal. ($C_9H_{12}O_2$) H; C: calcd, 71.06; found 70.20. The N-methyl carbamate was made by the treatment of a solution of the phenol (1 g in 75 mL hexane with 5 mL CH_2Cl_2 added) with 2 g methyl isocyanate and a few drops of triethyl amine. The pale pink solids that separated were recrystallized from MeOH to give a product that had a mp of 141-142 °C. Anal. ($C_{11}H_{15}NO_3$) C,H,N.

To a solution of 23.1 g flake KOH in 250 mL hot EtOH there was added 61.8 g 2,3-dimethyl-4-methoxyphenol followed by 60 g methyl iodide. This was held under reflux for 12 h, then stripped of solvent under vacuum. The residue was dissolved in 1.2 L H_2O, acidified with HCl, and extracted with 3x200 mL CH_2Cl_2. The combined extracts were washed with 3x100 mL 5% NaOH, and the solvent was removed under vacuum. The residue set up as an off-white mass of leaflets weighing 37.7 g after filtering and air drying. Recrystallization from MeOH gave 2,3-dimethyl-1,4-dimethoxybenzene as white solids, with a mp of 78-79 °C. Anal.

($C_{10}H_{14}O_2$) C,H. An alternate route leading from 2,3-xylenol to this diether via nitrogen-containing intermediates was explored. The sequence involved the reaction of 2,3-xylenol with nitrous acid (4-nitroso product, mp 184 °C dec.), reduction with sodium dithionite (4-amino product, mp about 175 °C), oxidation with nitric acid (benzoquinone, mp 58 °C), reduction with sodium dithionite (hydroquinone) and final methylation with methyl iodide. The yields were inferior with this process.

A mixture of 88 g $POCl_3$ and 99 g N-methylformanilide was allowed to incubate until a deep claret color had formed, then it was treated with 36.5 g 2,3-dimethyl-1,4-dimethoxybenzene and heated on the steam bath for 3 h. It was then poured into 1 L H_2O, and stirred until the formation of a loose, crumbly, dark crystalline mass was complete. This was removed by filtration, and dissolved in 300 mL CH_2Cl_2. After washing first with H_2O, then with 5% NaOH, and finally with dilute HCl, the solvent was removed under vacuum yielding 39.5 g of a black oil that solidified. This was extracted with 2x300 mL boiling hexane, the extracts were pooled, and the solvent removed under vacuum. The yellowish residue crystallized to give 32.7 g 2,5-dimethoxy-3,4-dimethylbenzaldehyde with a mp of 46-47 °C. Repeated recrystallization from MeOH raised the mp to 59-60 °C. The malononitrile derivative was prepared (aldehyde and malononitrile in EtOH with a few drops triethyl amine) as yellow crystals from EtOH, with a mp of 190-191 °C. Anal. ($C_{14}H_{14}N_2O_2$) C,H; N: calcd, 11.56; found, 11.06, 11.04.

To a solution of 16.3 g 2,5-dimethoxy-3,4-dimethylbenzaldehyde in 50 mL nitromethane there was added 3.0 g anhydrous ammonium acetate, and the mixture was heated on the steam bath overnight. There was then added an equal volume of MeOH, and with cooling there was obtained a fine crop of yellow crystals. These were removed by filtration, washed with MeOH, and air dried to provide 4.4 g of 2,5-dimethoxy-3,4-dimethyl-ß-nitrostyrene with a mp of 120-121 °C which was not improved by recrystallization from MeOH (50 mL/g). The mother liquors of the above filtration were diluted with H_2O to the point of permanent turbidity, then set aside in a cold box. There was a chunky, granular, tomato-red crystal deposited which weighed 2.5 g when dry. It had a mp of 118-119.5 °C, which was undepressed in mixed mp with the yellow sample. Both forms had identical NMR spectra (2.20, 2.25 CH_3; 3.72, 3.84 OCH_3; 6.80 ArH; 7.76, 8.28 CH=CH, with 14 cycle splitting), infrared spectra, ultra violet spectra (max. 324 nm with shoulder at 366 nm in EtOH, two peaks at 309 and 355 nm in hexane), and microanalyses. Anal. ($C_{12}H_{15}NO_4$) C,H,N.

A solution of LAH (56 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.52 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 3.63 g 2,5-dimethoxy-3,4-dimethyl-ß-nitrostyrene in 36 mL anhydrous THF over the course of 1 h. After a few minutes further stirring, the temperature was brought up to a gentle reflux on the steam bath for about 5 min, then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 9 mL IPA followed by 2.5 mL 15% NaOH and finally 7.5 mL H_2O. The reaction mixture was filtered, and the filter cake washed first with THF and then with IPA. The filtrate was stripped of solvent under vacuum and the residue was distilled at 110-120 °C at 0.2 mm/Hg to give 2.07 g of 2,5-dimethoxy-3,4-dimethylphenethylamine as a clear white oil. This was dissolved in 10 mL IPA, neutralized with concentrated HCl, and then diluted with 25 mL anhydrous Et_2O. The crystals that formed were filtered, Et_2O washed, and air dried to constant weight. There was obtained 2.13 g of beautiful white crystals of 2,5-dimethoxy-3,4-dimethylphenethylamine hydrochloride (2C-G) with a mp of 232-233 °C. Anal. ($C_{12}H_{20}ClNO_2$) C,H.

DOSAGE: 20 - 35 mg.

DURATION: 18 - 30 h.

QUALITATIVE COMMENTS: (with 22 mg) "I am completely functional, with writing and answering the telephone, but the coffee really tastes most strange. While the mental effects (to a ++ only) were dispersing, the body still had quite a bit of memory of the day. Sleep was fine, and desirable, in the early evening."

(with 32 mg) "Superb material, to be classified as a 'true psychedelic' unless one is publishing, in which case it could be best described as an 'insight-enhancer' and obviously of potential value in psychotherapy (if one would wish to spend 30 hours in a therapy session!). I suppose it would be best to simply stick with the insight-enhancing and skip the psychotherapy. Just too, too long. There was not any particular visual impact, at least for me. The non-sexual and the anorexic aspects might indeed change, with increasing familiarity. Remains to be seen. The length of the experience is against its frequent use, of course, which is a pity, since this one is well worth investigating as often as possible."

(with 32 mg) "There was, at the very beginning, a certain feeling of non-physical heat in the upper back which reminded me of the onset of various indoles, which this ain't. The energy tremor was quite strong throughout, but somehow the body was generally at ease."

(with 32 mg) "At a plateau at two hours, with just a bit of tummy queasiness. And I am still at the plateau several hours later. Sleep finally at the 18th hour, but even after getting up and doing all kinds of things the next day, I was not completely baseline until that evening. And a couple of days more for what is certainly complete repair. That is a lot of mileage for a small amount of material."

EXTENSIONS AND COMMENTARY: Here is the first example, ever, of a phenethylamine that is of about the same potency as therelated three-carbon amphetamine. At first approximation, one is hard put to distinguish, from the recorded notes, any major differences either in potency, in duration, or in the nature of activity, between 2C-G and GANESHA itself.

I had always thought of the phenethylamines as being somewhat weaker

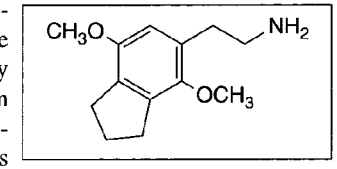
than the corresponding amphetamines. Sometimes a little weaker and sometimes a lot weaker. But that is a totally prejudiced point of view, an outgrowth of my earliest comparisons of mescaline and TMA. That's the kind of thing that can color one's thinking and obscure what may be valuable observations. It is equally valid to think of the phenethylamines as the prototypes, and that the amphetamines are somewhat stronger than the corresponding phenethylamines. Sometimes a little stronger and sometimes a lot stronger. Then the question suddenly shifts from asking what is different about the phenethylamines, to what is different about the amphetamines? It is simply a historic fact, that in most of my exploring, the amphetamine was made and evaluated first, and so tended to slip into the role of the prototype. In any case, here the two potencies converge.

#28 2C-G-3; 2,5-DIMETHOXY-3,4-(TRIMETHYLENE)-PHENETHYLAMINE; 5-(2-AMINOETHYL)-4,7-DIMETHOXYINDANE)

SYNTHESIS: To a solution of 22 g of KOH in 250 mL of hot EtOH, there was added 50 g of 4-indanol and 75 g methyl iodide. The mixture was held at reflux for 12 h. There was then added an additional 22 g KOH followed by an additional 50 g of methyl iodide. Refluxing was continued for an additional 12 h. The mixture was poured into 1 L H_2O, acidified with HCl, and extracted with 3x75 mL CH_2Cl_2. The pooled extracts were washed with 5% NaOH, then with dilute HCl, and the solvent was removed under vacuum. The residue of crude 2,3-(trimethylene)anisole weighed 56.5 g and was used without further purification in the following reaction.

A mixture of 327 g N-methylformanilide and 295 g $POCl_3$ was allowed to incubate until a deep claret color had formed. To this there was then added 110 g of crude 2,3-(trimethylene)anisole, and the mixture heated on the steam bath. There was a vigorous evolution of gases, which largely quieted down after some 4 h of heating. The reaction mixture was added to 4 L H_2O and stirred overnight. The oily aqueous phase was extracted with 3x200 mL CH_2Cl_2, and after combining the extracts and removal of the solvent there was obtained 147 g of a black, sweet-smelling oil. This was distilled at 182-194 °C at the water pump to yield 109.1 g of a pale yellow oil. At low temperature, this crystallized, but the solids melted again at room temperature. Gas chromatography of this product on OV-17 at 185 °C showed detectable starting anisole and N-methylformanilide (combined, perhaps 5% of the product) and a small but real isomeric peak, (about 5%, slightly faster moving than the title aldehyde, again about 5% of the product) of what was tentatively identified as the ortho-aldehyde (2-methoxy-3,4-(trimethylene)-benzaldehyde). The bulk of this crude product (74 g) was redistilled at 110-130 °C at 0.3 mm/Hg to give 66 g of 4-methoxy-2,3-(trimethylene)benzaldehyde as a nearly colorless oil which set up as a crystalline solid. A portion on porous plate showed a mp of 28-29 C. A gram of this aldehyde and a gram of malononitrile in 25 mL of

EtOH was treated with a few drops of triethylamine and gave pale yellow crystals of the malononitrile derivative. This, upon recrystallization from 50 mL boiling EtOH, had a mp of 176-176.5 °C. Anal. ($C_{14}H_{12}N_2O$) C,H,N. A side path, other than towards the intended targets 2C-G-3 and G-3, was explored. Reaction with nitroethane and anhydrous ammonium acetate gave the 2-nitropropene analogue which was obtained in a pure state (mp 74-75 °C from MeOH) only after repeated extraction of the crude isolate with boiling hexane. Reduction with elemental iron gave the phenylacetone analogue which was reductively aminated with dimethylamine and sodium cyanoborohydride to give N,N-dimethyl-4-methoxy-2,3-(trimethylene)amphetamine. This was designed for brain blood-flow volume studies after iodination at the 5-position, a concept that has been discussed under IDNNA. It has never been tasted by anyone. The corresponding primary amine, 4-methoxy-2,3-(trimethylene)amphetamine has not yet even been synthesized.



A solution of 34.8 g 4-methoxy-2,3-(trimethylene)benzaldehyde in 800 mL CH_2Cl_2 was treated with 58.6 g of 85% m-chloroperoxybenzoic acid and held at reflux for 3 days. After cooling and standing for a few days, the solids were removed by filtration and washed sparingly with CH_2Cl_2. The combined filtrate and washings were washed with 200 mL saturated $NaHCO_3$, and the solvent removed, yielding 43.5 g of a deeply colored oil. This was dissolved in 150 mL MeOH to which was added 9 g NaOH and all heated to reflux on the steam bath. After 1 h, a solution of 9 g NaOH in 20 mL H_2O was added, heated further, then followed by yet another treatment with 9 g NaOH in 20 mL H_2O followed by additional heating. All was added to 800 mL H_2O, washed once with CH_2Cl_2 (which removed a trivial amount of material) and then acidified with HCl. The dark crystals that were generated were filtered and air dried to constant weight, yielding 27.5 g dark but nice-looking crystals with a mp of 89-91 °C. By all counts, this should have been the product phenol, 4-methoxy-2,3-(trimethylene)phenol, but the microanalysis indicated that the formate ester was still there. Anal. ($C_{10}H_{12}O_2$) requires C = 73.08, H = 7.37. ($C_{11}H_{12}O_3$) requires C = 68.73, H = 6.29. Found: C = 69.04, 68.84; H = 6.64, 6.58. Whatever the exact chemical status of the phenolic hydroxyl group might have been, it reacted successfully in the following methylation step.

To a solution of 10 g KOH in 100 g EtOH (containing 5% IPA) there was added 27.5 g of the above 89-91 °C melting material, followed by 25 g methyl iodide. The mixture was held at reflux overnight. All was added to 800 mL H_2O, acidified with HCl, and extracted with 3x100 mL CH_2Cl_2. The combined extracts were washed with 3x100 mL 5% NaOH, then once with dilute HCl, and the solvent removed under vacuum yielding 20.4 g of a fragrant crystalline residue. This was recrystallized from 60 mL boiling MeOH to give, after filtering and air drying, 16.0 g of 1,4-dimethoxy-2,3-(trimethylene)benzene (4,7-dimethoxyindane) with a mp of 86-88 °C. Anal. ($C_{11}H_{14}O_2$) C,H.

To a mixture of 39.0 g of N-methylformanilide and 35.9 g $POCl_3$ that had been allowed to stand at ambient temperature until deeply claret (about 45 min) there was added 15.8 g of 1,4-dimethoxy-2,3-(trimethylene)benzene. The mixture was heated on the steam bath for 4 h and then poured into 600 mL H_2O. After stirring overnight there was produced a heavy crystalline mass. This was removed by filtration and, after air drying, was extracted with 3x100 mL boiling hexane. Pooling and cooling these extracts yielded 9.7 g of salmon-colored crystals with a mp of 67-68 °C. This was recrystallized from 25 mL boiling EtOH to give, after filtration, EtOH washing, and air drying to constant weight, 7.4 g of 2,5-dimethoxy-3,4-(trimethylene)benzaldehyde, with a mp of 71-72 °C. The mother liquors on cautious treatment with H_2O, yielded, after EtOH recrystallization, 1 g additional product. Anal. ($C_{12}H_{14}O_3$) C,H. A solution of 150 mg aldehyde and an equal weight of malononitrile in 2.3 mL EtOH treated with 3 drops triethylamine gave immediate yellow crystals of the malononitrile derivative, with a mp of 161-162 °C. Anal. ($C_{15}H_{14}N_2O_2$) C,H,N.

A solution 3.7 g 2,5-dimethoxy-3,4-(trimethylene)benzaldehyde in 15 g nitromethane was treated with 0.7 g anhydrous ammonium acetate and heated on the steam bath for 14 h. The volatiles were removed under vacuum, and the residue set up to 3.5 g dark crystals, which melted broadly between 126-138 °C. Recrystallization of the entire mass from 70 mL boiling EtOH gave 3.2 g burnished gold crystals with a mp of 129-137 °C. A further recrystallization of an analytical sample from MeOH gave 2,5-dimethoxy-3,4-(trimethylene)-ß-nitrostyrene as yellow crystals with a mp of 146-147 °C. Anal. ($C_{13}H_{15}NO_4$) C,H.

To a cold solution of LAH in THF (40 mL of a 1 M solution) well stirred and under an inert atmosphere, there was added dropwise 1.05 mL freshly prepared 100% H_2SO_4. There was then added, dropwise, a solution of 2.39 g 2,5-dimethoxy-3,4-(trimethylene)-ß-nitrostyrene in 25 mL THF. The bright yellow color was discharged immediately. After the addition was complete, stirring was continued for an additional 20 min, and the reaction mixture brought to a reflux on the steam bath for another 0.5 h. After cooling, the excess hydride was destroyed with IPA (8 mL required) followed by sufficient 15% NaOH to convert the inorganics into a loose, filterable mass. This was removed by filtration, and the filter cake washed with THF. The combined filtrate and washes were stripped of solvent under vacuum, and the residue dissolved in dilute H_2SO_4. After washing with CH_2Cl_2, the aqueous phase was made basic with 25% NaOH and extracted with 3x75 mL CH_2Cl_2. After removal of the solvent under vacuum, the residue was distilled at 125-160 °C at 0.45 mm/Hg to yield 0.80 g of a white oil. This was dissolved in 8 mL IPA, neutralized with 20 drops of concentrated HCl (the salt crystals started to form before this was completed) followed with the addition of 65 mL anhydrous Et_2O. The white crystalline mass was filtered, washed with Et_2O, and air dried to provide 1.16 g of 2,5-dimethoxy-3,4-(trimethylene)phenethylamine hydrochloride (2C-G-3) with a mp of 214-216 °C with decomposition. Anal. ($C_{13}H_{20}ClNO_2$) C,H.

DOSAGE: 16 - 25 mg.

DURATION: 12 - 24 h.

QUALITATIVE COMMENTS: (with 16 mg) "It came on in little leaps and bounds. All settled, and then it would take another little jump upwards. I am totally centered, and writing is easy. My appetite is modest. Would I drive to town to return a book to the library? No ever-loving way! I am very content to be right here where I am safe, and stay with the writing. It does take so much time to say what wants to be said, but there is no quick way. A word at a time."

(with 22 mg) "I walked out for the mail at just about twilight. That was the most courageous thing that I could possibly have done, just for one lousy postcard and a journal. What if I had met someone who had wanted to talk? Towards evening I got a call from Peg who said her bean soup was bubbling in a scary way and what should she do, and I said maybe better make soap. It was that kind of an experience! Way up there, lots of LSD-like sparkles, and nothing quite really making sense. Marvelous."

(with 25 mg) "There was easy talking, and no hint of any body concern. Sleep that evening was easy, and the next day was with good energy."

EXTENSIONS AND COMMENTARY: The positives of a completely intriguing altered state free from apparent physical threats, are here coupled with the negative of having to invest such a long period of time. There is a merry nuttiness which can give a joyous intoxication, but with the underlying paranoia of how it looks to others. There is an ease of communication, but only within surroundings that are well-known and friendly. This might be a truly frightening experience if it were in an unfamiliar or unstructured environment.

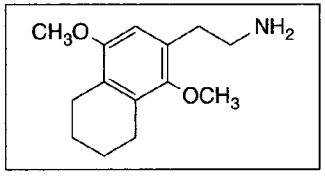
The numbering of this compound, and all the extensions of GANESHA, have been made on the basis of the nature of the stuff at the 3,4-position. Here there are three atoms (the trimethylene bridge) and so 2C-G-3 seems reasonable. With this logic, the dimethylene bridge would be 2C-G-2 (and the corresponding amphetamine would be G-2, of course). But these compounds call upon a common intermediate which is a benzocyclobutene, OK in principle but not yet OK in practice. The right benzyne reaction will be there someday, and the dimethylene analogues will be made and assayed. But, in the meantime, at least the names have been assigned.

#29 2C-G-4; 2,5-DIMETHOXY-3,4-(TETRAMETHYLENE)-PHENETHYLAMINE; 6-(2-AMINOETHYL)-5,8-DIMETHOXY-TETRALIN

SYNTHESIS: To a solution of 49.2 g 5,6,7,8-tetrahydronaphthol (5-hydroxytetralin) in 100 mL MeOH, there was added 56 g methyl iodide followed by a

solution of 24.8 g KOH pellets (85% purity) in 100 mL boiling MeOH. The mixture was heated in a 55 °C bath for 3 h (the first white solids of potassium iodide appeared in about 10 min). The solvent was stripped under vacuum, and the residues dissolved in 2 L H_2O. This was acidified with HCl, and extracted with 4x75 mL CH_2Cl_2. After washing the organic phase with 3x75 mL 5% NaOH, the solvent was removed under vacuum to give 48.2 g of a black residue. This was distilled at 80-100 °C at 0.25 mm/Hg to provide 33.9 g 5-methoxy-1,2,3,4-tetrahydronaphthalene as a white oil. The NaOH washes, upon acidification and extraction with CH_2Cl_2 gave, after removal of the solvent under vacuum and distillation of the residue at 0.35 mm/Hg, 11.4 g of recovered starting phenol.

A mixture of 61.7 g $POCl_3$ and 54.3 g N-methylformanilide was heated on the steam bath for 15 min which produced a deep red color. This was added to 54.3 g of 5-methoxy-1,2,3,4-tetrahydronaphthalene, and the mixture was heated on the steam bath for 2 h. The reaction mixture was quenched in 1.2 L H_2O with very good stirring. The oils generated quickly turned to brown granular solids, which were removed by filtration. The 79 g of wet product was finely triturated under an equal weight of MeOH, filtered, washed with 20 mL ice-cold MeOH, and air dried to yield 32.0 g of 4-methoxy-5,6,7,8-tetrahydronaphthaldehyde as an ivory-colored solid. The filtrate, on standing, deposited another 4.5 g of product which was added to the above first crop. An analytical sample was obtained by recrystallization from EtOH, and had a mp of 57-58 °C. Anal. ($C_{12}H_{14}O_2$) C,H.



To a solution of 25.1 g 4-methoxy-5,6,7,8-tetrahydronaphthaldehyde in 300 mL CH_2Cl_2 there was added 25 g 85% m-chloroperoxybenzoic acid at a rate that was commensurate with the exothermic reaction. Solids were apparent within a few min. The stirred reaction mixture was heated at reflux for 8 h. After cooling to room temperature, the solids were removed by filtration and washed lightly with CH_2Cl_2. The pooled filtrate and washes were stripped of solvent under vacuum and the residue dissolved in 100 mL MeOH and treated with 40 mL 25% NaOH. This was heated on the steam bath for an hour, added to 1 L H_2O, and acidified with HCl, producing a heavy crystalline mass. This was removed by filtration, air dried, and distilled at up to 170 °C at 0.2 mm/Hg. There was thus obtained 21.4 g of 4-methoxy-5,6,7,8-tetrahydronaphthol as an off-white solid with a mp of 107-114 °C. An analytical sample was obtained by recrystallization from 70% EtOH, and melted at 119-120 °C. Hexane is also an excellent recrystallization solvent. Anal. ($C_{11}H_{14}O_2$) C,H. As an alternate method, the oxidation of the naphthaldehyde to the naphthol can be achieved through heating the aldehyde in acetic acid solution containing hydrogen peroxide. The yields using this route are consistently less than 40% of theory.

A solution of 21.0 g of 4-methoxy-5,6,7,8-tetrahydronaphthol in 100 mL acetone in a 1 L round-bottomed flask, was treated with 25 g finely ground

anhydrous K_2CO_3 and 26 g methyl iodide. The mixture was held at reflux on the steam bath for 2 h, cooled, and quenched in 1 L H_2O. Trial extraction evaluations have shown that the starting phenol, as well as the product ether, are extractable into CH_2Cl_2 from aqueous base. The aqueous reaction mixture was extracted with 3x60 mL CH_2Cl_2, the solvent removed under vacuum, and the residue (19.6 g) was distilled at 90-130 °C at 0.3 mm/Hg to give 14.1 g of an oily white solid mixture of starting material and product. This was finely ground under an equal weight of hexane, and the residual crystalline solids removed by filtration. These proved to be quite rich in the desired ether. This was dissolved in a hexane/CH_2Cl_2 mixture (3:1 by volume) and chromatographed on a silica gel preparative column, with the eluent continuously monitored by TLC (with this solvent system, the Rf of the ether product was 0.5, of the starting phenol 0.1). The fractions containing the desired ether were pooled, the solvent removed under vacuum and the residue, which weighed 3.86 g, was dissolved in 1.0 mL hexane and cooled with dry ice. Glistening white crystals were obtained by filtration at low temperature. The weight of 5,8-dimethoxytetralin isolated was 2.40 g and the mp was 44-45 °C. GCMS analysis showed it to be largely one product (m/s 192 parent peak and major peak), but the underivitized starting phenol has abysmal GC properties and TLC remains the best measure of chemical purity.

A well-stirred solution of 3.69 g 5,8-dimethoxytetralin in 35 mL CH_2Cl_2 was placed in an inert atmosphere and cooled to 0 °C with an external ice bath. There was then added, at a slow rate, 4.5 mL anhydrous stannic chloride, which produced a transient color that quickly faded to a residual yellow. There was then added 2.0 mL dichloromethyl methyl ether, which caused immediate darkening. After a few min stirring, the reaction mixture was allowed to come to room temperature, and finally to a gentle reflux on the steam bath. The evolution of HCl was continuous. The reaction was then poured into 200 mL H_2O, the phases separated, and the aqueous phase extracted with 2x50 mL CH_2Cl_2. The organic phase and extracts were pooled, washed with 3x50 mL 5% NaOH, and the solvent removed under vacuum. The residue was distilled at 120-140 °C at 0.3 mm/Hg to give 3.19 g of a white oil that spontaneously crystallized. The crude mp of 1,4-dimethoxy-5,6,7,8-tetrahydro-2-naphthaldehyde was 70-72 °C. An analytical sample from hexane had the mp 74-75 °C. The GCMS analysis showed only a single material (m/s 220, 100%) with no apparent starting dimethoxytetralin present. Attempts to synthesize this aldehyde by the Vilsmeier procedure ($POCl_3$ and N-methylformanilide) gave complex mixtures of products. Synthetic efforts employing butyllithium and DMF gave only recovered starting material.

To a solution of 1.5 g 1,4-dimethoxy-5,6,7,8-tetrahydro-2-naphthaldehyde in 20 g nitromethane there was added 0.14 g anhydrous ammonium acetate and the mixture heated on the steam bath for 50 min. The rate of the reaction was determined by TLC monitoring, on silica gel with CH_2Cl_2 as the moving solvent; the Rf of the aldehyde was 0.70, and of the product nitrostyrene, 0.95. Removal of the volatiles under vacuum gave a residue that spontaneously crystallized. The fine yellow

crystals that were obtained were suspended in 1.0 mL of MeOH, filtered, and air dried to yield 1.67 g 2,5-dimethoxy-ß-nitro-3,4-(tetramethylene)styrene with a mp of 151.5-152.5 °C. Anal. ($C_{14}H_{17}NO_4$) C,H.

DOSAGE: unknown.

DURATION: unknown

EXTENSIONS AND COMMENTARY: The road getting to this final product reminded me of the reasons why, during the first few billion years of the universe following the big bang, there was only hydrogen and helium. Nothing heavier. When everything had expanded enough to cool things sufficiently for the first actual matter to form, all was simply very energetic protons and neutrons. These were banging into one-another, making deuterium nuclei, and some of these got banged up even all the way to helium, but every time a helium nucleus collided with a particle of mass one, to try for something with mass five, the products simply couldn't exist. Both Lithium-5 and Helium-5 have the impossible half-lives of 10 to the minus 21 seconds. Hence, in the primordial soup, the only way to get into something heavier than helium was to have a collision between a couple of the relatively scarcer heavy nuclei, or to have a three body collision. Both of these would be extremely rare events, statistically. And if a few got through, there was another forbidden barrier at mass 8, since Beryllium-8 has a half life of 10 to the minus 16 seconds. So everything had to wait for a few suns to burn down so that they could process enough helium into heavy atoms, to achieve some nuclear chemistry that was not allowed in the early history of the universe.

And in the same way, there were two nearly insurmountable barriers encountered in getting to 2C-G-4 and G-4. The simple act of methylating an aromatic hydroxyl group provided mixtures that could only be resolved into components by some pretty intricate maneuvers. And when that product was indeed gotten, the conversion of it into a simple aromatic aldehyde resisted the classic procedures completely, either giving complex messes, or nothing. And even now, with these two hurdles successfully passed, the presumed simple last step has not yet been done. The product 2C-G-4 lies just one synthetic step (the LAH reduction) away from completion, and the equally fascinating G-4 also that one last reduction step from being completed. Having gotten through the worst of the swamp, let's get into the lab and finish up this challenge. They will both be active compounds.

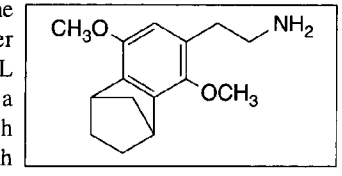
#30 2C-G-5; 3,6-DIMETHOXY-4-(2-AMINOETHYL)-BENZONORBORNANE

SYNTHESIS: To a stirred solution of 25 g 3,6-dihydroxybenzonorbornane (from Eastman Kodak Company) in 200 mL acetone there was added 200 mg decyl-

triethylammonium iodide, 40 g of powdered anhydrous K_2CO_3, and 55 g methyl iodide. The mixture was held at reflux with a heating mantle overnight. After removal of the solvent under vacuum, the residue was added to 2 L of H_2O, acidified with concentrated HCl, and extracted with 3x100 mL CH_2Cl_2. The pooled extracts were washed with 2x150 mL 5% NaOH and once with dilute HCl, and the solvent was removed under vacuum to give 19.0 g of a black oil as a residue. This was distilled at 90-115 °C at 0.3 mm/Hg to yield 15.5 g of an orange oil which set up as a crystalline solid. The product, 3,6-dimethoxybenzonorbornane, had a mp of 35-37 °C from hexane or 40-41 °C from MeOH. Anal. ($C_{13}H_{16}O_2$) C,H.

A solution of 4.6 g $POCl_3$ and 4.6 g N-methylformanilide was heated briefly on the steam-bath until the color had become deep claret. There was then added 3.05 g of 3,6-dimethoxybenzonorbornane and the solution was heated on the steam bath for 12 h. The black, tarry reaction mixture was poured into H_2O, and after hydrolysis, the H_2O was decanted and the insoluble residues were washed alternately with H_2O and with CH_2Cl_2. The combined washes were separated, and the aqueous phase extracted with 2x50 mL CH_2Cl_2. The combined organic fractions were washed with 5% NaOH, and the solvent removed under vacuum. The fluid, black residue was distilled at 130-140 °C at 0.3 mm/Hg to give 1.17 g of an almost white oil. This was dissolved in 1 mL MeOH, and cooled to -50 °C to give a white crystalline solid that was removed by filtration and washed sparingly with -50 °C MeOH and air dried. There was obtained 0.83 g 3,6-dimethoxy-4-formylbenzonorbornane with a mp of 37-40 °C which could be increased, by wasteful recrystallization from MeOH, to 53-54 °C. An intimate mixture of this product with the starting diether (mp 40-41 °C) was a liquid at room temperature. Anal. ($C_{14}H_{16}O_3$) C,H.

To a solution of 3.70 g 3,6-dimethoxy-4-formylbenzonorbornane in 20 g nitromethane, there was added 1.3 g anhydrous ammonium acetate and the mixture was heated on the steam bath for 45 min. The excess reagent/solvent was removed under vacuum, and the residue was dissolved in 20 mL boiling MeOH. A speck of seed crystal started a heavy crystallization of orange crystals which were removed by filtration and washed with MeOH. After drying, the product 3,6-dimethoxy-4-(2-nitrovinyl)benzonorbornane was yellow, weighed 3.47 g, and had a mp of 88-89 °C. Recrystallization of an analytical sample from MeOH did not improve this mp. Anal. ($C_{15}H_{17}NO_4$) C,H.



A solution of LAH (46 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.25 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 3.4 g 3,6-dimethoxy-4-(2-nitrovinyl)benzonorbornane in 30 mL anhydrous THF. After a few min further stirring, the temperature was brought up to a gentle reflux on the steam bath for 10 min, and then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 7 mL IPA, followed by 2 mL 15% NaOH and 5 mL H_2O, which gave an easily filtered white granular solid. This was

removed by filtration, and the filter cake was washed with THF. The combined filtrate and washes were stripped of solvent under vacuum providing a pale amber oil which was distilled at 150-160 °C at 0.3 mm/Hg to give 1.45 g of a white oil. This was dissolved in 7 mL IPA, and neutralized with 15 drops of concentrated HCl. There was then added 25 mL anhydrous Et_2O and, after a short delay, white crystals formed spontaneously. These were removed by filtration, Et_2O washed, and air dried to constant weight, yielding 1.13 g of 3,6-dimethoxy-4-(2-aminoethyl)-benzonorbornane hydrochloride (2C-G-5). The mp was 199-200 °C. Anal. ($C_{15}H_{22}ClNO_2$) C,H.

DOSAGE: 10 - 16 mg.

DURATION: 32 - 48 h.

QUALITATIVE COMMENTS: (with 14 mg) "I was well aware of things at the end of two hours, and I was totally unwilling to drive, or even go out of the house. I was reminded continuously of 2C-B with its erotic push, and the benign interplay of colors and other visual effects. But it is so much longer lived. I am a full +++, very stoned, and there is no believable sign of dropping for another several hours. There is a good appetite (again, 2C-B like), and I managed to sleep for a few hours, and all the next day I was spacey and probably still a plus one. The day yet following, I was finally at a believable baseline. Both of these days were filled with what might be called micro doze-offs, almost like narcolepsy. Maybe I am just sleep deprived."

(with 16 mg) "The first effects were felt within one hour, and full effects between 2 1/2 and 3 hours. Tremendous clarity of thought, cosmic but grounded, as it were. This is not at all like LSD, and is a lot mellower than the 2C-T family. For the next few hours it was delightful and fun and I felt safe and good-humored. I got to sleep without much difficulty while still at a plus three, and my dreams were positive and balanced, but I awoke irritable and emotionally flattened. I did not want to interact with anyone. The first 16 hours of this stuff were great, and the second 16 hours were a bit of a drag. Just twice as long as it ought to be."

(with 16 mg) "I was at full sparkle within three hours, and I continued to sparkle for the longest time. The tiredness that comes after a while probably reflects the inadequacy of sleep. I was aware of something still going on some two days later."

EXTENSIONS AND COMMENTARY: In the eventual potency assessment of a drug, there must be some consideration of not only the dosage needed, but the duration of effects. The area under the curve, so to speak. By these measures, this phenethylamine is a record breaker, in that it is not only amongst the most potent, but it goes on and on and on.

There are a couple of chemical commentaries. One, the miserable phenol-to-ether-to-aldehyde series of steps, so maddeningly unsatisfactory in the 2C-G-4 process, was completely comfortable here. The reactions rolled, and the yields were most satisfactory. Secondly, this is one of the few phenethylamines that is a racemate. The strange geometry of the norbornane ring carries within it a chiral character, so this compound is potentially resolvable into two optically active forms. That might be quite a task, but it would have the value of providing for the first time a pair of isomers that were asymmetric in the 3,4-aliphatic part of the molecule. To the extent that some insight into the geometry of the receptor site can be gleaned from the absolute configurations of active agonists, here is a compound where the subtle variations are over there at the ring substitution area of the structure, rather than at the well-explored alpha-carbon atom. Some day I might try to resolve this drug into its optical isomers. But I suspect that it might be quite difficult.

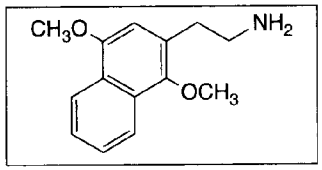
A number of chemical variations of 2C-G-5 are obvious. The dihydroxy-benzonorbornane compound that was the starting point of all this was certainly the adduct of cyclopentadiene and benzoquinone, with the double bond reduced. The same chemistry with 1,3-cyclohexadiene would give a two-carbon bridge instead of the one-carbon bridge of norbornane and, after hydrogenation, would provide a non-chiral analog with two ethylene bridges between the 3- and 4-position carbons. This is a cyclohexane ring connected, by its 1- and 4-positions, to the two methyl groups of 2C-G. With six carbons in this aliphatic mess, the compound is probably best called 2C-G-6. It should be easily made, and it is certain to be very potent. And there are potentially several other Diels Alder dienes that might serve with benzoquinone as the dieneophile. There are aliphatic things such as hexa-2,4-diene and 2,3-dimethylbutadiene. The textbooks are filled with dozens of diene candidates, and benzquinone will always provide the two oxygens needed for the eventual 2,5-dimethoxy groups of the phenethylamine.

#31 2C-G-N; 1,4-DIMETHOXYNAPHTHYL-2-ETHYLAMINE

SYNTHESIS: A solution of 17.5 g 1,4-naphthaquinone in 200 mL MeOH was heated to the boiling point, and treated with 28.5 g stannous chloride at a rate that maintained a continuous rolling boil. At the completion of the addition, the reaction mixture was saturated with anhydrous hydrogen chloride, and held at reflux on the steam bath for 2 h. The reaction mixture was poured into 700 mL H_2O and treated with aqueous NaOH. During the addition there was transient development of a curdy white solid which redissolved when the system became strongly basic. This was extracted with 3x200 mL CH_2Cl_2 and the pooled extracts were washed first with H_2O, then with dilute HCl, and finally again with H_2O. Removal of the solvent under vacuum yielded 15.75 g of a low melting black flaky crystalline material which was distilled at 160-180 °C at 0.05 mm/Hg to give 14.5 g of an amber, solid mass with a mp of 78-86 °C. Recrystallization from 75 mL boiling MeOH provided 1,4-

dimethoxynaphthalene as white crystals melting at 87-88 °C.

A mixture of 20.0 g $POCl_3$ and 22.5 g N-methylformanilide was allowed to stand at room temperature for 0.5 h which produced a deep claret color. To this there was added 9.4 g 1,4-dimethoxynaphthalene and the mixture was heated on the steam bath. The reaction mixture quickly became progressively darker and thicker. After 20 min it was poured into 250 mL H_2O and stirred for several h. The solids were removed by filtration, and washed well with H_2O. The wet crude product (a dull yellow-orange color) was dissolved in 125 mL boiling EtOH to give a deep red solution. On cooling, this deposited a heavy crop of crystals that was removed by filtration, and washed with cold EtOH. There was obtained, after air-drying to constant weight, 7.9 g 1,4-dimethoxy-2-naphthaldehyde as white crystals with a mp of 119-121 °C. This was not improved by further recrystallization. The malononitrile derivative, from the aldehyde and malononitrile in EtOH with a drop of triethylamine, had a mp of 187-188 °C.



A solution of 3.9 g 1,4-dimethoxy-2-naphthaldehyde in 13.5 g nitromethane was treated with 0.7 g anhydrous ammonium acetate, and heated on the steam bath for 1 h. The excess reagent/solvent was removed under vacuum giving a residue that spontaneously crystallized. This crude product was removed with the aid of a few mL MeOH, and pressed on a sintered funnel with modest MeOH washing. There was obtained 3.6 g (when dry) of old-gold colored crystals with a mp of 146-148 °C. Recrystallization from 140 mL boiling EtOH gave 3.0 g 1,4-dimethoxy-2-(2-nitrovinyl)naphthalene as deep gold-colored crystals with a mp of 146-147 °C. A small sample, upon recrystalization from MeOH, melted at 143-144 °C. Anal. ($C_{14}H_{13}NO_4$) C,H.

A solution of LAH (50 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.32 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 2.80 g 1,4-dimethoxy-2-(2-nitrovinyl)naphthalene in 40 mL anhydrous THF. There was an immediate loss of color. After 1 h stirring at 0 °C, the temperature was brought up to a gentle reflux on the steam bath for 20 min, then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 7 mL IPA followed by 5.5 mL 5% NaOH. The reaction mixture was filtered, and the filter cake washed with several portions of THF. The combined filtrate and washings were stripped of solvent under vacuum providing 3.6 g of a pale amber oil that was distilled at 145-160 °C at 0.2 mm/Hg to give 1.25 g of product as an absolutely white oil. This was dissolved in 7 mL IPA, and neutralized with concentrated HCl forming immediate crystals of the hydrochloride salt in the alcohol solvent. Thirty mL of anhydrous Et_2O was added, and after complete grinding and mixing, the hydrochloride salt was removed by filtration, Et_2O washed, and air dried to constant weight. The spectacular white crystals of 1,4-dimethoxynaphthyl-2-ethylamine hydrochloride (2C-G-N) weighed 1.23 g and had melting properties of darkening at 190 °C, and decomposing in the 235-245 °C area. Anal. ($C_{14}H_{18}ClNO_2$) C,H.

DOSAGE: 20 - 40 mg.

DURATION: 20 - 30 h.

QUALITATIVE COMMENTS: (with 24 mg) "The effects were interestingly colored by the reading of Alan Watts' Joyous Cosmology during the coming-on period. The only body negatives were some urinary retention and a feeling of a shallow but continuing amphetamine stimulation. But not enough to be actually jingly, nor to interfere with sleep that evening. There is not much psychedelic here, but there is something really going on anyway. This has some similarities to the antidepressant world."

(with 35 mg) "Much writing, much talking, and there was considerable residual awareness the next day. Somehow this material is not as friendly as the other 2C-G's."

(with 35 mg) "Thinking is clear. No fuzziness, no feeling of being pushed. None of the walking on the fine middle line between light and dark that is the excitement and the threat of LSD. This is just a friend, an ally, which invites you to do anything you wish to." [comment added two days later] "My sleep was not deep enough, but it was pleasant and relatively resting. The whole next day I was feeling happy, but with an overlay of irritability. Strange mixture. By bedtime the irritability had become a mild depression. I feel that there might have been a threshold continuing for a couple of days. The character of my dreaming had the stamp of drug on it. This compound, in retrospect, presents some problems that cause a faint unease."

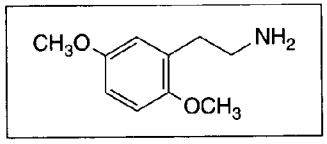
EXTENSIONS AND COMMENTARY: There is always a wish in the design of new compounds to find something that is of interesting activity, with an aromatic ring at some location pretty much away from the site of activity. This would then allow some subtle fine-tuning of the nature of the action by putting any of a wide range of electron pushing or electron pulling groups on that ring. But here, with 2C-G-N, by the time the ring got put into place, the activity was already on the wane, and the action was too long, and there are indicators of some not completely friendly effects. Ah well, some other molecule, some other time.

#32 2C-H; 2,5-DIMETHOXYPHENETHYLAMINE

SYNTHESIS: A solution of 50 g 2,5-dimethoxybenzaldehyde in 100 g nitromethane was treated with 5 g of anhydrous ammonium acetate, and heated on the steam bath for 4 h. The solution was decanted from a little insoluble material, and the solvent

removed under vacuum. The clear oily residue was dissolved in 100 mL boiling IPA which, after standing a moment, set up as dense crystals. After returning to room temperature, these were removed by filtration, the product was washed with IPA and air dried, yielding 56.9 g 2,5-dimethoxy-ß-nitrostyrene as spectacular yum-yum orange crystals with a mp of 119-120 °C. An analytical sample, from ethyl acetate, melted at 120-121 °C.

A suspension of 60 g LAH in 500 mL anhydrous THF was placed under an inert atmosphere, stirred magnetically, and brought up to reflux temperature. There was added, dropwise, 56 g of 2,5-dimethoxy-ß-nitrostyrene dissolved in THF, and the reaction mixture was maintained at reflux for 36 h. After being brought to room temperature, the excess hydride was destroyed with 40 mL IPA, followed by 50 mL of 15% NaOH. An additional 100 mL THF was required for easy stirring, and an additional 150 mL H_2O was needed for complete conversion of the aluminum salts to a loose, white, filterable consistency. This solid was removed by filtration, and the filter cake washed with additional THF. The combined filtrate and washes were stripped of solvent under vacuum, and the residue dissolved in dilute H_2SO_4. Washing with 3x75 mL CH_2Cl_2 removed most of the color, and the aqueous phase was made basic with aqueous NaOH and reextracted with 3x100 mL CH_2Cl_2. Removal of the solvent yielded 39.2 g of a pale amber oil that was distilled. The fraction boiling at 80-100 °C at 0.4 mm/Hg weighed 24.8 g and was water-white product amine. As the free base, it was suitable for most of the further synthetic steps that might be wanted, but in this form it picked up carbon dioxide rapidly when exposed to the air. It was readily converted to the hydrochloride salt by dissolution in 6 volumes of IPA, neutralization with concentrated HCl, and addition of sufficient anhydrous Et_2O to produce a permanent turbidity. Crystals of 2,5-dimethoxyphenethylamine hydrochloride (2C-H) spontaneously formed and were removed by filtration, washed with Et_2O, and air dried. The mp was 138-139 °C.



DOSAGE: unknown.

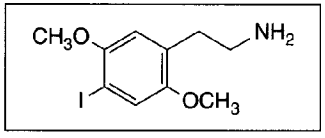
DURATION: unknown.

EXTENSIONS AND COMMENTARY: I know of no record of 2C-H ever having been tried by man. It has been assumed by everyone (and probably correctly so) that this amine, being an excellent substrate for the amino oxidase systems in man, will be completely destroyed by the body as soon as it gets into it, and thus be without action. In virtually all animal assays where it has been compared with known psychoactive drugs, it remains at the "less-active" end of the ranking.

It is, however, one of the most magnificent launching pads for a number of rather unusual and, in a couple of cases, extraordinary drugs. In the lingo of the chemist, it is amenable to "electrophilic attack at the 4-position." And, in the lingo of the psychopharmacologist, the "4-position is where the action is." From this (presumably) inactive thing have evolved end products such as 2C-B, 2C-I, 2C-C, and 2C-N. And in the future, many possible things as might come from a carbinol group, an amine function, or anything that can stem from a lithium atom.

#33 2C-I; 2,5-DIMETHOXY-4-IODOPHENETHYLAMINE

SYNTHESIS: A mixture of 7.4 g phthalic anhydride and 9.05 g of 2,5-dimethoxyphenethylamine (see the recipe for 2C-H for its preparation) was heated with an open flame. A single clear phase was formed with the loss of H_2O. After the hot melt remained quiet for a few moments, it was poured out into a crystallizing dish yielding 14.8 g of a crude solid product. This was recrystallized from 20 mL CH_3CN, with care taken for an endothermic dissolution, and an exothermic crystallization. Both transitions must be done without haste. After filtration, the solids were washed with 2x20 mL hexane and air dried to constant weight. A yield of 12.93 g of N-(2-(2,5-dimethoxyphenyl)ethyl)phthalimide was obtained as electrostatic yellow crystals, with a mp of 109-111 °C. A sample recrystallized from IPA was white, with a mp of 110-111 °C. Anal. ($C_{18}H_{17}NO_4$) C,H,N.



To a solution of 12.9 g N-(2-(2,5-dimethoxyphenyl)ethyl)phthalimide in 130 mL warm (35 °C) acetic acid which was being vigorously stirred, there was added a solution of 10 g iodine monochloride in 40 mL acetic acid. This was stirred for 1 h, while being held at about 30 °C. The reaction mixture was poured into 1500 mL H_2O and extracted with 4x75 mL CH_2Cl_2. The extracts were pooled, washed once with 150 mL H_2O containing 2.0 g sodium dithionite, and the solvent removed under vacuum to give 16.2 g of N-(2-(2,5-dimethoxy-4-iodophenyl)-ethyl)phthalimide as yellow amber solids with a mp of 133-141 °C. This mp was improved by recrystallization from 75 mL CH_3CN, yielding 12.2 g of a pale yellow solid with mp 149-151 °C. A small sample from a large quantity of IPA gives a white product melting at 155.5-157 °C.

A solution of 12.2 g N-(2-(2,5-dimethoxy-4-iodophenyl)ethyl)phthalimide in 150 mL hot IPA was treated with 6.0 mL of hydrazine hydrate, and the clear solution was heated on the steam bath. After a few minutes there was the generation of a white cottage cheese-like solid (1,4-dihydroxyphthalizine). The heating was continued for several additional h, the reaction mixture cooled, and the solids removed by filtration. These were washed with 2x10 mL EtOH, and the pooled filtrate and washes stripped of solvent under vacuum giving a residue which, when treated with aqueous hydrochloric acid, gave 3.43 g of voluminous white crystals. This, after recrystallization from 2 weights of H_2O, filtering, washing first with IPA and then with Et_2O, and air drying, gave 2.16 g 2,5-dimethoxy-4-iodophenethylamine

hydrochloride (2C-I) as a white microcrystalline solid, with a mp of 246-247 °C. Anal. ($C_{10}H_{15}ClINO_2$) C,H,N.

DOSAGE: 14 - 22 mg.

DURATION: 6 - 10 h.

QUALITATIVE COMMENTS (with 0 mg) "I was present at a group meeting, but was only an observer. With zero milligrams of 2C-I, I was able to get to a delightful plus 2.5 in about five minutes after I arrived at your place, and absorbed the ambience of the folks who had actually imbibed the material. My level lasted about four hours and came down at about the same time as did the others. There were no after-effects experienced except for a pleasant languor."

(with 15 mg) "Comfortable onset. Most notable are the visuals, patterning like 2C-B (Persian carpet type), very colorful and active. Much more balanced emotional character, but still no feeling of insight, revelation, or progress toward the true meaning of the universe. And at 5 1/2 hours drop-off very abrupt, then gentle decline. I would like to investigate museum levels."

(with 16 mg) "There was an immediate alert within minutes. As usual, it was only an awareness, then nothing happened for a while. In retrospect, I see some type of activity or awareness within 40 minutes, which then builds up over time. The peak was at 2 hours and seemed to maintain itself for a while. Near the peak, there was some hallucinogenic activity, though not a lot. The pictures in the dining room had color and pattern movement that was fairly detailed. Focusing on other areas, such as walls or the outside of the house, produced little activity, though I tried. There was certainly a lot of color enhancement. There was also that peculiar aspect of the visual field having darkened or shadowed areas. These darker areas seemed to shift around to some degree. That aspect seems to be similar to 2C-B. I don't think I was more than +2.5 at the peak. Coming down was uneventful. I was down within 6 hours. I had no problems driving home, nor were there any difficulties with sleep. There were no body problems with this material. I ate like a horse."

(with 16 mg) "The 16 was a bit much, I realized, because my body was not sure of what to do with all the *energy*. Next time I'll try 14 or 15. However, my conversations were extremely clear and insightful. The degree of honesty was incredible. I was not afraid to say anything to anyone. Felt really good about myself. Very centered, in fact. A bit tired at day's end. Early bedtime."

(with 20 mg) "I think there is slightly less than full immersion in the sensual, with this material, compared with 2C-B, but I suspect it's more a matter of getting used to the language of 2C-I and the feelings — getting tuned to a slightly different frequency, really — rather than that the material is less sensual or less easy to use sensually. Just different frequency, and we are very, very used to 2C-B. Good on the body. Transition, for me, not as strongly dark as 2C-B. But it could certainly take a lot more exploring, if we were able to give the time (about 9 hours) to it. Next day: sleep excellent. Energy next day unusually good. Quite tired by evening."

EXTENSIONS AND COMMENTARY: The frequent comparisons between 2C-I and 2C-B stem, without doubt, from a bit of chemical suggestion. The two compounds have structures that are truly analogous, in technical terms. In one, there is a strategically located iodine atom, and in the other, an identically placed bromine atom. These are directly above and below one-another in the periodic table. And what is particularly maddening to the synthetic diddler, is that they cannot be lengthened, or shortened, or squooshed around in any way. You can't make a longer and narrower version of a bromine atom, as you can do with, say, a butyl group. You've got what you've got, like it or not. No subtle variations.

But, on the brighter side of the picture, you have a heavy atom here, and this atom is intrinsic to the central activity of the compound. So, these materials are naturals for radio-labelling experiments. 2C-I has been made radioactive with radio-iodine, but the most impressive findings have been made with the 3-carbon analog, DOI.

One quotation from an observer of a group experiment is enclosed; an experiment with zero milligrams being taken. This is a instructive observation of what has been called a "contact high."

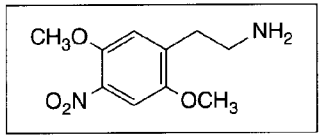
There is one Iodotweetio known. In Scrabble, would you challenge a word that had seven of its eleven letters as vowels? Especially if the vowels were, specifically, iooeeio? It sounds just a little like the noise coming out of Old McDonald's farm. But a Tweetio there is, namely, the 2-EtO-homologue of 2C-I. This is 2-ethoxy-4-iodo-5-methoxyphenethylamine, or 2CI-2ETO. The hydrochloride salt was a white, crystalline product with a melting point of 175-175.5 °C. The threshold level of activity was seen at an oral dose of 5 milligrams, and the generated effects were completely dispersed in a couple of hours. Most interestingly, larger doses, of up to 50 milligrams orally, seem to produce no more intense an effect, but simply to stretch out this threshold for an additional couple of hours. At no level that has been tried, has 2CI-2EtO produced even a plus-two response.

Where else can one go, from 2C-I? The iodine is the fourth, and the last of the so-called halogens, at the bottom of the classical periodic table. But, thanks to the miracles that have accompanied us into the nuclear age, there is a fifth halide now known, Astatine. All of its isotopes are radioactive, however, and it seems unlikely that there will ever be an entry (other than this one) for 2,5-dimethoxy-4-astatophenethylamine. What might be speculated as to its activity? Probably similar in potency to 2C-I, requiring maybe 10 or 20 milligrams. The duration would be dicey to measure, since the isotope with the longest known half-life is half decayed in about 8 hours, and the longest lived natural isotope (for those who insist on natural rather than man-made things) is half decayed in less than a minute. Two predictions would be pretty solid. You might have quite a job accumulating your 10 milligrams of Astatine, as the most that has so far been made at one time is only about 0.05 micrograms, approximately a millionth of the amount needed. And the

second prediction? You would not survive the screaming radiation that would bombard you if you could get the needed 5 or 10 milligrams of radio-astatine onto that magic 4-position, and the resulting 2C-A into your tummy!

#34 2C-N; 2,5-DIMETHOXY-4-NITROPHENETHYLAMINE

SYNTHESIS: A cooled, stirred solution of 1.0 g 2,5-dimethoxyphenethylamine (see the recipe for 2C-H for its preparation) in 20 mL glacial acetic acid was treated with 3.3 mL 70% HNO_3 in small portions, with the reaction temperature kept down with periodic cooling. After the addition was completed, the stirring was continued until there was the spontaneous separation of a yellow solid. This was 2,5-dimethoxy-4-nitrophenethylamine nitrate (2C-N) which was obtained after removal by filtration, washing with Et_2O and air drying, as a fluffy yellow solid. This weighed 1.04 g and melted, with decomposition, in the area of 170-180 °C, depending on the rate of heating. A solution of 0.8 g of this nitrate salt in 50 mL H_2O was made basic with aqueous NaOH. Extraction with 3x50 mL CH_2Cl_2, and removal of the solvent under vacuum gave the free base as a residue. This was distilled at 130-150 °C at 0.35 mm/Hg to give an orange-red oil that weighed 0.5 g and set up as crystals. This was dissolved in 3 mL IPA, neutralized with 7 drops of concentrated HCl (the color lightened considerably at the titration end point) and diluted with 5 mL anhydrous Et_2O. There was the formation of the hydrochloride salt which was a pumpkin-colored crystalline mass. After removal by filtration, Et_2O washing and air drying, these crystals weighed 0.44 g. The mp, 193-195 °C, was not improved by recrystallization from any of several solvents (MeOH, IPA, CH_3CN). The perchlorate salt was a yellow solid from MeOH, with a mp of 211 °C, with decomposition. Nitration of 2C-H in a mixture of acetic acid and acetic anhydride produced the acetamide derivative of 2C-N as yellow crystals with a mp 142.5-143 °C. For the nitrate salt: Anal. ($C_{10}H_{15}N_3O_7$) C,H. This was the form used for all human titrations.



DOSAGE: 100 - 150 mg.

DURATION: 4 - 6 h.

QUALITATIVE COMMENTS: (with 120 mg) "This came on very fast — I was aware of it within a half hour, and it got as far as it would go by an hour. There are similarities to MDMA, but missing is the benign anti-stress component. I am light-headed, and there just might be a little eye wiggling. And then it dropped right off to nothing within a couple of hours."

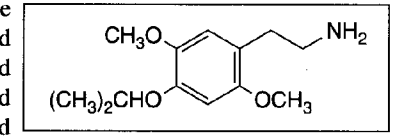
(with 150 mg) "There may have been some visual changes, I'm not sure. But the talking was extremely easy. If there were no other things to use, this would be excellent, but there are other compounds available. This doesn't have too high a priority."

(with 150 mg) "Am I enjoying it? Not exactly, but I am in a good mood. There is not the light-filled energy that some other materials can provide. By six hours, pretty much baseline. Strange material, but okay. Final score: body +3, mind +2, barely."

EXTENSIONS AND COMMENTARY: A most consistent feature with 2C-N was the fact that in every report, somewhere, there is the note that it somehow came up just a little short of expectations. From the esthetic point of view, the pure salt is yellow rather than the usual white color, so the solutions that are to be consumed are by definition also yellow colored. From the structural point of view, the 4-nitro group, like the 4-bromo group of 2C-B, is a dead-end. It cannot be stretched or compressed or lengthened or shortened. This unique aspect demands that you have to live with what you have, as there are no subtle ways of modifying the molecule. With 2C-B, the end product was a total winner; there was no wish to modify it. With 2C-N the end product is something a little less, and there is no way to modify it.

#35 2C-O-4; 2,5-DIMETHOXY-4-(i)-PROPOXYPHENETHYLAMINE

SYNTHESIS: To a solution of 3.10 g 85% KOH pellets in 30 mL warm MeOH there was added 6.16 g 2,5-dimethoxyphenol (there was immediate darkening) followed by 8.5 g isopropyl iodide. The reaction mixture was heated on the steam bath for 3.5 h. White crystals of KI appeared at the end of the first h. The mixture was poured into 800 mL H_2O (it was still basic) and acidified with HCl. This was extracted with 3x100 mL CH_2Cl_2, and the combined extracts washed with 2x100 mL 5% NaOH. The organic phase was stripped of solvent under vacuum, and the residual dark amber oil (6.4 g) distilled at 110-130 °C at 0.7 mm/Hg. There was obtained 5.7 g of 1,4-dimethoxy-2-(i)-propoxybenzene as a white oil.



A mixture of 10 g N-methylformanilide and 10 g $POCl_3$ was heated on the steam bath for 10 min producing a deep claret color. To this there was added 5.1 g of 1,4-dimethoxy-2-(i)-propoxybenzene, and the immediately exothermic reaction mixture was heated on the steam bath for 45 min. It was then poured into 800 mL H_2O which was stirred until the dark oil changed into loose, light-colored solids. These were removed by filtration giving 5.7 g of an amber crystalline product with

a mp of 76-78 °C. This was dissolved in an equal weight of MeOH, and heated to a solution which was clear at the boiling point. This was brought to 0 °C and held there for several hours, yielding 2,5-dimethoxy-4-(i)-propoxybenzaldehyde as a fine, off-white crystalline product which, after filtering and air drying, weighed 4.03 g. The mp was 79-80 °C with prior shrinking at 71 °C. Anal. ($C_{12}H_{16}O_4$) C,H.

A solution of 3.9 g 2,5-dimethoxy-4-(i)-propoxybenzaldehyde in 20 g nitromethane was treated with 0.17 g anhydrous ammonium acetate and heated on the steam bath for 1.25 h. The progress of the condensation was readily followed by a TLC analysis of the reaction mixture. With silica gel plates, the starting aldehyde and the product nitrostyrene had Rf's of 0.16 and 0.50 resp., using CH_2Cl_2 as a developing solvent. The excess solvent was removed under vacuum to give a red residue that was dissolved in 10 mL boiling MeOH. The solution spontaneously crystallized giving, after filteration and air drying, 4.1 g of orange crystals of 2,5-dimethoxy-ß-nitro-4-(i)-propoxystyrene.

A solution of LAH (60 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.60 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 4.0 g 2,5-dimethoxy-ß-nitro-4-(i)-propoxystyrene as a solid, perhaps 200 mg at a time. There was an immediate loss of color after each addition. The final pale salmon-colored solution was stirred for 2 h as it returned to room temperature. The excess hydride was destroyed by the cautious addition of 8 mL IPA, which was followed by 5 mL 15% NaOH followed, in turn, by sufficient additional THF to make the suspension of inorganic salts loose and filterable. The reaction mixture was filtered, and the filter cake washed with additional THF. The filtrate and washings were combined and stripped of solvent under vacuum providing 4.6 g of a pale amber oil. This was dissolved in dilute H_2SO_4, washed with 2x50 mL CH_2Cl_2, made basic with aqueous NaOH, and extracted with 3x50 mL CH_2Cl_2. Removal of the solvent under vacuum yielded 2.3 g of residue which was distilled at 115-125 °C at 0.3 mm/Hg to give 0.94 g of a clear white oil. This was dissolved in 5 mL IPA, neutralized with 12 drops of concentrated HCl, and diluted with 10 mL anhydrous Et_2O. White crystals of 2,5-dimethoxy-4-(i)-propoxyphenethylamine hydrochloride (2C-O-4) separated, and were removed by filtration, Et_2O washed, and air dried. The final weight was 0.58 g.

DOSAGE: greater than 60 mg.

DURATION: unknown

QUALITATIVE COMMENTS: (with 60 mg) "I became aware of something in the front part of my head, and there was a lot of yawning. The body was aware of the experiment. But also there was a general exhilaration and excitement, which lasted for a few hours. At best, I am at a plus one."

EXTENSIONS AND COMMENTARY: The full activity of 2C-O-4 is yet to be discovered. It represents an interesting hybrid lying in between several fascinating compounds.

First and foremost, all these carry the 2,4,5-trisubstitution which has consistently proven to be the most interesting and the most active of the phenethylamines. And with very few exceptions, the 2- and the 5- are methoxyl groups.

The sulfur analogues in this area, compounds with an alkylthio group at the 4-position of the 2,5-dimethoxyphenethylamine backbone, are the 2C-T things. The replacement of a sulfur with an oxygen, quite rightly, should give rise to the 2C-O counterparts. And they have been given the same numbering system that was bestowed upon the "T" series. 2C-T-4 was the 4-isopropylthio compound and one of the most interesting of this family. And so, quite reasonably, the oxygen counterpart should be the 2C-O-4 analogue, and should be one of the first explored.

The extension of the 4-alkoxy-group led to the discovery of the TMA-2 — MEM — MIPM — MPM — MBM series of amphetamine analogues. The 2-carbon counterparts of these would be a fascinating series to explore, I thought, if there was some encouragement to be had from a preliminary try in this field.

This was a first shot in the dark, the actual trial example, and it certainly didn't provide much encouragement. The three-carbon analogue, MIPM, was made (q.v.) but not explored, following the disappointing trials of MPM. If this area is ever re-opened, the numbering should reasonably follow the sulfur materials. The 4-ethoxy material would be 2C-O-2, the 4-(n)-propoxy compound 2C-O-7, and the 4-(n)-butoxy compound 2C-O-19. These are the exact analogues of 2C-T-2, 2C-T-7, and 2C-T-19, resp., and the 2-carbon homologues of MEM, MPM, and MBM. The simplest member of this series, the methyl counterpart, is 2C-O, and it is the obvious analogue of 2C-T. This is also called 2,4,5-TMPEA, and its story is presented elsewhere.

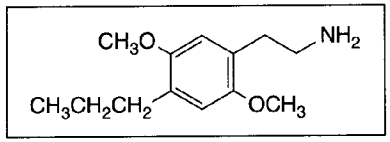
But, with the probable low eventual potency of 2C-O-4, I feel that the 2C-O series will not be an exciting one.

#36 2C-P; 2,5-DIMETHOXY-4-(n)-PROPYLPHENETHYLAMINE

SYNTHESIS: To a stirred solution of 138 g p-dimethoxybenzene in 400 mL CH_2Cl_2 there was added a suspension of 172 g anhydrous $AlCl_3$ in 500 mL CH_2Cl_2 which contained 92.5 g propionyl chloride. After stirring for 1.5 h the reaction mixture was poured into 2 L H_2O containing ice. The phases were separated, and the aqueous fraction was extracted with 2x100 mL CH_2Cl_2. The organic phase and the extracts were pooled, washed once with H_2O, and then with 2x100 mL 5% NaOH. The solvent from the organic phase was removed under vacuum, yielding a deeply colored residue. This was distilled at 150-165 °C at 20 mm/Hg yielding 170 g of 2,5-dimethoxypropiophenone as a pale amber-colored oil. Acidification of the sodium hydroxide extract, extraction with CH_2Cl_2, and evaporation of the solvent,

yielded 3 g of an oil that slowly crystallized. These solids, on recrystallization from MeOH, provided 1.0 g of 2-hydroxy-5-methoxypropiophenone with a mp of 47-48 °C. The same Friedel Crafts reaction, conducted on the same scale in CS_2 rather than in CH_2Cl_2, required reduced temperature (5 °C) and a 24 h reaction period. This solvent variation, with the same workup and isolation, gave 76 g of 2,5-dimethoxypropiophenone as a pale amber oil boiling at 130-137 °C at 4 mm/Hg.

A total of 150 g mossy zinc was amalgamated by treatment with a solution of 15 g mercuric chloride in 1 L H_2O. After swirling for 0.5 h, the H_2O phase was removed by decantation and the zinc added to a 1 L three neck flask. To this there was added 20 mL H_2O and 20 mL concentrated HCl, followed by 20 g of 2,5-dimethoxypropiophenone dissolved in 50 mL EtOH. This mixture was held at reflux with a heating mantle overnight, with the occasional addition of HCl as needed to maintain acidic conditions. After cooling to room temperature, the residual solids were removed by filtration, and the filtrate extracted once with 100 mL CH_2Cl_2 (this was the upper phase). Sufficient H_2O was then added to allow extraction with 2x100 mL additional CH_2Cl_2 with the organic solvent being the lower phase. The combined organic extracts were washed twice with 5% NaOH, followed by one washing with dilute acid. Removal of the solvent under vacuum yielded 18 g of a dark brown oil that was distilled at the water pump to yield 7.2 g of 2,5-dimethoxypropylbenzene as a light yellow oil boiling at 90-130 °C.



A mixture of 22 g 2,5-dimethoxypropylbenzene, 23 g $POCl_3$ and 22 g N-methylformanilide was heated on the steam bath for 1.5 h. The hot, dark reaction mass was poured into 1 L H_2O, which allowed the eventual separation of 2,5-dimethoxy-4-(n)-propylbenzaldehyde as a clear yellow oil weighting 14 g. Although the homologous 4-ethyl and 4-butyl benzaldehydes were clean crystalline solids, this propyl homologue remained an oil. Gas chromatographic analysis showed it to be about 90% pure, and it was used as obtained in the nitrostyrene steps with either nitromethane (here) or nitroethane (under DOPR).

To a solution of 13 g 2,5-dimethoxy-4-(n)-propylbenzaldehyde in 100 mL nitromethane, there was added 1.3 g anhydrous ammonium acetate and the mixture held at reflux for 1 h. Removal of the solvent/reactant under vacuum yielded a spontaneously crystallizing mass of orange solids that was removed with the help of a little MeOH. After filtering and air drying there was obtained 7.5 g 2,5-dimethoxy-ß-nitro-4-(n)-propylstyrene with a mp of 118-122 °C. Recrystallization from CH_3CN gave an analytical sample with a mp 123-124 °C. Anal. ($C_{13}H_{17}NO_4$) N.

In a 1 L round bottomed flask with a magnetic stirrer under a He atmosphere there was added 120 mL 1 M LAH in tetrahydrofuran. This stirred solution was cooled with an external ice bath, and there was added, dropwise, 3.2 mL of 100% H_2SO_4, freshly made by the addition of 13.5 g 20% fuming H_2SO_4 to

15.0 g of ordinary 96% concentrated H_2SO_4. When the addition was complete, a total of 7.2 g of dry 2,5-dimethoxy-ß-nitro-4-(n)-propylstyrene was introduced as solids in several batches, against a flow of He, over the course of 20 min. The reaction mixture was allowed to come to room temperature, and stirred for an additional 0.5 h, then brought to reflux for 10 min on the steam bath. The excess hydride was destroyed with 18 mL IPA, and then sufficient 15% NaOH was added which made the aluminum oxides distinctly basic and of a filterable texture. The inorganics were removed by filtration, and the filter cake washed with additional THF. The combined filrate and washes were stripped of solvent, yielding several g of a pale yellow oil that was suspended in a large quantity of dilute H_2SO_4. The aqueous phase was filtered free of insolubles, washed with a little CH_2Cl_2, and made basic with aqueous NaOH. This was extracted with 3x40 mL CH_2Cl_2 and, after the removal of the solvent under vacuum, the residual 2 g of off-white oil was distilled. A fraction that distilled at 100-110 °C at 0.3 mm/Hg was water white, weighed 1.59 g and spontaneously crystallized. This fraction was dissolved in 7.5 mL warm IPA and neutralized with 0.6 mL concentrated HCl. The spontaneous crystals of 2,5-dimethoxy-4-(n)-propylphenethylamine hydrochloride (2C-P) were suspended in 20 mL anhydrous Et_2O, filtered, Et_2O washed, and air dried. The weight was 1.65 g and the mp was 207-209 °C with prior sintering at 183 °C., Anal. ($C_{13}H_{22}ClNO_2$) N.

DOSAGE: 6 - 10 mg.

DURATION: 10 - 16 h.

QUALITATIVE COMMENTS: (with 6 mg) "I was not feeling so good. Hangover, I guess. The material was so gentle in coming on, and soon my body became jangled. Thinking was easy. Verbalizing was easy. Being comfortable with my body was not. My back hurt and then my legs hurt. My lower back was in spasm. At first I did not particularly like what this drug was doing to my body, but took a good look at it and decided that I was the culprit. Took a good look at my drinking so much, and decided that I didn't need it. So much energy was going through me I didn't know what to do with it. The whole day was spent in physical discomfort. Food tasted good, and we nibbled all day. My stomach was bloated. Next day I was more or less like a zombie. I was wiped out."

(with 8 mg) "Comes on slowly, not feeling intently until into 2nd hour. I feel slight discomfort but override it responding to music. I take in air, directing it inside to heal uncomfortable places, open up my clogged sinuses. Wonderful experience of clean, fresh, healing air. Find that discomfort zone is places where I think there is something wrong with me. I dissolve these places with the feeling I'm OK. Like myself better and better, and find more reasons to enjoy and appreciate myself. I find this material powerful, and an excellent working material. Under other circumstances, would probably spend more time working alone inside, where there were great openings, and some of the most beautiful visuals I have seen

for a long time. Usually I do not get visuals. I like the long action. I feel that this material worked for a good week after the experience, with internal processes taking place, many insights, and energy running. At times the energy was a little uncomfortable, but could always be quelled by taking a moment for deep relaxation or looking directly at the internal process. I feel that much good internal work has been done, a lot of it unconscious."

(with 9 mg) "At the one hour point, I am barely off of baseline. It is not until almost the third hour that the experience is fully developed, and once there it is maintained for another four hours. I was well grounded but rather diffuse. I explored writing (which went quite well), interpretation (pictures and reading both OK) and talking (very good). This is an excellent level, and probably near the max."

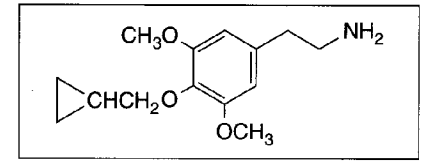
(with 12 mg) "Slow and even rise. At five minutes to seven (suddenly the clock time makes no sense at all) I am at a 3+ and feel that I have not yet plateau'd. Erotic was excellent. Music good. Eyes-closed imagery very different place than usual experiences. Slow, calm, strong images from an area that has no apparent connection with usual waking world, yet underlies all of it. A cool, wise place which has its own rules. All emotions and feeling available, but there is a cool perspective which informs all thinking. Talking superb and fun, and it was possible to feel our bodies healthy and full of determination to remain so, despite obvious faults and self-indulgences. Could do a lot of learning with this material, but probably not a group thing. It would lend itself too easily to hypnotic power-games, and it would be too easy to open up the shared consciousness level, which would be frightening to a lot of people and bring about necessary escapes such as sickness. Excellent feeling the next day."

EXTENSIONS AND COMMENTARY: There is certainly a broad mixture of experiences with 2C-P but, on the whole, probably more favorable than not. There was one report of an experience in which a single dosage of 16 mg was clearly an overdose, with the entire experiment labeled a physical disaster, not to be repeated. A consistent observation is that there may not be too much latitude in dosage between that which would be modest, or adequate, and that which would be excessive. The need for individual titration would be most important with this compound.

#37 CPM; CYCLOPROPYLMESCALINE; 4-CYCLOPROPYLMETHOXY-3,5-DIMETHOXYPHENETHYLAMINE

SYNTHESIS: To a solution of 2.8 g homosyringonitrile (see under E for synthesis) in 20 ml acetone containing about 50 mg decyltriethylammonium iodide, there was added 3.0 g cyclopropylmethyl chloride and 5.0 g NaI. Stirring was continued during a color change from pale yellow to blue. There was then added 2.9 g of finely

powdered anhydrous K_2CO_3, resulting in a beautiful turquoise color. The mixture was held at reflux on the steam bath for 3 h, which discharged all color. The solvent was removed under vacuum, and the residues were added to 100 mL H_2O. This solution was extracted with 3x75 mL CH_2Cl_2, the extracts were pooled, washed with 2x50 mL 5% NaOH, and the organic solvent removed under vacuum. The residual oil weighed 4.2 g, and was distilled at 140-155 °C at 0.4 mm/Hg to yield 4-cyclopropylmethoxy-3,5-dimethoxyphenylacetonitrile as a colorless oil weighing 2.8 g which spontaneously crystallized. Its mp was 44-44.5 °C after recrystallization from MeOH/H_2O. Anal. ($C_{14}H_{17}NO_3$) C,H.



A suspension of 1.3 g LAH in 65 mL anhydrous THF under He was cooled to 0 °C with stirring, and 0.85 mL of 100% H_2SO_4 was slowly added. Then, with continued stirring, a THF solution of 2.7 g of 4-cyclopropylmethoxy-3,5-dimethoxyphenylacetonitrile in 50 mL THF was added dropwise. After the addition was complete, the mixture was brought to a boil briefly on the steam bath, cooled, and treated with sufficient IPA to destroy the excess hydride. Then there was added an amount of 15% NaOH sufficient to produce a loose filterable solid form of aluminum oxide. This was removed by filtration, and the filter cake washed with THF. The pooled filtrate and washes were stripped of solvent, and the residue was dissolved in dilute H_2SO_4, washed with 2x50 mL CH_2Cl_2, made basic with aqueous NaOH, and then extracted with 2x50 mL of CH_2Cl_2. After removal of the solvent, the residue was distilled at 128-140 °C at 0.4 mm/Hg to yield 2.5 g of a white oil. This was dissolved in 10 mL IPA, and treated with 30 drops of concentrated HCl which was just sufficient to demonstrate acidity as judged by external dampened pH paper. The addition of 25 mL anhydrous Et_2O to the stirred solution allowed, in a few minutes, the product 4-cyclopropylmethoxy-3,5-dimethoxyphenethylamine hydrochloride (CPM) to spontaneously crystallize as a fine white solid. The yield was 1.8 g, and a second crop of 0.8 g was obtained from the IPA/Et_2O mother liquors. The mp was 172-173 °C. Anal. ($C_{14}H_{22}ClNO_3$) C,H.

DOSAGE: 60 - 80 mg.

DURATION: 12 - 18 h.

QUALITATIVE COMMENTS: (with 70 mg) "I was surprised at the fast development of this drug, with the knowledge that it was a long-laster. Twenty minutes into it I was aware of some changes, and by the end of one and a half hours there was a complete plus three. The most remarkable property is the eyes-closed imagery. No, not just imagery but fantasy. It is not completely benign, but it locks into music with an extraordinary fit. I was at one moment keenly aware of my body touching the rug, the tactile aspects of my surroundings, and then I would find that

my world was simply my personal sphere of reality that kept engulfing everything about me, all completely augmented by the music. Constructed by the music. I hoped that I wouldn't offend anyone else around me with this growing world of mine. Eyes open, there was not that much of note. Not much insight. Not much in the way of visuals. By the eighth hour an effort to sleep showed me how exposed and vunerable I was, and when I closed my eyes I needed my guards against this fantasy world. Even at the twelth hour there was no easy way to relax and sleep. Use higher dosages with caution."

(with 70 mg) "There is a goodly amount of eyes-closed patterning but I found external sounds to be irritating. Voices, and even music, seemed to be intrusive. I didn't want to share my space with anyone. I was reminded of mescaline, in that I kept losing the awareness of the drug's role in my experience. Visual exaggerations are probably right around the corner. The residual effects were too much to ignore, but 100 milligrams of phenobarb at about the twelth hour allowed me to lie down quietly."

(with 80 mg) "A wild day of profound philosophy, with discussions of the art of molecules, the origins of the universe, and similar weighty trivia. Much day-dreaming in erotic areas, but by and large, it went on a bit too long. I was tired."

EXTENSIONS AND COMMENTARY: In the literary world, the guy who is on your side, your leader, your champion, is the protagonist and the guy he battles, your enemy, is the antagonist. These same roles are played in the world of pharmacology, but the names are slightly changed. A drug which does the needed or expected thing is called the agonist rather than protagonist, but the drug that gets in its way is still called the antagonist.

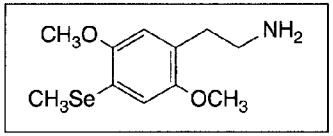
The cyclopropylmethyl group plays an interesting role in the world of narcotics. There are numerous examples of opiates with a methyl group attached to a nitrogen atom which are famous for being valuable in producing analgesia and sedation. These run the gamut from natural alkaloids such as morphine and codeine, to synthetic variants such as Dilaudid and Percodan. And yet, with most of these narcotics, when the methyl on the nitrogen is removed, and a cyclopropylmethyl group put into its place, the agonist becomes an antagonist. Oxycodone (the active narcotic thing in Percodan) becomes Naltrexone, a drug that will immediately snap a heroin victim out of his overdose.

Cyclopropylmescaline (CPM) is a molecule that is very simply mescaline itself, with a methyl group removed from an oxygen atom and a cyclopropylmethyl group put on instead. Might CPM be not only inactive, but actually block the action of mescaline? Interesting concept. But it turned out to be entirely wrong.

The amphetamine analog of CPM should be easily made from the alkylation of syringaldehyde with cyclopropyl chloride, followed by conventional reaction of the resulting aldehyde with nitroethane, and finally a reduction step. There is no reason to believe that the resulting compound 3,5-dimethoxy-4-cyclopropyloxyamphetamine (3C-CPM) would be any shorter acting than CPM.

#38 2C-SE; 2,5-DIMETHOXY-4-METHYLSELENEO-PHENETHYLAMINE

SYNTHESIS: A suspension of 5.65 g 1,4-dimethoxybenzene in 100 mL petroleum ether containing 6.5 mL N,N,N',N'-tetramethylethylenediamine was magnetically stirred, placed in an inert atmosphere, and cooled to 0 °C with an external ice bath. There was then added 27 mL of 1.6 M butyllithium in hexane. The solids present went into solution, and after a few min continued stirring, a fine precipitate appeared. The reaction was allowed to stir while coming up to room temperature. There was then added 4.8 g dimethyl diselenide which led to an exothermic reaction, bringing the petroleum ether up to a reflux and showing a color change from white to yellow, to light green, to an eventual brown, all over the course of 30 min. After 2 h additional stirring, the reaction was quenched by pouring into dilute NaOH. The organic phase was separated, and the aqueous phase extracted with 2x75 mL Et_2O. The pooled organics were washed first with dilute NaOH, then with dilute HCl, and then the solvent was removed under vacuum. Distillation of the residue at 0.4 mm/Hg gave an early fraction (75-100 °C) that solidified in the receiver and was largely unreacted dimethoxybenzene. A pale yellow oil distilled from 100 to 120 °C which proved to be largely 2,5-dimethoxyphenyl methyl selenide. Microanalysis gave C = 49.86, 49.69; H = 5.32, 5.47. As $C_9H_{12}SeO_2$ requires C = 46.76, H = 5.23, there is approximately 13% dimethoxybenzene present ($C_8H_{10}O_2$ requires C = 69.54, H = 7.29). This mixture was used as such, without further purification.



A mixture of 1.25 g $POCl_3$ and 1.1 g N-methylformanilide was warmed on the steam bath for several min until the color had become a deep claret. There was then added 1.5 g of the 87% pure 2,5-dimethoxyphenyl methyl selenide and the steam bath heating continued for an additional 25 min. The very tarry reaction mixture was poured into 100 mL H_2O, producing fine yellow solids almost immediately. These were removed by filtration and distilled at 0.2 mm/Hg. A first fraction distilling up to 100 °C was a mixture of unreacted ethers and what appeared to be 2,5-dimethoxybenzaldehyde. A second cut distilled at 140-150 °C, solidified to a yellow solid in the receiver, and weighed 1.2 g. A small amount of this product (with mp 91-96 °C) was recrystallized from MeOH to give an analytic sample of 2,5-dimethoxy-4-(methylseleneo)benzaldehyde with a mp 88-92 °C. All efforts to achieve a tighter melting range were unsuccessful. Anal. ($C_{10}H_{12}O_3$ Se) C,H. Although this benzaldehyde migrates normally on a silica gel TLC plate (Rf of 0.4 employing CH_2Cl_2 as a solvent) when it is once completely dried on the plate, there seems to be some irreversible reaction with the silica, and the spot will no longer move at all.

To a solution of 0.85 g 2,5-dimethoxy-4-(methylseleneo)benzaldehyde in 10 mL nitromethane there was added 150 mg anhydrous ammonium acetate, and the solution was heated for 35 min on the steam bath. Removal of the volatiles under

vacuum yielded brick-red solids (1.1 g) which were ground under a small amount of MeOH, filtered, and air dried. This yielded 0.88 g of solid 2,5-dimethoxy-4-methylseleneo-ß-nitrostyrene with a mp of 170.5-171.5 °C. Recrystallization from IPA or from toluene gave no improvement of mp. Anal. ($C_{11}H_{13}NO_4Se$) C,H.

A solution of LAH (20 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 0.53 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 0.85 g 2,5-dimethoxy-4-methylseleneo-ß-nitrostyrene in 20 mL hot anhydrous THF. There was an immediate discoloring. After a few minutes further stirring, the temperature was brought up to a gentle reflux on the steam bath for 0.5 h, then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of IPA and, when there was no further activity, the reaction mixture was poured into 500 mL dilute H_2SO_4. This was washed with 2x100 mL CH_2Cl_2, and then made basic with 5% NaOH. The milky aqueous phase was extracted with 2x100 mL CH_2Cl_2, and extensive centrifuging was required to obtain a clear organic phase. Evaporation of the pooled extracts gave 1.6 g of an oil that crystallized. This was distilled at 130-140 °C at 0.15 mm/Hg providing 0.6 g of a white oil that set to a crystalline solid melting at 87-89 °C. This was dissolved in 4 mL boiling IPA, neutralized with 8 drops of concentrated HCl and the formed solids further diluted with IPA with a little anhydrous Et_2O. This crystalline product was removed by filtration, washed with Et_2O, and air dried to constant weight, yielding 2,5-dimethoxy-4-methylseleneophenethylamine hydrochloride (2C-SE) with a mp of 240-241 °C.

DOSAGE: perhaps 100 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 50 mg) "My tongue feels as if I had eaten hot food. Overall I got up to a plus 1, and found the effects to be completely benign. I wandered about within the Graves exhibit at the Oakland Museum but there seemed to be only minor enhancement of the visual input."

(with 70 mg) "The water solution of this material has an unspeakable smell. But there is no lasting taste, thank heaven. This is up to a 1.5 + and probably half again would be an effective dose. The first awareness was at 45 minutes, and the plateau lasted from 1.5 hours to about the fourth hour. I was at certain baseline at 8 hours."

EXTENSIONS AND COMMENTARY: With an entirely new hetero atom in the molecule (the selenium), and with clear indications that large dosages would be needed (100 milligrams. or more), some discretion was felt desirable. There was certainly an odd taste and an odd smell. I remember some early biochemical work where selenium replaced sulfur in some amino acid chemistry, and things got pretty toxic. It might be appropriate to get some general animal toxicity data before

exploring those dosages that might get to a +++.

What doors are opened by the observation that the selenium analog of 2C-T is an active compound? The potency appears to be in the same ball park, whether there is a sulfur atom or a selenium atom there.

From the point of view of the thing that is hung onto the hetero-atom, the selenium, the most active (and as first approximation the most safe) analogue would be the same ones that are the most potent with sulfur. These would probably be the Se-ethyl, the Se-propyl, or the Se-isopropyl, the analogs of S-ethyl, S-propyl, and S-isopropyl. If one were to be systematic, these would be called 2C-SE-2, 2C-SE-4, and 2C-SE-7. And a very special place might be held for 2C-SE-21, the analogue of 2C-T-21. Not only is this of high potential potency, but it would certainly be the first time that both fluorine and selenium are in the same centrally active drug. In fact, might not this compound, 2C-SE, be the first compound active within the human CNS with a selenium atom in it? It is certainly the first psychedelic with this atom in it!

From the point of view of the hetero-atom itself, there are two more known below selenium in the Periodic Table. Each deserves some special comment. The next atom, directly below selenium, is tellurium. It is more metallic, and its compounds have a worse smell yet. I heard a story about a German chemist, many years ago, who was carrying a vial of dibutyl telluride in his pocket in a passenger coach from here to there in Germany, back at about the turn of the century. It fell to the floor and broke. No one could remain in the car, and no amount of decontamination could effectively make the smell tolerable. Scratch one railway coach. But the compound, 2C-TE, would be readily makeable. Dimethyl ditelluride is a known thing.

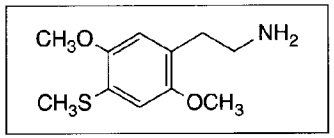
However, the atom below tellurium (and at the bottom of that particular column of the Periodic Table) is the element polonium. Here one must deal in terms of theory, as far as human activity goes, since there are no non-radioactive isotopes of polonium. The only readily available isotope is that with mass 210, which is also called Radium F, and is an alpha-particle emitter. If this were ever to be put into a living organism, and if it were to seek out and hang around some particular site of action, that area would be thoroughly and completely cooked by alpha-particle emission. It would be a fun academic exercise to make 2C-PO (2,5-dimethoxy-4-methylpoloneophenethylamine), but in no way could it ever go into anyone. I knew an eminent physiologist named Dr. Hardin Jones (now dead) who always argued that the continuing use of drugs would burn out the pleasure center of the brain. It is a certainty that 2C-PO would, quite literally, do this. If I ever made it, I would call it HARDINAMINE in his honor.

There was an interesting observation associated with the making of 2C-SE. In the synthesis of many of the sulfur compounds (of the 2C-T family) is was quite common to find, when there was a quantity of some organic sulfide let go as a by-product of a reaction on a warm summer night, a number of flies coming into the lab to pay a visit. On the first synthesis of the starting material for 2C-SE, a

quantity of CH_3SeH was let go into the environment. Within minutes, there were two beautiful dragonflies in the lab. A coincidence certainly, but somehow, it was a nice message to receive.

#39 2C-T ; 2,5-DIMETHOXY-4-METHYLTHIO-PHENETHYLAMINE

SYNTHESIS: A solution of 149 g sodium thiosulfate in 300 mL H_2O was vigorously stirred. To this there was added, over the course of 10 min, a solution of 43.2 g benzoquinone in 200 mL acetic acid. After an additional 1 h stirring at room temperature, all volatiles were removed under vacuum. The residual syrup slowly set up as crystals which, after grinding under brine, were removed by filtration and washed with additional brine. These were dissolved in MeOH, clarified by filtration through a Celite bed, and the clear filtrate stripped of solvent under vacuum. The yellow, powdery sodium 2,5-hydroxyphenylthiosulfate weighed 67 g when dry. This intermediate was dissolved in aqueous HCl (50 g in 200 mL H_2O containing 400 mL concentrated HCl), cooled with an external ice bath, and treated with 250 g zinc dust added at a rate that kept the temperature below 60 °C. About 1.5 h were required, and caution must be taken concerning the poisonous hydrogen sulfide that evolves. An additional 50 mL concentrated HCl was added, and the aqueous phase decanted from the unreacted zinc metal. This was extracted with 6x100 mL Et_2O, and these extracts were pooled, washed with brine, and the solvent removed under vacuum to yield 33.1 g of 2,5-dihydroxythiophenol as pale yellow needles with a mp of 118-119 °C.



A solution of 118.6 g KOH pellets in 200 mL H_2O was placed under N_2, and to it was added 24.0 g 2,5-dihydroxythiophenol. With vigorous stirring, there was then added 160 g methyl sulfate at a rate that maintained the temperature at about 60 °C. This took about 2 h. After the addition was complete, the mixture was held at reflux for 3 h, and allowed to stir at ambient temperature overnight. It was then filtered, and the filtrate extracted with 6x100 mL Et_2O, the extracts pooled, washed with 2x50 mL brine, dried over anhydrous Na_2SO_4, and the solvent removed under vacuum. The residue was distilled at 86-88 °C at 0.04 mm/Hg to provide 25.9 g of 2,5-dimethoxythioanisole as a white oil that crystallized on standing. Its mp was 33-34 °C. An alternate preparation of this compound follows the direct methylation of 2,5-dimethoxythiophenol (see under 2C-T-2 for the preparation of this common intermediate) with methyl iodide.

To 40 mL dry CH_2Cl_2 there was added 6.07 g 2,5-dimethoxythioanisole, and this was cooled to 0 °C under N_2. To this well stirred solution there was added 13.02 g stannic chloride over the course of 2 min. This was followed by the dropwise addition of dichloromethyl methyl ether over 5 min, and the reaction mixture

allowed to stir for an additional 15 min. After returning to room temperature, it was stirred for an additional 1 h. The reaction mixture was poured over 15 g ice, and the organic phase separated, washed with 3x25 mL 3 N HCl, with 3x50 mL brine and, after drying over anhydrous Na_2SO_4 the solvent was removed under vacuum. The residue was a solid and, after recrystallization from MeOH/H_2O, gave 5.86 g 2,5-dimethoxy-4-(methylthio)benzaldehyde with a mp of 95-97 °C. Purification via the bisulfite complex provided an analytical sample with mp of 99-100 C. Anal. ($C_{10}H_{12}O_3S$) C,H,S. The malononitrile derivative (from equal weights of the aldehyde and malononitrile in EtOH with a drop of triethylamine as catalyst) was recrystallized from an equal volume of EtOH to give orange crystals with a mp of 185-186 °C. Anal. ($C_{13}H_{12}N_2O_2S$) C,H,N,S.

A solution of 2.1 g 2,5-dimethoxy-4-(methylthio)benzaldehyde in 7.5 mL nitromethane was treated with 0.45 g anhydrous ammonium acetate and held at steam bath temperature for 6 h. The deep red solution was stripped of solvent to give a residue that spontaneously crystallized. This was ground up under 12 mL MeOH, filtered, and washed with MeOH to yield, after air-drying, 1.7 g of 2,5-dimethoxy-4-methylthio-ß-nitrostyrene as orange solids. Recrystallization from EtOH provided rust-orange colored crystals with a mp of 165.5-166 °C. Anal. ($C_{11}H_{13}NO_4S$) C,H,N; S: calcd, 12.56; found, 11.96.

To a gently refluxing mixture of 1.4 g LAH in 40 mL anhydrous THF under an inert atmosphere there was added, dropwise, 1.7 g 2,5-dimethoxy-4-methylthio-ß-nitrostyrene in 25 mL THF. The refluxing was continued for 18 h, and the stirring continued for another day at room temperature. There was then added 1.5 mL H_2O (diluted with a little THF), 1.5 mL 15% NaOH, and finally 4.5 mL H_2O. The white aluminum oxide salts were removed by filtration, and the filter cake washed with THF. The filtrate and washings were combined and stripped of solvent under vacuum yielding a straw-colored residue that crystallized (mp 81-92 °C without purification). This residue was dissolved in 25 mL IPA and neutralized with concentrated HCl. The slightly pink solution spontaneously crystallized. There was added 100 mL anhydrous Et_2O, and the white crystalline mass of 2,5-dimethoxy-4-methylthiophenethylamine hydrochloride (2C-T) was removed by filtration, washed with Et_2O, and air dried. The final weight was 1.0 g, and had a mp of 232-237 °C. Recrystallization from EtOH provided an analytical sample with mp 240-241 °C. IPA was not a good recrystallization solvent. Anal. ($C_{11}H_{18}ClNO_2S$) C,H,N,S.

DOSAGE: 60 - 100 mg.

DURATION: 3 - 5 h.

QUALITATIVE COMMENTS: (with 60 mg) "Poetry was an easy and natural thing. Both the reading of it and the writing of it. This is a potential MDMA substitute since it opens things up but it doesn't do anything to get in the way."

(with 75 mg) "I am already aware at a quarter of an hour into it! It develops

very quickly but very quietly. There are no visuals at all but, rather, a tactile sensitivity, with warm close feelings. This could be very erotic. There is some fantasy to music, but nothing very demanding. The viewing of pictures doesn't do much either. The drop-off was extremely relaxed, with a good body feeling. At the fifth hour I was able to drift into an excellent, deep sleep with busy dreams. In the morning I felt refreshed and active, without apparent deficit."

(with 75 mg) "I got up to a thin and fragile plus two, but there was a continuing feeling of a hooded cloak brought down over my head. Nothing obvious — it is transparent — but it somehow separated me from everything around me. I do not think the overall experiment was worth it."

(with 100 mg) "Material all right, but a little bit along the lines of a 'generic' psychedelic effect. Sharper edges than 2C-B. The one true negative, which has been pretty consistent with this drug, is that there is a certain emotional removal. One teeny step removed. One is connected with feelings, certainly, but there is a tendency for the intellect to be more evident, in me, than the heart. All this is moderately so. Nothing extreme. Pretty good material, but there are more interesting ones. However, if you are looking for a really short one, this is one of the answers. For most people. For me, it's still around 5 to 6 hours long. I wish we had more shorties, indeed."

(with 125 mg) "There was some physical tummy uncertainty, but once that was past, talking was extremely easy. This is probably really psychedelic, but I am not really sure why, as there is not much in the way of visuals. Dropping was noted just after hour number three, and I was at baseline three hours later."

EXTENSIONS AND COMMENTARY: The earliest work with the sulfur atom was with the three-carbon chain materials, the ALEPHs. It was only after a considerable time of working with them, and trying to come to peace with their property of being so different from person to person as to potency, that the two-carbon homologues were looked at. Although the first of these (this compound, called 2C-T) was prepared at the same time as ALEPH-1, there was a lapse of about four years between their trials. The relatively low potency of 2C-T was a bit discouraging. But the methodical pursuit of the higher 2C-T's (to parallel the higher ALEPHs) proved to be a treasure house, and they have been explored much further than any of the ALEPHs.

A note on the "T" in 2C-T. Many, in fact most, of the 2C's have their name based on the last letter of the amphetamine prototype. 2C-B from DOB, 2C-C from DOC, 2C-I from DOI, 2C-N from DON, etc. And since the original name for ALEPH-1 was DOT (the desoxy- and a thiomethyl group at the 4-position), the 2C-T naming followed this general pattern. And as a note on the subsequent numbering, they (both the ALEPHs and the 2C-T's) are assigned numbers as they are thought up. There is no structural significance in the number but they have been, like the houses on the streets in residential Tokyo, assigned numbers in strict historical order, documenting the sequence of construction rather than the relative position

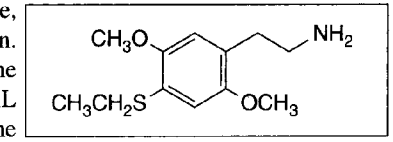
down the side of the street.

Both of the homologous mono-ethoxy Tweetios of 2C-T have been synthesized and evaluated. The 2-EtO-homologue of 2C-T is 2-ethoxy-5-methoxy-4-methylthiophenethylamine, or 2CT-2ETO. The benzaldehyde (2-ethoxy-5-methoxy-4-(methylthio)benzaldehyde) was an oil, the nitrostyrene intermediate had a melting point of 137-138 °C, and the final hydrochloride a melting point of 215-216 °C. The effects were felt very quickly, and there was a blurring of vision. However, the highest dose tried, 50 milligrams, was not able to produce a greater-than-plus one state, and what did occur, lasted for only 4 hours.

The 5-EtO-homologue of 2C-T is 5-ethoxy-2-methoxy-4-methylthiophenethylamine, or 2CT-5ETO. The benzaldehyde (5-ethoxy-2-methoxy-4-(methylthio)benzaldehyde) was impure, and had a melting point of about 66 °C, the nitrostyrene intermediate a melting point of 133-134 °C, and the final hydrochloride a melting point of 184-185 °C. There was a body awareness and modest eyes-closed visuals following the use of 30 milligrams of 2CT-5ETO. The experience was quiet, peaceful, contemplative, and insightful. The duration was perhaps 15 hours and Halcion was needed to allow sleep. There were a lot of dreams, and the next day was restful.

#40 2C-T-2; 2,5-DIMETHOXY-4-ETHYLTHIOPHENETHYLAMINE

SYNTHESIS: To a solution of 165 g 1,4-dimethoxybenzene in 1 L of CH_2Cl_2, in a well ventilated place and well stirred, there was cautiously added 300 mL chlorosulfonic acid. With about half the acid chloride added, there was a vigorous evolution of HCl gas and the generation of a lot of solids. As the addition was continued, these redissolved to form a clear, dark green solution. Towards the end of the addition, some solids were again formed. When everything was stable, there was added 2 L H_2O, a few mL at a time, commensurate with the vigor of the reaction. The two phases were separated, and the aqueous phase extracted with 2x75 mL CH_2Cl_2. The original organic phase and the extracts were combined and the solvent removed under vacuum. The residue weighed 162 g and was quite pure 2,5-dimethoxybenzenesulfonyl chloride, a yellow crystalline solid with a mp of 115-117 °C. It need not be further purified for the next step, and it appears to be stable on storage. The sulfonamide, from this acid chloride and ammonium hydroxide, gave white crystals from EtOH, with a mp of 147.5-148.5 °C.



The following reaction is also a very vigorous one and must be performed in a well ventilated place. To a solution of 400 mL 25% H_2SO_4 (V/V) in a beaker at least 2 L in size, there was added 54 g of 2,5-dimethoxybenzenesulfonyl chloride,

and the mixture was heated on a steam bath. The yellow crystals of the acid chloride floated on the surface of the aqueous layer. There should be 80 g of zinc dust at hand. A small amount of Zn dust was placed at one spot on the surface of this chapeau. With occasional stirring with a glass rod, the temperature was allowed to rise. At about 60 or 70 °C an exothermic reaction took place at the spot where the zinc was placed. Additional dollups of zinc were added, and each small exothermic reaction site was spread about with the glass stirring rod. Finally, the reaction spread to the entire solid surface layer, with a melting of the acid chloride and an apparent boiling at the H_2O surface. The remainder of the 80 g of zinc dust was added as fast as the size of the reaction container would allow. After things subsided again, the heating was continued for 1 h on the steam bath. After the reaction mixture had cooled to room temperature, it was filtered through paper in a Buchner funnel, and the residual metal washed with 100 mL CH_2Cl_2. The two-phase filtrate was separated, and the lower, aqueous phase was extracted with 2x75 mL CH_2Cl_2. The addition of 2 L H_2O to the aqueous phase now made it the upper phase in extraction, and this was again extracted with 2x75 mL CH_2Cl_2. The organic extracts were pooled (H_2O washing is more trouble than it is worth) and the solvent removed under vacuum. The light amber residue (30.0 g) was distilled at 70-80 °C at 0.3 mm/Hg to yield 25.3 g 2,5-dimethoxythiophenol as a white oil. This chemical is certainly not centrally active, but it is a most valuable precursor to all members of the 2C-T family.

To a solution of 3.4 g of KOH pellets in 75 mL boiling EtOH, there was added a solution of 10.0 g 2,5-dimethoxythiophenol in 60 mL EtOH followed by 10.9 g ethyl bromide. The reaction was exothermic with the immediate deposition of white solids. This was heated on the steam bath for 1.5 h, added to 1 L H_2O, acidified with HCl, and extracted with 3x100 mL CH_2Cl_2. The pooled extracts were washed with 100 mL of 5% NaOH, and the solvent removed under vacuum. The residue was 2,5-dimethoxyphenyl ethyl sulfide which was a pale amber oil, weighed about 10 g and which was sufficiently pure for use in the next reaction without a distillation step.

A mixture of 19.2 $POCl_3$ and 18.0 g N-methylformanilide was heated briefly on the steam bath. To this claret-colored solution there was added the above 2,5-dimethoxyphenyl ethyl sulfide, and the mixture heated an additional 20 min on the steam bath. This was then added to 500 mL of well-stirred warm H_2O (pre-heated to 55 °C) and the stirring continued for 1.5 h by which time the oily phase had completely solidified to a brown sugar-like consistency. The solids were removed by filtration, and washed with additional H_2O. After being sucked as dry as possible, these solids were dissolved in 50 mL boiling MeOH which, after cooling in an ice-bath, deposited almost-white crystals of 2,5-dimethoxy-4-(ethylthio)-benzaldehyde. After filtration, modest washing with cold MeOH, and air drying to constant weight, there was obtained 11.0 g of product with a mp of 86-88 °C. Recrystallization of a small sample again from MeOH provided an analytical sample with mp 87-88 °C. Anal. ($C_{11}H_{14}O_3S$) C,H.

To a solution of 11.0 g 2,5-dimethoxy-4-(ethylthio)benzaldehyde in 100 g of nitromethane there was added 0.5 g of anhydrous ammonium acetate, and the mixture was heated on the steam bath for 80 min (this reaction progress must be monitored by TLC, to determine the point at which the starting aldehyde has been consumed). The excess nitromethane was removed under vacuum leaving a residue that spontaneously set to orange-red crystals. These were scraped out to provide 12.9 g crude 2,5-dimethoxy-4-ethylthio-ß-nitrostyrene with a mp of 152-154 °C. A sample recrystallized from toluene was pumpkin colored and had a mp of 148-149 °C. Another sample from acetone melted at 149 °C sharp, and was light orange. From IPA came spectacular fluorescent orange crystals, with a mp 151-152 °C. Anal. ($C_{12}H_{15}NO_4S$) C,H.

A suspension of 12.4 g LAH in 500 mL anhydrous THF was stirred under He. To this there was added 12.4 g 2,5-dimethoxy-4-ethylthio-ß-nitrostyrene in a little THF, and the mixture was held at reflux for 24 h. After the reaction mixture had returned to room temperature, the excess hydride was destroyed by the cautious addition of 60 mL IPA, followed by 20 mL of 5% NaOH followed, in turn, by sufficient H_2O to give a white granular character to the oxides. The reaction mixture was filtered, and the filter cake washed first with THF and then with MeOH. Removing the solvents from the combined filtrate and washings under vacuum provided 9.5 g of a yellow oil. This was added to 1 L dilute HCl and washed with 2x100 mL CH_2Cl_2 which removed all color. After making the aqueous phase basic with 25% NaOH, it was extracted with 3x100 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum to provide 7.3 g of a pale amber oil. Distillation at 120-130 °C at 0.3 mm/Hg gave 6.17 g of a clear white oil. This was dissolved in 80 mL IPA and neutralized with concentrated HCl, forming immediate crystals of 2,5-dimethoxy-4-ethylthiophenethylamine hydrochloride (2C-T-2). An equal volume of anhydrous Et_2O was added and, after complete grinding and mixing, the salt was removed by filtration, washed with Et_2O, and air dried to constant weight. The resulting white crystals weighed 6.2 g.

DOSAGE: 12 - 25 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 12 mg) "I don't feel this for fully an hour, but when I do it is quite a weight. It feels good to work it through. It is OK to be with pain. You can't eliminate it. And it is OK to contact your deep pools of anger. And all of it stems from the lack of acknowledgment. All the macho carrying on, the fights, the wars, are ways of demanding attention, and getting even for not having had it in one's life. I am experiencing more deeply than ever before the importance of acknowledging and deeply honoring each human being. And I was able to go through and resolve some judgments with particular persons."

(with 20 mg) "I chose 2C-T-2 at this dose level because the lateness of getting started, and I wanted a shorter experience with my daughter and her family

around. I feel, however, that I have somewhat less of a body load with 2C-T-7. Today I was badly in need of the help that might possibly come from this material, and today it was my ally. I sorely needed the type of help that it afforded. The result was to work off the heavy feeling of tiredness and lack of motivation that had been hounding me. The next day I felt that I had dropped my burden."

(with 20 mg) "There is a neutralness to this. I am at the maximum, and I am asking myself, 'Am I enjoying this?' And the answer is, 'No, I am experiencing it.' Enjoyment seems beside the point. It is a rather intensely matter-of-fact +3. Is it interesting? Yes, but mostly in expectation of further developments. Is it inspiring? No. Is it negative? No. Am I glad I took it? Yes. Not glad. Satisfied and contented. This is a controlled +3. No threat. The body is all right. Not superbly healthy — but OK. Of no interest, either way. If I were to define the body's state, I would have to define it in image. The image is of a not comfortable state of being clenched. Clenched? Well, carefully bound in control."

(with 22 mg) "A slow onset. It took an hour for a plus one, and almost another two hours to get to a +++. Very vivid fantasy images, eyes closed, but no blurring of lines between "reality" and fantasy. Some yellow-grey patterns a la psilocybin. Acute diarrhea at about the fourth hour but no other obvious physical problems. Erotic lovely. Good material for unknown number of possible uses. Can explore for a long time. Better try 20 milligrams next time."

(with 25 mg) "I was at a +++ in an hour! It is most difficult to do even ordinary things. I took notes but now I can't find them. This is much too high for anything creative, such as looking at pictures or trying to read. Talking is OK. And to my surprise I was able to get to sleep, and a good sleep, at the seven hour point."

EXTENSIONS AND COMMENTARY: There is a considerable parallel between 2C-T-2 and 2C-T-7, and both have proven to be excellent tools for introspection. The differences are largely physical. With 2C-T-2, there is more of a tendency to have physical disturbances such as nausea and diarrhea. And the experience is distinctly shorter. With 2C-T-7, physical disturbances are less common, but you are into the effects for almost twice as long. Both have been frequently used in therapy as follow-ups to MDMA.

A point of potential misidentification should be mentioned here. 2C-T-2 has occasionally been called, simply, T-2. This abbreviated nickname has also been used for T-2 Toxin, a mycotoxin of the Tricothecene group, formed mainly by the *Fusarium* spp. This is the infamous "warfare agent" in Southeast Asia, which was finally identified as bee feces rather than a Soviet military adventure. T-2 and 2C-T-2 are radically different compounds.

All three Tweetios of 2C-T-2 have been made and looked at through human eyes. The 2-EtO-homologue of 2C-T-2 is 2-ethoxy-4-ethylthio-5-methoxyphenethylamine, or 2CT2-2ETO. The benzaldehyde (2-ethoxy-4-ethylthio-5-methoxybenzaldehyde) had a melting point of 73-75 °C, the nitrostyrene intermediate a melting point of 122-123 °C, and the final hydrochloride a melting point of 202-204 °C. Fifty milligrams was a completely effective level. The effects were felt very quickly. Vision was blurred, and there were intense eyes-closed visuals and the generation of a pleasant, contemplative mood. Baseline was re-established in five or six hours, but sleep was restless, with weird dreams. Nasal administration showed considerable variation between individuals, but a typical dose was 10 milligrams.

The 5-EtO-homologue of 2C-T-2 is 5-ethoxy-4-ethylthio-2-methoxyphenethylamine, or 2CT2-5ETO. The benzaldehyde (5-ethoxy-4-ethylthio-2-methoxybenzaldehyde) had a melting point of 49 °C, but it was impure. The nitrostyrene intermediate melted at 107-108 °C, and the final hydrochloride had a melting point of 180 °C. At levels of 20 milligrams, there was a slow, gentle climb to a full effect at the third or fourth hour. The flooding of thoughts and easy conversation lasted for many hours, and on some occasion a sedative was needed at the 16 hour point. There was a feeling of being drained for the following day or two. Some intoxication was still noted in the second day. Again it is true here, as had been stated as a generality, that the 5-Tweetio analogues have potencies similar to that of the parent compound, but show a much longer duration. The nickname of "forever yours" had been applied. There may indeed be insight, but 24 hours' worth is an awful lot of insight.

The 2,5-DiEtO-homologue of 2C-T-2 is 2,5-diethoxy-4-ethylthiophenethylamine, or 2CT2-2,5DIETO. The benzaldehyde, 2,5-diethoxy-4-(ethylthio)-benzaldehyde, had a melting point of 84-85 °C, the nitrostyrene intermediate a melting point of 123-124 °C, and the final hydrochloride a melting point of 220-221 °C. Levels that were evaluated from 10 to 50 milligrams were not particularly different in intensity, but were progressively longer in duration. At 50 milligrams there was a nervousness and edginess during the early part of the experience, but for the next several hours there was evident both energy and high attentiveness. There were few if any sensory alterations. There were no negatives on the following day. The duration was perhaps nine hours.

#41 2C-T-4; 2,5-DIMETHOXY-4-(i)-PROPYLTHIO-PHENETHYLAMINE

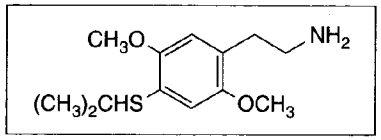
SYNTHESIS: To a solution of 2.5 g of KOH pellets in 40 mL hot EtOH, there was added 5.4 g 2,5-dimethoxythiophenol (see under 2C-T-2 for its preparation) and 8.7 g isopropyliodide. White solids appeared in a few min, and the reaction mixture was heated on the steam bath overnight. This mixture was added to 200 mL H_2O followed by additional aqueous NaOH to raise the pH to a deep purple-blue on universal pH paper. This was extracted with 3x75 mL CH_2Cl_2. The pooled extracts were stripped of solvent under vacuum, and the residue distilled at 100-110 °C at 0.2 mm/Hg to yield 6.9 g of 2,5-dimethoxyphenyl isopropyl sulfide as a pale yellow

oil. It has a very light, pleasant smell of apples.

A mixture of 4.8 g $POCl_3$ and 4.5 g N-methylformanilide was stirred and allowed to stand at room temperature for 1 h To this claret-colored solution was added 3.0 g of 2,5-dimethoxyphenyl isopropyl sulfide, producing an exothermic reaction and immediate reddening. This was heated for 0.5 h on the steam bath, then quenched in 200 mL of warm H_2O producing immediate crystals. Stirring was continued for a few min, and then the solids were removed by filtration, washed with H_2O and sucked as dry as possible. When they were ground up under an equal weight of cold MeOH, refiltered and air dried, they gave 2.35 g of 2,5-dimethoxy-4-(i-propylthio)benzaldehyde as pale yellow solids (in some runs this was a pale lime-green color) with a mp of 89-90 °C. A wasteful recrystallization from MeOH gave pale yellow crystals with a mp of 90 °C sharp.

To a solution of 6.7 g 2,5-dimethoxy-(i-propylthio)benzaldehyde in 40 g of nitromethane there was added 0.10 g of anhydrous ammonium acetate, and the mixture was heated on the steam bath for 2 h. The excess reagent/solvent was removed under vacuum yielding 8.9 g of orange solids. This was recrystallized from 200 mL boiling MeOH providing 6.2 g of 2,5-dimethoxy-ß-nitro-4-(i-propylthio)styrene as lustrous golden orange platelets.

A solution of LAH (80 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 2.1 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 5.74 g 2,5-dimethoxy-ß-nitro-4-(i-propylthio)styrene as a solid, a bit at a time. After 15 min further stirring, the temperature was brought up to a gentle reflux on the steam bath for another 15 min, then allowed to stand at room temperature overnight. After cooling again to 0 °C, the excess hydride was destroyed by the addition of 7 mL IPA followed by 6 mL 15% NaOH which was sufficent to give a white granular character. The reaction mixture was filtered and the filter cake washed with THF. The filtrate and washings were pooled, stripped of solvent under vacuum providing 3.9 g of a pale amber oil which was dissolved in 250 mL dilute H_2SO_4. This was washed with 3x75 mL CH_2Cl_2 which removed the residual yellow color. After making basic with 25% NaOH, the product was extracted with 3x75 mL CH_2Cl_2 and the solvent removed under vacuum to give 2.72 g of a residue which was distilled at 140-145 °C at 0.2 mm/Hg to give 2.42 g of a clear white oil. This was dissolved in 25 mL IPA, and neutralized with concentrated HCl. This gave a clear solution which, with good stirring, was diluted with 100 anhydrous Et_2O to provide 2.40 g 2,5-dimethoxy-4-(i)-propylthiophenethylamine hydrochloride (2C-T-4) as white crystals.



DOSAGE: 8 - 20 mg.

DURATION: 12 - 18 h.

QUALITATIVE COMMENTS: (with 8 mg) "Visual effects set in at about two hours. There was much color enhancement, particularly of green, and some flowing of colors. The bright impressionistic picture of the little girl, in the bathroom, was particularly good for the visuals to take over, especially when I was concentrating on urinating. The shadows in the large picture above the fireplace would change constantly. I could not either control or turn off these effects during the middle period (3-6 hours). From the physical point of view, something early in the experience simply didn't feel right. Both my lower legs tended to fall asleep, and this seemed to spread to my hands and lower arms. It was uncomfortable and although I was apprehensive at first it didn't get any worse with time so I ignored it. This is not one my favorite materials, and it takes too long to wear off. If I were to do it again I would settle for 4 or 5 milligrams. It may well cut out the extremity problem amd still allow for a pleasant experience."

(with 9 mg) "An important characteristic of this experience was the sense of letting go and flowing with it. Just follow where it leads. This seemed to lead to a growing euphoria, a feeling of clearing out of body residues, and the handling of very impressive insights. My thinking continued to grow in clarity, visual perception was crystal clear, and it was a joy to simply look over the scenery, enjoy the beauty, enjoy the companionship, and ponder whatever came to mind. This clarity of body and mind lasted the rest of the evening with a wonderful feeling of peace and centeredness. I still felt a lot of push from the chemical at bed time, causing some tiredness, and allowing very little sleep. I kept working at what had taken place, all night, just to release the experience."

(with 14 mg) "Very rational, benign, and good humored. The insight and calm common to the 2C-T's are present, with less of the push of body-energy which makes 2C-T-2 difficult for some people. There are no particular visuals, but then I tend to screen them out consistently, except in cases of mescaline and LSD and psilocybin, so I can't judge what others would experience in the visual area. The eyes-closed imagery is very good without being compelling. The decline is as gradual and gentle as the onset. I am fully capable of making phone calls and other normal stuff. Music is marvelous, and the body feels comfortable throughout."

(with 14 mg) "Persistent cold feet, and an uncertain stomach when moving around. Brilliant color trails reminiscent of 2C-B. But a change is occurring and I can't talk myself out of it. There are dark corners. If I were with other people, this would bring out the worst in me, which can be pretty bad."

(with 19 mg) "I was caught by the TV. Leonard Bernstein conducting West Side Story. I think I know every note. This was a 1985 rehearsal with the goofs and the sweat. And now Peter, Paul and Mary, grown older along with the songs we all sang. *Where Have All the Flowers Gone* — and an audience of grown-older people singing *Puff the Magic Dragon* like earnest children and probably crying along with me. It is good to have lived through the 60's and not to be in them now. Now there's a new song about El Salvador and it's the battle all over again on a different field, but it will always be so, until and unless. Now, in the 80's, I don't

get really angry anymore. I am more warrior than angry protester, and that's a much better way to be. In fact, I am quite happy to be where I am. I know a lot more about the game, and what it is, and why it is played, and I have a good idea about my part in it, and I like the part I've chosen."

(with 22 mg) "The transition took place over three hours, an alert in 30 minutes followed by a slow and gentle climb. I found it difficult, not physically but mentally since I was for a while locked into the illogical and disconnected aspects of human experiences and expressions, particularly laws and pronouncements and unseeing prejudices, m ·f which I was picking up from reading the Sunday paper book reviews. As tim : on, things became less pushy and I came to be at ease with very positive feelings about everything going on. No self-rejecting aspect at all. Sleep was excellent, but the next day things went slowly and I had to nap a bit. Next time, maybe 18 milligrams."

EXTENSIONS AND COMMENTARY: There are shades of the variability of the Alephs. Some observers are overwhelmed with colors and visual activity; others volunteer their absence. And a very wide range of dosages represented, from an estimated 4 or so milligrams for full effects, to something over 20 milligrams without any loss of control. That is an unusually wide lattitude of activity. And a rich variety of effects that might be experienced. The same wide range of effective dosages was also observed with the corresponding Tweetio. The 2-EtO-homologue of 2C-T-4 is 2-ethoxy-5-methoxy-4-(i)-propylthiophenethylamine, or 2CT4-2ETO. The benzaldehyde (2-ethoxy-5-methoxy-4-(i-propylthio)benzaldehyde had a melting point of 43-44 °C, the nitrostyrene intermediate a melting point of 77-79 °C, and the final hydrochloride a melting point of 153.5-154 °C. There were practically no differences between trials at 5 milligram increments within the 10 and 25 milligram range. Each produced a gentle plus two level of effect which lasted for some 10 hours. A code name of "tenderness" was felt to be appropriate, as there was a peaceful meditative inner receptiveness and clarity noted, with an honest connection felt with those who were present during the experience. Sleep was not comfortable.

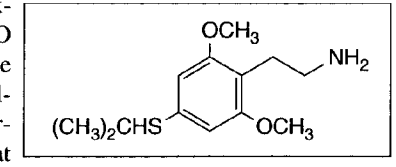
I have heard 2C-T-4 referred to as T-4. There is a potent explosive used by terrorists called cyclotrimethylenetrinitramine, known by the code name RDX, or T-4. There is also a T-4 term that refers to thyroxine, an amino acid in the body. The drug 2C-T-4 is neither an explosive nor an amino acid, I am happy to say.

#42 Ψ-2C-T-4; 2,6-DIMETHOXY-4-(i)-PROPYLTHIO-PHENETHYLAMINE)

SYNTHESIS: A stirred solution of 8.3 g 3,5-dimethoxy-1-chlorobenzene and 7.2 g isopropylsulfide in 100 mL anhydrous Et_2O was cooled with an external ice bath, and then treated with 67 mL 1.5 M lithium diisopropylamide in hexane which was

added over the course of 10 min. The reaction mixture was allowed to return to room temperature and the stirring was continued for 0.5 h. The mixture was poured into dilute H_2SO_4, the organic layer was separated, and the aqueous phase extracted with 3x75 mL EtOAc. The organic phases were combined, dried over anhydrous K_2CO_3, and the solvent removed under vacuum. The resulting 4.54 g of almost colorless oil was distilled at 85-95 °C at 0.1 mm/Hg to give 4.2 g of 3,5-dimethoxyphenyl isopropyl sulfide as a colorless oil, showing a single spot on TLC with no indication of starting chlorobenzene. The product formed a picrate salt, but this had an unsatisfactory mp character (partly melting at 45-47 °C, and then completely at about 80-90 °C). The microanalysis for this picrate was low in the carbon value, although the hydrogen and nitrogen were excellent. Anal. ($C_{17}H_{19}N_3O_9S$) H,N; C: calcd, 46.25; found, 44.58, 44.45.

To a well-stirred solution of 4.1 g 3,5-dimethoxyphenyl isopropyl sulfide and 3.5 mL N,N,N',N'-tetramethylethylenediamine in 25 mL anhydrous Et_2O that had been cooled to -78 °C with a dry-ice/acetone bath, there was added 10 mL 2.5 M hexane solution of butyllithium. The mixture was allowed to return to room temperature, and there was added 3.5 mL DMF which caused the yellow color to progressively darken. The reaction mixture was poured into dilute H_2SO_4, the Et_2O layer was separated, and the aqueous phase extracted with 3x75 mL EtOAc. The solvent was removed from the combined organic phases, and the residue distilled at 0.15 mm/Hg to give two fractions. One, boiling at 120-140 °C, was 0.98 g of a pale yellow mobile liquid, which was part starting sulfide and part product aldehyde by TLC. The second cut, boiling at 160-180 °C, was a viscous liquid, weighed 1.66 g, and was largely 2,6-dimethoxy-4-(i-propylthio)benzaldehyde. This formed a crystalline anil with 4-methoxyaniline (by fusing equimolar amounts of the two with a flame) which, after recrystallization from MeOH, gave fine yellow crystals with a mp of 87.5-89 °C. Anal. ($C_{19}H_{23}NO_3S$) C,H.



A solution of 0.8 g 2,6-dimethoxy-4-(i-propylthio)benzaldehde in 10 mL nitromethane was treated with 0.2 g anhydrous ammonium acetate and heated on the steam bath for 1 h. The excess reagent/solvent was removed under vacuum, and the residue spontaneously solidified. This was recrystallized from 5 mL MeOH to give 0.70 g 2,6-dimethoxy-ß-nitro-4-(i)-propylthiostyrene as a pale yellow fluffy solid, with a mp of 83-84.5 °C. Anal. ($C_{13}H_{17}NO_4S$) C,H.

A solution of LAH (20 mL of a 1 M solution in THF) was cooled, under He to 0 °C with an external ice bath. With good stirring there was added 0.54 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 0.54 g 2,6-dimethoxy-ß-nitro-4-(i)-propylthiostyrene in a small volume of anhydrous THF. The color was discharged immediately. After a few minutes further stirring, the temperature was brought up to a gentle reflux on the steam bath for about 10 min, and then all was cooled again to 0 °C. The excess hydride was

destroyed by the cautious addition of IPA followed by sufficent 15% NaOH to give a white granular character to the oxides, and to assure that the reaction mixture was basic. The reaction mixture was filtered, and the filter cake washed well with THF. The filtrate was stripped of solvent under vacuum and the residue dissolved in 100 mL of dilute H_2SO_4. This was washed with 2x50 mL CH_2Cl_2 (the washes were saved, see below), made basic with aqueous NaOH, and then extracted with 2x50 mL CH_2Cl_2. The residue remaining after the removal of the solvent was distilled at 130-140 °C at 0.05 mm/Hg to give 0.11 g of a white oil. This was dissolved in 10 mL IPA, neutralized with 5 drops of concentrated HCl and diluted with 50 mL anhydrous Et_2O. After filtration of the formed crystals, Et_2O washing, and air drying, there was obtained 80 mg of 2,6-dimethoxy-4-(i)-propylthiophenethylamine hydrochloride (ψ-2C-T-4) as fine white crystals. The removal of the solvent from the CH_2Cl_2 washes of the dilute H_2SO_4 solution gave a H_2O-soluble white solid that proved to be the sulfate salt of the product. This provided, after making the H_2O solution basic, extraction with CH_2Cl_2, and solvent removal, the free base that was converted, as described above, to a second crop of the hydrochloride salt.

DOSAGE: above 12 mg.

DURATION: probably short.

QUALITATIVE COMMENTS: (with 8 mg) "I might actually be up to a plus 1, and with a very good feeling. But I cannot say how long it lasted, and it was probably pretty short. It just sort of faded away."

(with 12 mg) "At the 25 minute point I am reminded of the experiment, and in another quarter hour I am into something. Will this be another forever threshold? I feel very good, but there is no sparkle."

EXTENSIONS AND COMMENTARY: Here is another example of the presentation of a compound for which there has not yet been an effective level determined. Why? For a very good reason. This is an example of a whole class of compounds that I have called the pseudos, or the ψ-compounds. Pseudo- as a prefix in the literary world generally stands for "false." A pseudopod is a thing that looks like a foot, but isn't one. A pseudonym is a fictitious name. But in chemistry, it has quite a different meaning. If something has a common name, and there is a second form (or isomer, or shape, or orientation) that is possible and it doesn't have a common name, it can be given the name of the first form with a "pseudo-" attached. Ephedrine is the erythro-isomer of N-methyl-ß-hydroxyamphetamine. There is a second stereoisomer, the threo- isomer, but it has no trivial name. So it is called pseudoephedrine, or the "Sudafed" of sinus decongestant fame.

The pseudo-psychedelics are the 2,4,6-trisubstituted counterparts of the 2,4,5-trisubstituted psychedelics. Almost all of the 2,5-dimethoxy-4-something-or-other compounds are active and interesting whether they be phenethylamines or

amphetamines, and it is an exciting fact that the 2,6-dimethoxy-4-something-or-other compounds are going to be just as active and just as interesting. A number of examples have already been mentioned. TMA-2 is 2,4,5-trimethoxyamphetamine (a 2,5-dimethoxy-substituted compound with a methoxyl at the 4-position). The pseudo- analogue is TMA-6 (2,4,6-trimethoxyamphetamine) and it is every bit as potent and fascinating. Z-7 could be called pseudo-DOM, and although it is quite a bit down in potency, it is an active drug and will both demand and receive much more clinical study some day.

Will the other 2,4,5-things spawn 2,4,6-things that are active? Without a shadow of a doubt. Chemically, they are much more difficult to synthesize. The 2,5-dimethoxy orientation made the 4-position a natural and easy target. The 2,6-dimethoxy orientation pushes for 3-substitution, and the 4-position is completely unnatural. Tricks are needed, but tricks have now been found. The above synthesis of pseudo-2C-T-4 shows one such trick. This is, in my opinion, the exciting chemistry and psychopharmacology of the next decade. Well over half of all the psychedelic drugs mentioned in Book II are 2,4,5-trisubstituted compounds, and every one of them has a (potentially active) 2,4,6-pseudo-counterpart.

It goes yet further. The antidepressant series of "Ariadne" compounds are 1-phenyl-2-aminobutanes. But the 1-phenyl is again a 2,4,5-trisubstituted compound. The 2,4,6-isomer will give rise to a pseudo-Ariadne family, and I will bet that they too will be antidepressants. The 1-phenyl-2-aminobutane analog of ψ-2C-T-4 is the 2,4,6-analogue and it has been prepared as far as the nitrostyrene. It has not yet been reduced, so it is not yet been evaluated, but it could be a most remarkable psychopharmacological probe.

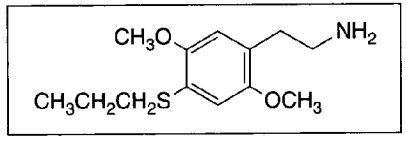
And it goes yet yet further. Think back to the six possible TMA's. TMA and TMA-3 were relatively inactive. And TMA-2 and TMA-6 were the interesting ones. The first gave rise to the last twenty years of psychedelic chemistry, and the other (as speculated upon above) will give rise to the forthcoming ten years. But what of TMA-4 and TMA-5? Both showed activity that was more than TMA but less than that of the -2 or -6 isomers. Could they, some day, provoke yet other families of psychedelics? Maybe the 3-position of these two might be focal points of leverage as to psychological activity. What are the letters that follow ψ in the Greek alphabet? If I remember correctly, the next letter is the last letter, omega. So, I guess that Nature is trying to tell us something, that the -4 and -5 isomers will not engender interesting families. What a pity. The chemistry is so unthinkably difficult that it would have been a true challenge. My next incarnation, maybe?

#43 2C-T-7; 2,5-DIMETHOXY-4-(n)-PROPYLTHIO-PHENETHYLAMINE

SYNTHESIS: To a solution of 3.4 g of KOH pellets in 50 mL hot MeOH, there was added a mixture of 6.8 g 2,5-dimethoxythiophenol (see under the recipe for 2C-T-

2 for its preparation) and 7.4 g (n)-propylbromide dissolved in 20 mL MeOH. The reaction was exothermic, with the deposition of white solids. This was heated on the steam bath for 0.5 h, added to 800 mL H_2O, additional aqueous NaOH added until the pH was basic, and extracted with 3x75 mL CH_2Cl_2. The pooled extracts were washed with dilute NaOH, and the solvent removed under vacuum. The residue was 2,5-dimethoxyphenyl (n)-propyl sulfide which was obtained as a pale yellow oil, and which weighed 8.9 g. It had a light pleasant fruity smell, and was sufficiently pure for use in the next reaction without distillation.

A mixture of 14.4 g $POCl_3$ and 13.4 g N-methylformanilide was heated for 10 min on the steam bath. To this claret-colored solution was added 8.9 g of 2,5-dimethoxyphenyl (n)-propyl sulfide, and the mixture heated an additional 25 min on the steam bath. This was then added to 800 mL of well-stirred warm H_2O (preheated to 55 °C) and the stirring continued until the oily phase had completely solidified (about 15 minutes).



The resulting brown sugar-like solids were removed by filtration, and washed with additional H_2O. After sucking as dry as possible, they were dissolved in an equal weight of boiling MeOH which, after cooling in an ice-bath, deposited pale ivory colored crystals. After filtration, modest washing with cold MeOH, and air drying to constant weight, there was obtained 8.3 g of 2,5-dimethoxy-4-(n-propylthio)benzaldehyde with a mp of 73-76 °C. Recrystallization from 2.5 volumes of MeOH provided a white analytical sample with mp 76-77 °C. The NMR spectrum in $CDCl_3$ was textbook perfect, with the two aromatic protons showing singlet signals at 6.81 and 7.27 ppm, giving assurance that the assigned location of the introduced aldehyde group was correct.

To a solution of 4.0 g 2,5-dimethoxy-(n-propylthio)benzaldehyde in 20 g of nitromethane there was added 0.23 g of anhydrous ammonium acetate, and the mixture was heated on the steam bath for 1 h. The clear orange solution was decanted from some insoluble material and the excess nitromethane removed under vacuum. The orange-yellow crystalline material that remained was crystallized from 70 mL boiling IPA which, on slow cooling, deposited 2,5-dimethoxy-ß-nitro-4-(n)-propylthiostyrene as orange crystals. After their removal by filtration and air-drying to constant weight, they weighed 3.6 g, and had a mp of 120-121 °C. Anal. ($C_{13}H_{17}NO_4S$) C,H.

A solution of LAH (132 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 3.5 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 8.4 g 2,5-dimethoxy-ß-nitro-4-(n)-propylthiostyrene in 50 mL anhydrous THF. There was an immediate loss of color. After a few min further stirring, the temperature was brought up to a gentle reflux on the steam bath, then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of IPA (21 mL required) followed by sufficent 5% NaOH to give a white granular character

to the oxides, and to assure that the reaction mixture was basic (15 mL was used). The reaction mixture was filtered and the filter cake washed first with THF and then with IPA. The filtrate and washes were combined and stripped of solvent under vacuum providing about 6 g of a pale amber oil. Without any further purification, this was distilled at 140-150 °C at 0.25 mm/Hg to give 4.8 g of product as a clear white oil. This was dissolved in 25 mL IPA, and neutralized with concentrated HCl forming immediate crystals of the hydrochloride salt in the alcohol solvent. An equal volume of anhydrous Et_2O was added, and after complete grinding and mixing, 2,5-dimethoxy-4-(n)-propylthiophenethylamine hydrochloride (2C-T-7) was removed by filtration, Et_2O washed, and air dried to constant weight. The resulting spectacular white crystals weighed 5.2 g.

DOSAGE: 10 - 30 mg.

DURATION: 8 - 15 h.

QUALITATIVE COMMENTS (with 20 mg) "A wonderful day of integration and work. Took about 2 hours for the onset. Some nausea on and off — that seemed to cycle periodically throughout the day. Visuals were great, much like mescaline but less sparkly. Lots of movement and aliveness — velvety appearance and increased depth perception. Neck and shoulder tension throughout the day along with legs. I would periodically notice extreme tightness of muscles, and then relax. Working was very integrative. Back and forth constantly between wonderful God-space — similar to MDMA but more grounded — then always back to sadness. I felt that it really showed me where I was unfinished, but with self-loving and tolerance. Tremendous processing and letting go. Seeing things very clearly and also able to laugh at my trips. Lots of singing. In spite of shoulder tension, vocal freedom and facility were very high. I felt my voice integrated and dropped in a way it never had before, and that remained for several days. Able to merge body, voice, psyche and emotions with music and then let go of it as a role. I also realized and gave myself permission to do whatever it takes to get free. I let go of Dad with tragic arias. The next day I let go of Mom by singing Kaddish for her, and merging with it."

(with 20 mg) "I lay down with music, and become engrossed with being as still as possible. I feel that if I can be totally, completely still, I will hear the inner voice of the universe. As I do this, the music becomes incredibly beautiful. I see the extraordinary importance of simply listening, listening to everything, to people and to nature, with wide open receptivity. Something very, very special happens at the still point, so I keep working on it. When I become totally still, a huge burst of energy is released. And it explodes so that it takes enormous effort to quiet it all down in order to be still again. Great fun."

(with 25 mg) "This was a marvelous and strange evening. This 2C-T-7 is good and friendly and wonderful as I remember it. I think it is going to take the

place of 2C-T-2 in my heart. It is a truly good material. I got involved with a documentary on television. It was about certain people of Bolivia, people living in the high mountains and about a small village which — perhaps alone among all the places in the country — maintains the old Inca ways, the old traditions, the old language. Which is, I gather, against the law in Bolivia. It showed a yearly meeting of shamans and it was quite clear that hallucinogens played a major part in this meeting. The shaman faces, male and female, were startling in their intensity and earthy depth. The Virgin Mary is worshipped as another version of the ancient Pacha Mama, the Earth Mother. Wonderful dark, vivid look at places and people who are not usually to be seen or even known about."

(with 30 mg) "The visuals have an adaptable character to them. I can use them to recreate any hallucinogenic substance I have known and loved. With open eyes, I can go easily into LSD flowing visuals, or into the warm earth world of Peyote, or I can stop them altogether. With closed eyes, there are Escher-like graphics with a lot of chiaroscuro, geometric patterns with oppositional play of sculptured light and dark values. Green light."

EXTENSIONS AND COMMENTARY: If all the phenethylamines were to be ranked as to their acceptability and their intrinsic richness, 2C-T-7 would be right up there near the top, along with 2C-T-2, 2C-B, mescaline and 2C-E. The range is intentionally extended on the lower side to include 10 milligrams, as there have been numerous people who have found 10 or so milligrams to be quite adequate for their tastes.

One Tweetio related to 2C-T-7 has been made and evaluated. This is the 2-EtO-homologue of 2C-T-7, 2-ethoxy-5-methoxy-4-(n)-propylthiophenethylamine, or 2CT7-2ETO. The benzaldehyde (2-ethoxy-5-methoxy-4-(n-propylthio)benzaldehyde had a melting point of 69-71 °C, the nitrostyrene intermediate a melting point of 106-106.5 °C, and the final hydrochloride a melting point of 187-189 C°. At the 20 milligram level, the effects were felt quickly, and the eyes-closed visuals were modest but real. It was very short-lived, with baseline recovery at about the fifth hour. The next day there was an uncomfortable headache which seemed on an intuitive level to be an after-effect of the compound.

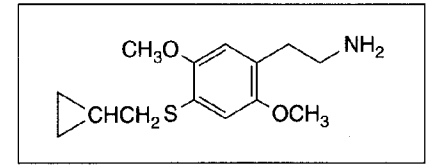
The unusual properties of a number of N-methyl-N-(i)-propyltryptamines suggested the possibility of something like a similar set of N-methyl-N-(i)-propylphenethylamines. Why not try one from 2C-T-7? The thought was, maybe N-methylate this compound, then put on an isopropyl group with reductive alkylation, using acetone as the carbon source and sodium cyanoborohydride. Towards this end, the free base of 2C-T-7 (from one gram of the hydrochloride) was refluxed for 2 h in 1.3 g butyl formate, and on removing the solvent/reactant the residue spontaneously crystallized. This formamide (0.7 g) was reduced with lithium hydride in cold THF to provide 2,5-dimethoxy-4-(n)-propyl-N-methylphenethylamine, METHYL-2C-T-7, which distilled at 150-170 °C at 0.4 mm/Hg. A very small amount of the hydrochloride salt was obtained (65 milligrams) and it

had a brown color. Too small an amount of an impure product; the entire project was dropped.

#44 2C-T-8; 2,5-DIMETHOXY-4-CYCLOPROPYLMETHYLTHIOPHENETHYLAMINE

SYNTHESIS: To a solution of 2.8 g of KOH pellets in 25 mL hot MeOH, there was added a mixture of 5.9 g 2,5-dimethoxythiophenol (see under 2C-T-2 for its preparation) and 5.0 g of cyclopropylmethyl bromide. There was an immediate exothermic reaction with spontaneous boiling and the formation of white crystals. This was heated on the steam bath for 4 h, and then added to 400 mL of H_2O. After extraction with 3x75 mL CH_2Cl_2, the pooled extracts were washed first with dilute NaOH, then with saturated brine, then the solvent was removed under vacuum. The residue, 8.45 g of crude 2,5-dimethoxyphenyl cyclopropyl methyl sulfide, was distilled at 120-140 °C at 0.3 mm/Hg to give a white oil weighing 7.5 g.

A mixture of 13.5 g $POCl_3$ and 13.5 g N-methylformanilide was heated for 10 min on the steam bath. To this claret-colored solution was added 7.28 g of 2,5-dimethoxyphenyl cyclopropylmethyl sulfide, and the spontaneously exothermic mixture was heated for an additional 10 min on the steam bath, and then quenched in 400 mL of 55 °C H_2O with good stirring. After a few minutes a reddish solid phase separated. This was removed by filtration, and washed with additional H_2O. After sucking as dry as possible, this 8.75 g of ochre-colored solid was dissolved in 14 mL of boiling MeOH, and after cooling, filtering, washing sparsely with MeOH, and air drying, gave 7.27 g of white solid crystals of 2,5-dimethoxy-4-(cyclopropylmethylthio)benzaldehyde. The proton NMR spectrum was impeccable; CHO 9.38, ArH 7.27, 6.81 2 s., OCH_3 3.93, 3.90 2 s., SCH_2 t. 2.96, CH_2, m. 1.72, and CH_2, t. 1.11.



To a solution of 6.6 g 2,5-dimethoxy-4-(cyclopropylthio)benzaldehyde in 82 g of nitromethane there was added 0.12 g of anhydrous ammonium acetate, and the mixture was heated on the steam bath for 6 h. The reaction mixture was allowed to stand overnight producing a heavy crystallization crop. Filtration, washing lightly with MeOH, and air drying gave 4.72 g of orange crystals of 2,5-dimethoxy-4-cyclopropylmethylthio-ß-nitrostyrene as yellow crystals. The evaporation of the mother liquors and grinding of the resulting solids with MeOH provided another 2.0 g of the product.

A solution LAH (40 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.05 mL 100% H_2SO_4 dropwise over 10 min, to minimize charring. This was followed by the

addition of 2.95 g 2,5-dimethoxy-4-cyclopropylmethylthio-ß-nitrostyrene as a solid, over the course of 10 min. After a few min further stirring, the temperature was brought up to a gentle reflux on the steam bath, then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 6 mL IPA followed by 3 mL 15% NaOH which gave the aluminum oxide as a curdy white solid. The reaction mixture was filtered, and the filter cake washed with additional THF. The filtrate and washes were stripped of solvent under vacuum providing about 1.8 g of a colorless oil. The addition of dilute H_2SO_4 produced a thick mass of white solids. This was washed with CH_2Cl_2, and the remaining aqueous phase, still containing solids, was made basic with 25% NaOH. The aqueous phase was extracted with 3x75 mL CH_2Cl_2, and the combined extracts stripped of solvent under vacuum. The result was 1.4 g of colorless oil. This was distilled at 150-165 °C at 0.2 mm/Hg to give 1.2 g of a white oil. This was dissolved in 6 mL IPA, neutralized with 0.6 mL concentrated HCl producing spontaneous white crystals. These were diluted with 8 mL additional IPA, and suspended under 60 mL anhydrous Et_2O to provide, after filtering and air drying, 1.13 g of 2,5-dimethoxy-4-cyclopropylmethylthiophenethylamine hydrochloride (2C-T-8) as white crystals.

DOSAGE: 30 - 50 mg.

DURATION: 10 - 15 h.

QUALITATIVE COMMENTS: (with 30 mg) "Bad taste, worse smell. But I like it. I can paint easily, and wouldn't hesitate to take a little more next time, but this is enough with no one to talk to. Manual dexterity good. Body rather warm. Wouldn't mind fooling around. In retrospect, it has a smooth onset, and is not too stimulating. This is a good one."

(with 40 mg) "This is beginning to develop at one and a half hours into it. High energy, good feeling. I have had a heavy, dense feeling between me and my work for several days now, but this is rapidly dissolving, and with this loss, the day continues into one of the most remarkable experiences I have ever had. Excellent feelings, tremendous opening of insight and understanding, a real awakening as if I had never used these materials effectively before. For the next several hours it was an internal journey for me; I wished to interact with myself. I cannot recall all the details, but I did review many aspects of myself and my personal relations. I know that I am the better for all of this."

(with 40 mg) "I first noted the effects at three quarters of an hour, and at two hours I have pain in my sinuses. My head is split in two — this is not being two or three different people — this is one person with a head living in two different universes at the same time. Not a crisis experience, but one of extreme and prolonged discomfort. Hypersensitivity to light, noise, motion, with the belief that it would not go away when the chemical wore off. My visual and spatial perceptions were divided in two along a vertical axis, with both halves moving in uncoordinated ways. A feeling that the eyes were working independently of each other. Nausea without vomiting, even when I tried to. Vertigo became intolerable if I closed my eyes or lay down, so I felt that I would never lie down or close my eyes again. Problems with 'boundaries.' The outside environment seemed to be getting inside my head. The parts of myself seemed to either separate uncontrollably or run together into someone I didn't know. A late movie, and Tranxene, and a little sleep all helped me out of this. However, a buzzing in the head, an uncertain balance, and an out-of-it feeling lasted for 3 days, and was still faintly present after a week."

(with 43 mg) "For the first two hours I rocked in place and felt quite happy not trying to 'do' anything useful or expected, but watched some excellent programs on TV. Later I sat at the typewriter and felt the energy and the opening of the particular kind of thinking-connection that I associate with 2C-T-2. I felt this very strongly; I was fully into my own energy and capable of being aggressive if I decided to. I was very good humored and completely anchored to the earth. In the late evening I went to bed and felt that I would not allow myself to sleep, since the tendency to go completely out of conscious body was quite strong. However, before I could get up and continue happily writing, as I intended, I fell asleep. I slept thoroughly, well, and woke up the next day with good energy and a willingness to get on with the day."

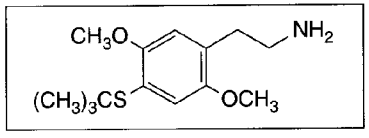
(with 50 mg) "The whole experience was somewhat negative, self-doubting, paranoid. Basically, I am not in a good place. No constructive values ever knit, and although there was a lot of talking, nothing positive developed. I was glad of sleep at about twelve hours into it, and this aspect of it was completely friendly. Next day, no deficit. Strange. Maybe too much."

EXTENSIONS AND COMMENTARY: With 2C-T-8, there are as many negatives as there are positives, and the particular substitution pattern is not one to set the world on fire. The first step was made towards the synthesis of the 3-carbon counterpart, 2,5-dimethoxy-4-cyclopropylmethylthioamphetamine, ALEPH-8. The above benzaldehyde (2.2 g) was cooked overnight on the steam bath in nitroethane (20 mL) containing ammonium acetate (0.4 g) and when the solvent was removed, the residue was converted to orange crystals by the addition of a little MeOH. This was not pursued further. Although the cyclopropylmethyl group was quite something on the mescaline oxygen atom, it is less appealing on the 2C-T-X sulfur atom, and there is even less enthusiasm to put it into an ALEPH. That's the way it is, and who could have guessed!

#45 2C-T-9; 2,5-DIMETHOXY-4-(t)-BUTYLTHIO-PHENETHYLAMINE

SYNTHESIS: To a well-stirred ice-cold suspension of 2.8 g p-dimethoxybenzene and 3.2 mL N,N,N',N'-tetramethylethylenediamine in 100 mL petroleum ether

under an inert atmosphere of He, there was added 13 mL of a 1.6 N solution of butyllithium in hexane. The suspended dimethoxybenzene became opaque and there was a pale yellow color generated. The reaction mixture was warmed to room temperature which converted it to light white solids. After an additional 0.5 h stirring, there was added, slowly, 3.6 g of di-(t)-butyldisulfide. The yellow color deepened, the solids dissolved and, after 1 h, the color was a clear deep brown. This solution was poured into 100 mL dilute HCl and the organic phase was separated. The aqueous fraction was extracted with 3x75 mL CH_2Cl_2. The combined organic phases were washed with dilute aqueous NaOH, with H_2O, and then stripped of solvents under vacuum. The residue was distilled at 95-105 °C at 0.5 mm/Hg to provide 3.7 g of 2,5-dimethoxyphenyl (t)-butyl sulfide as a white, mobile liquid. Anal. ($C_{12}H_{18}O_2S$) C,H. A solid derivative was found in the nitration product, 2,5-dimethoxy-4-(t)-butylthio-1-nitrobenzene, which came from the addition of 0.11 mL of concentrated HNO_3 to a solution of 0.23 g of the above sulfide in 5 mL ice cold acetic acid. Dilution with H_2O provided yellow solids which, on recrystallization from MeOH, had a mp of 92-93 °C. Anal. ($C_{12}H_{17}NO_4S$) C,H. Attempts to make either the picrate salt or the sulfonamide derivative were not satisfactory.



A mixture of 72 g $POCl_3$ and 67 g N-methylformanilide was heated for 10 min on the steam bath. To this claret-colored solution was added 28 g of 2,5-dimethoxyphenyl (t)-butyl sulfide, and the mixture heated for 10 min on the steam bath. This was then added to 1 L of H_2O and stirred overnight. The residual brown oil was separated from the water mechanically, and treated with 150 mL boiling hexane. The hexane solution was decanted from some insoluble tars, and on cooling deposited a dark oil which did not crystallize. The remaining hexane was removed under vacuum and the residue combined with the above hexane-insoluble dark oil, and all distilled at 0.2 mm/Hg. An early fraction (70-110 °C) was largely N-methylformanilide and was discarded. Crude 2,5-dimethoxy-4-(t-butylthio)benzaldehyde came over at 120-130 °C and weighed 12.0 g. This was never satisfactorily crystallized despite the successful formation of seed. It was a complex mixture by TLC, containing several components. It was used for the next step as the crude distilled fraction.

To a solution of 10 g impure 2,5-dimethoxy-(t-butylthio)benzaldehyde in 75 mL of nitromethane there was added 1.0 g of anhydrous ammonium acetate, and the mixture was heated on the steam bath 1.5 h. Removal of the excess solvent/reagent under vacuum produced an orange oil that was (not surprisingly) complex by TLC and which would not crystallize. A hot hexane solution of this oil was allowed to slowly cool and stand at room temperature for several days, yielding a mixture of yellow crystals and a brown viscous syrup. The solids were separated and recrystallized from 40 mL MeOH to give 3.7 g 2,5-dimethoxy-4-(t)-butylthio-ß-nitrostyrene as fine lemon-yellow crystals, with a mp of 93-94 °C. A second crop

of 1.4 g had a mp of 91-92 °C. Anal. ($C_{14}H_{19}NO_4S$) C,H.

A solution of LAH (70 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 2.1 mL 100% H_2SO_4 dropwise, over the course of 20 min. This was followed by the addition of 4.7 g 2,5-dimethoxy-4-(t)-butylthio-ß-nitrostyrene in 20 mL anhydrous THF. There was an immediate loss of color. After a few min further stirring, the mixture was allowed to come to room temperature, and the stirring was continued for 5 h. The excess hydride was destroyed by the cautious addition of 10 mL IPA followed by 6 mL 15% NaOH and finally 6 mL H_2O. The loose white solids were removed by filtration, and the filter cake washed with THF. The filtrate and washes were combined and, after stripping off the solvent under vacuum, there was obtained 4.66 g of a pale yellow oil. Without any further purification, this was distilled at 0.2 mm/Hg. A first fraction came over at up to 120 °C and was a light colorless oil that was not identified. The correct product distilled at 130-160 °C as a pale yellow viscous oil that weighed 1.66 g. This was dissolved in 10 mL IPA, neutralized with 20 drops of concentrated HCl and diluted with 80 mL anhydrous Et_2O. After standing a few min there was the spontaneous generation of white crystals of 2,5-dimethoxy-4-(t)-butylthiophenethylamine hydrochloride (2C-T-9) which were removed by filtration, and air dried. The weight was 1.10 g.

DOSAGE: 60 - 100 mg.

DURATION: 12 - 18 h.

QUALITATIVE COMMENTS: (with 90 mg) "2C-T-9 tastes the way that old crank-case motor oil smells. I was up to something above a plus two at the third hour. Although there were no visuals noted, I certainly would not choose to drive. Somehow this does more to the body than to the head. I feel that the effects are waning at maybe the sixth hour, but there is a very strong body memory that makes sleeping difficult. Finally, at sometime after midnight and with the help of a glass of wine, some sleep."

(with 125 mg) "There was a steady climb to a +++ over the first couple of hours. So far, the body has been quite peaceful without any strong energy push or stomach problems, although my tummy insists on being treated with quiet respect, perhaps out of habit, perhaps not. At the fifth hour, the body energy is quite strong, and I have the choice of focusing it into some activity, such as love-making or writing, or having to deal with tapping toes and floor-pacing. For a novice this would be a murderously difficult experience. Too much energy, too long a time. I suppose I could get used to it, but let me judge by when I get to sleep, and just what kind of sleep it is. It turned out that sleep was OK, but for the next couple of days there was a continuing awareness of some residue in the body — some kind of low-level poisoning. I feel in general that there is not the excitement or creativity to connect with, certainly not enough to justify the cost to the body."

EXTENSIONS AND COMMENTARY: The three-carbon analog of 2C-T-9 (this would be one of the ALEPH series) has never been made and, for that matter, none of the higher numbered 2C-T's have had the amphetamine counterparts synthesized. They are, as of the present time, unknown compounds. This nifty reaction with di-(t)-butyl disulfide worked so well, that three additional disulfides that were at hand were immediately thrown into the chemical program, with the quick assignment of the names 2C-T-10, 2C-T-11, and 2C-T-12.

The lithiated dimethoxybenzene reaction with 2,2-dipyridyl disulfide produced 2,5-dimethoxyphenyl 2-pyridyl sulfide which distilled at 135-150 °C at 0.4 mm/Hg and could be recrystallized from cyclohexane containing 2% EtOH to give a product that melted at 66-67.5 °C. Anal. ($C_{13}H_{13}NO_2S$) C,H. This would have produced 2,5-dimethoxy-4-(2-pyridylthio)phenethylamine (2C-T-10) but it was never pursued.

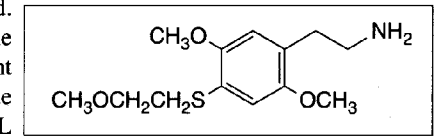
The same reaction with di-(4-bromophenyl) disulfide produced 2,5-dimethoxyphenyl 4-bromophenyl sulfide which distilled at 150-170 °C at 0.5 mm/Hg and could be recrystallized from MeOH to give a product that melted at 72-73 °C. Anal. ($C_{14}H_{13}BrO_2S$) C,H. This was being directed towards 2,5-dimethoxy-4-(4-bromophenylthio)phenethylamine (2C-T-11) but it also was abandoned.

The same reaction with N,N-dimorpholinyl disulfide produced virtually no product at all, completely defusing any plans for the synthesis of a novel sulfur-nitrogen bonded base 2,5-dimethoxy-4-(1-morpholinothio)phenethylamine (2C-T-12). One additional effort was made to prepare a 2C-T-X thing with a sulfur-nitrogen bond. The acid chloride intermediate in the preparation of 2,5-dimethoxythiophenol (as described in the recipe for 2C-T-2) is 2,5-dimethoxybenzenesulfonyl chloride. It reacted smoothly with an excess of diethylamine to produce 2,5-dimethoxy-N,N-diethylbenzenesulfonamide which distilled at 155 °C at 0.13 mm/Hg and which could be recrystallized from a 4:1 mixture of cyclohexane/benzene to give a product with a melting point of 41-42 °C and an excellent proton NMR. This amide proved totally refractory to all efforts at reduction, so the target compound, 2,5-dimethoxy-4-diethylaminothiophenethylamine, has not been made. It has not even been given a 2C-T-X number.

#46 2C-T-13; 2,5-DIMETHOXY-4-(2-METHOXYETHYLTHIO)PHENETHYLAMINE

SYNTHESIS: To a solution of 3.25 g of KOH pellets in 25 mL hot MeOH, there was added 6.8 g of 2,5-dimethoxythiophenol (see under 2C-T-2 for its preparation) followed by 4.73 g of 2-methoxyethylchloride. This mixture was heated on the steam bath for 0.5 h, then added to 500 mL H_2O. This very basic aqueous phase was extracted with 3x100 mL CH_2Cl_2, the extracts pooled, and back-washed with 5% NaOH. The solvent was removed under vacuum to give 8.82 g of a white oil. Distillation gave 2,5-dimethoxyphenyl 2-methoxyethyl sulfide with a bp 115-125 °C at 0.3 mm/Hg, and a weight of 6.65 g.

A mixture of 10 g $POCl_3$ and 10 g N-methylformanilide was heated for 10 min on the steam bath. To this claret-colored solution was added 6.16 g of 2,5-dimethoxyphenyl 2-methoxyethyl sulfide. There was an immediate exothermic reaction and gas evolution. The mixture was heated for 15 min on the steam bath, at which time there was no starting sulfide present by TLC. This was then added to 500 mL of well-stirred warm H_2O (pre-heated to 55 °C) and the stirring continued until only a thin oily phase remained. This was extracted with CH_2Cl_2, the extracts were combined, and the solvent removed under vacuum. The residue was extracted with 5 sequential 20 mL portions of boiling hexane which deposited crystals on cooling. Filtering gave a total of 4.12 g crystalline solids. Recrystallization from MeOH gave a poor yield of a cream-colored crystal with a mp of 68-69 °C. A more efficient purification was achieved by distillation (155-168 °C at 0.3 mm/Hg) yielding 3.50 g of 2,5-dimethoxy-4-(2-methoxyethylthio)benzaldehyde as a pale yellow solid, with a mp of 67-68 °C. A faster moving (by TLC) trace component with an intense fluorescence persisted throughout the entire purification scheme, and was still present in the analytical sample. Anal. ($C_{12}H_{16}O_4S$) C,H.



To a solution of 3.41 g 2,5-dimethoxy-4-(2-methoxyethylthio)benzaldehyde in 50 g of nitromethane there was added 0.11 g of anhydrous ammonium acetate, and the mixture was heated on the steam bath for 2 h, at which time the starting aldehyde had largely disappeared by TLC (silica gel plates with CH_2Cl_2 as the developing solvent) and a faster moving nitrostyrene product was clearly visible. The clear orange solution was stripped of the excess nitromethane under vacuum producing a yellow oil that crystallized yielding 3.97 g of a yellow solid with a mp of 99-104 °C. Recrystallization of a small sample from MeOH produced (when dry) yellow electrostatic crystals of 2,5-dimethoxy-4-(2-methoxyethylthio)-ß-nitrostyrene with a mp of 107 °C sharp. From IPA the product is a burnished gold color with the mp 106-107 °C. Anal. ($C_{13}H_{17}NO_5S$) C,H.

A solution of LAH (40 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.05 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 3.07 g 2,5-dimethoxy-4-(2-methoxyethylthio)-ß-nitrostyrene in small portions, as a solid, over the course of 10 min. There was a considerable amount of gas evolved, and a little bit of charring. After a few min further stirring, the temperature was brought up to a gentle reflux on the steam bath, and then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 8 mL IPA followed by 3 mL 15% NaOH which gave the reaction mixture a curdy white granular character. The reaction mixture was filtered, the filter cake washed with THF, and filtrate and washes were stripped of solvent under vacuum providing about 3 g of a pale amber oil. This was dissolved in about 40 mL CH_2Cl_2 and

extracted with 200 mL dilute H_2SO_4 in three portions. All of the color remained in the organic phase. The pooled aqueous extracts were washed with CH_2Cl_2, then made basic with 25% NaOH, extracted with 3x75 mL CH_2Cl_2, and the combined extracts pooled and stripped of solvent under vacuum. The 2 g pale yellow oily residue was distilled at 155-165 °C at 0.2 mm/Hg to give 1.23 g of a clear white oil. This was dissolved in IPA, neutralized with concentrated HCl, and diluted with anhydrous Et_2O to produce crystals of 2,5-dimethoxy-4-(2-methoxyethylthio)phenethylamine hydrochloride (2C-T-13). After filtration, washing with Et_2O, and air drying, this white crystalline product weighed 0.89 g.

DOSAGE: 25 - 40 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 25 mg) "I felt it was somewhat noisy as we went into the experience. This noisiness lasted only about an hour, then stopped. At the peak, which seemed to be at about 1 to maybe 1.5 hours, some eyes-closed visuals appeared. There was a white field with colored visuals, at times geometric in shape. These eye-closed images were pleasant and I enjoyed them when I did not concern myself with, or listen to, the conversation. There was an eyes-open change in color, the ivy became a little lighter or maybe a little stronger in color. I'm not sure which. I felt there was a gradual diminishing of activity (whatever that undefined activity was) starting at 2 to 2.5 hours, and coming close to baseline at 6 PM. The descent was pleasant and I would say pleasurable. The experience did not lead to any confusion which I sometimes notice in other experiences. There was no problem with anorexia. We ate constantly during the experience. The grapes and other fruit were lovely. This is one of the few times I would say that I would try a higher dose. Maybe 30 or 33 milligrams. I suspect the experience would be similar, with just a heightened peak at 1 hour and perhaps a little more body effect. It may well be one to try with one's wife."

(with 28 mg) "There was a strange, disturbing twinge exactly eight minutes after starting this, that asked me, 'Should I have done this?' I answered, 'Yes' and the twinge disappeared. And then there was nothing until the expected time of development, at a half hour when I felt a light head and slight dizziness. There was a solid plus two for a couple of hours. I paid careful attention for auditory oddities that I had noted before, but they were not there. In an earlier trial (with 20 milligrams) the radio had the sound of being located in the outdoors with the sounds coming through the wall and into the room where I was. I was at a neutral baseline at about seven hours."

(with 35 mg) "There was a quiet climb, but it was marred with some tummy unquiet, and an annoying persistence of diarrhea. I was very impressed with eyes-closed patterning, which seemed to do its own thing independently of the music. I was clearly up to a +++, but there was a feeling that as soon as it got there it started to go away again. There was no there, there. Yet there were a couple of touches of introspection, of seriousness which I had to respect."

(with 40 mg) "There were four of us, and the entry was individual for each of us. Two of us were nauseous. One volunteered a statement, almost a confession, of too much food and drink in the immediate past. One of us needed his cigarette right now, and then he saw that he was killing himself, and he swore off. Don't know if it will last, however. At the two and a half hour point there is a consensus that this has gone its route and will lose its impact, so three of us decided to supplement on 2C-T-2. Six milligrams proves to be a little light so, some four hours later, we each took another six milligrams. Excellent. In a while we discoved that we were very hungry, and food tasted marvelous. Headaches acknowledged in the early evening, but the extension from T-13 to T-2 seemed to be absolutely correct. And as of the next day, the non-smoker was still a non-smoker.

EXTENSIONS AND COMMENTARY: Most of the synthetic adventures of putting a basic something aways out from the benzene ring, at the four-position, have involved subtle things such as unsaturated bonds or three-membered rings. This was the first try with the actual use of a different atom (an oxygen). What about other heteroatoms such as sulfur or nitrogen or silicon or phosphorus, or some-such?

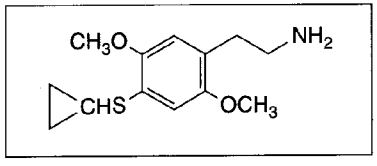
The sulfur counterpart of 2C-T-13 was named 2C-T-14, and was immediately launched. The reaction of 2,5-dimethoxythiophenol and KOH with 2-methylthioethyl chloride in hot MeOH gave 2,5-dimethoxyphenyl 2-methylthioethyl sulfide as a white oil (boiling point of 140-160 °C at 0.3 mm/Hg). This underwent a normal Vilsmeier reaction (phosphorous oxychloride and N-methylformanilide) to give 2,5-dimethoxy-4-(2-methylthioethylthio)benzaldehyde with a melting point of 64-64.5 °C from MeOH. This, in nitromethane containing a little ammonium acetate, was heated on the steam bath for 10 hours and worked up to give an excellent yield of 2,5-dimethoxy-4-(2-methylthioethylthio))-ß-nitrostyrene as garish orange-red "Las Vegas" colored crystals from acetonitrile, with a melting point of 126-127 °C. And as of the moment, this is sitting on the shelf waiting to be reduced to the target compound 2,5-dimethoxy-4-(2-methylthioethylthio)phenethylamine hydrochloride, or 2C-T-14. Will it be active? I rather suspect that it will be, and I'll bet it will be longer-lived than the oxygen model, 2C-T-13.

#47 2C-T-15; SESQUI; 2,5-DIMETHOXY-4-CYCLOPROPYLTHIOPHENETHYLAMINE

SYNTHESIS: To a solution of 3.3 g of KOH pellets in 150 mL hot MeOH, there was added 10 g 2,5-dimethoxythiophenol (see recipe for 2C-T-2 for its preparation) followed by 10 g 1-bromo-3-chloropropane. The reaction was exothermic, and immediately deposited white solids of KCl. The reaction mixture was warmed for a few min on the steam bath, and then quenched in H_2O. The basic reaction mixture

was extracted with 3x75 mL CH_2Cl_2. The pooled extracts were stripped of solvent under vacuum. The residual oil was distilled at 145-155 °C at 0.2 mm/Hg to give 16.5 g of 2,5-dimethoxyphenyl 3-chloropropyl sulfide as a clear, colorless oil.

A solution of the lithium amide of 2,2,6,6-tetramethylpiperidine was prepared by the addition of 20 mL of 2.6 M butyllithium in hexane to a well stirred hexane solution of the piperidine in 100 mL hexane, under an atmosphere of He. The reaction was exothermic, formed a white solid precipitate, and was allowed to continue stirring for a few min. There was then added 6.5 g 2,5-dimethoxphenyl 3-chloropropyl sulfide, and a strongly exothermic reaction ensued. This was stirred for 30 min and then poured into dilute H_2SO_4 (the progress of the reaction must be followed by TLC, silica gel plates, CH_2Cl_2:petroleum ether 50:50 to determine when it is done; in one run over 2 h were required for completion of the reaction). The organic phase was separated, and the aqueous phase extracted with 3x75 mL EtOAc. The combined organic phases were washed first with dilute NaOH, then with dilute HCl, then the solvents were removed under vacuum. The residue was distilled to provide 2,5-dimethoxyphenyl cyclopropyl sulfide as a pale yellow liquid that boiled at 100-115 °C at 0.1 mm/Hg. The use of other bases to achieve this cyclization were less successful. Incomplete cyclization resulted from the use of lithium diisopropyl amide and, if the conditions were made more vigorous, there was dehydrohalogenation to the allyl sulfide. An unexpected difficulty was that the allyl sulfide (from elimination) and the 3-chloropropyl sulfide (starting material) behaved in an identical manner on TLC analysis. They were easily separated, however, by GC analysis.



A completely different approach to the synthesis of this sulfide was explored through the reaction of cyclopropyllithium with an aromatic disulfide, thus avoiding the base-promoted cyclization step. A solution of 2.6 g di-(2,5-dimethoxyphenyl)disulfide (from 2,5-dimethoxythiophenol and hydrogen peroxide, bp 220-230 °C at 0.3 mm/Hg) was made in anhydrous Et_2O, and well stirred. In a separate flask, under an atmosphere of He, 4 mL of 2.6 M butyllithium was added to a solution of 1.2 g cyclopropyl bromide in 20 mL anhydrous Et_2O. This mildly exothermic combination turned a bit cloudy, was stirred for 1 h, then transferred with an air-tight syringe to the above-described Et_2O solution of the aromatic disulfide. A heavy precipitate formed, and stirring was continued for an additional 0.5 h. The reaction mixture was then poured into H_2O, the layers separated, and the aqueous phase extracted with CH_2Cl_2. The extracts were pooled, washed with dilute aqueous KOH, and the solvents removed under vacuum. Distillation gave 0.7 g of 2,5-dimethoxyphenyl cyclopropyl sulfide with identical gas chromatographic behavior to the sample prepared by the cyclization of the chloropropylthio compound.

A mixture of 7.2 g $POCl_3$ and 6.7 g N-methylformanilide was heated on the steam bath until it was claret red. To this there was added 4.5 g of 2,5-dimethoxyphenyl cyclopropyl sulfide, and the exothermic combination heated on the steam bath for about 5 min. The deep red, bubbling reaction mixture was added to 150 mL H_2O and stirred until all oils had been converted into loose solids. These were then removed by filtration, washed with H_2O, and sucked as dry as possible. They were dissolved in boiling MeOH which, after cooling in an ice-bath, deposited yellow crystals of 2,5-dimethoxy-4-(cyclopropylthio)benzaldehyde that weighed 3.43 g after air drying, and had a mp of 97-99 °C. Anal. ($C_{12}H_{14}O_3S$) C,H.

To a solution of 3.0 g 2,5-dimethoxy-4-(cyclopropylthio)benzaldehyde in 40 g of nitromethane there was added 0.2 g of anhydrous ammonium acetate, and the mixture was heated on the steam bath for 3 h. The excess nitromethane was removed under vacuum yielding 3.4 g orange crystals. These were recrystallized from 150 mL boiling IPA containing a little toluene. After cooling, filtering, and air drying there were obtained 2.75 g of 2,5-dimethoxy-4-cyclopropylthio-ß-nitrostyrene as pumpkin-colored crystals with a mp of 159-160 °C. Anal. ($C_{13}H_{15}NO_4S$) C,H.

A solution of LAH (40 mL of a 1 M. solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.05 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 2.5 g 2,5-dimethoxy-4-cyclopropylthio-ß-nitrostyrene in 40 mL anhydrous THF over the course of 15 min. There was an immediate loss of color. After a few min further stirring, the temperature was brought up to a gentle reflux on the steam bath and held there for 2 h. After recooling, there was added IPA (to destroy the excess hydride) followed by sufficent 15% NaOH to give a white granular character to the oxides, and to assure that the reaction mixture was basic. The reaction mixture was filtered, and the filter cake washed with THF. The filtrate and washes were stripped of solvent under vacuum providing a yellow oil that was treated with dilute H_2SO_4. This produced a flocculant white solid, apparently the sulfate salt of the product. This was washed with 4x75 mL CH_2Cl_2 which removed most of the yellow color. The aqueous phase was made basic with aqueous NaOH and extracted with 3x75 mL CH_2Cl_2. Removal of the solvent under vacuum gave a light yellow colored oil that was distilled at 0.3 mm/Hg. The fraction boiling at 140-150 °C was a colorless, viscous oil that weighed 1.97 g. This was dissolved in a few mL IPA, and neutralized with concentrated HCl forming immediate cottage cheese-like crystals of the hydrochloride salt. This was diluted by suspension in anhydrous Et_2O, removed by filtration, and air dried to give 1.94 g of 2,5-dimethoxy-4-cyclopropylthiophenethylamine hydrochloride (2C- T-15) that had a mp of 203-5-204.5 °C. Anal. ($C_{13}H_{20}ClNO_2S$) C,H.

DOSAGE: greater than 30 mg.

DURATION: several hours.

QUALITATIVE COMMENTS: (at 30 mg) "I was somewhere between a threshold

and a plus one for several hours, and appeared to be quite talkative in the evening."

EXTENSIONS AND COMMENTARY: The commonly used name for 2C-T-15, during its synthesis, was SESQUI. The general name for a 15-carbon terpene is sesquiterpene, from the Latin prefix for one and a half. The active level of 2C-T-15 is not known. The highest level yet tried was 30 milligrams orally, and there had been threshold reports pretty regularly all the way up from 6 milligrams. But no definite activity yet. This compound is isosteric with the isopropyl group as seen in the analogous compound 2C-T-4 (the three carbons are in exactly the same positions, only the electrons are located differently) and it is a little surprising that the potency appears to be considerably less. Just over 20 milligrams of the latter compound was overwhelmingly psychedelic.

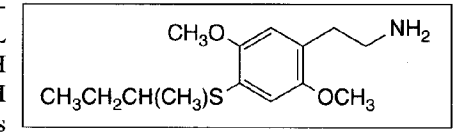
The entire mini-project of hanging cyclic things onto the sulfur atom was an interesting problem. This is the three carbon ring. The six carbon ring (the cyclohexyl homologue) was discussed as 2C-T-5 in the recipe for of ALEPH-2. The cyclobutyl and cyclopentyl homologs were assigned the names of 2C-T-18 and 2C-T-23, respectively, and their preparations taken as far as the nitrostyrene and the aldehyde stages, respectively, before the project ran out of steam.

Towards the cyclobutyl homologue, a solution of 2,5-dimethoxythiophenol and cyclobutyl bromide in DMSO containing anhydrous potassium carbonate was stirred for several hours at room temperature and yielded 2,5-dimethoxyphenyl cyclobutyl sulfide as a white oil that boiled at 135-140 °C at 0.3 mm/Hg. Anal. ($C_{12}H_{16}O_2S$) C,H. This was brought to react with a mixture of phosphorus oxychloride and N-methylformanilide producing 2,5-dimethoxy-4-(cyclobutylthio)-benzaldehyde that had a melting point of 108-109.5 °C from MeOH. Anal. ($C_{13}H_{16}O_3S$) C,H. Coupling with nitromethane in the presence of ammonium acetate produced 2,5-dimethoxy-4-cyclobutylthio-ß-nitrostyrene as lustrous orange crystals from boiling acetonitrile, melting point 160-161 °C. Anal, ($C_{14}H_{17}NO_4S$) C,H. This will some day be reduced to 2,5-dimethoxy-4-cyclobutylthiophenethylamine hydrochloride, 2C-T-18.

Towards the cyclopentyl homologue, a solution of 2,5-dimethoxythiophenol and cyclopentyl bromide in DMSO containing anhydrous potassium carbonate was stirred for several hours at room temperature and yielded 2,5-dimethoxyphenyl cyclopentyl sulfide as a white oil that boiled at 135-145 °C at 0.3 mm/Hg. This was brought to react with a mixture of phosphorus oxychloride and N-methylformanilide producing 2,5-dimethoxy-4-(cyclopentylthio)benzaldehyde as yellow crystals from MeOH. This will some day be converted to the nitrostyrene and then reduced to 2,5-dimethoxy-4-cyclopentylthiophenethylamine hydrochloride, 2C-T-23.

#48 2C-T-17; NIMITZ; 2,5-DIMETHOXY-4-(s)-BUTYLTHIO-PHENETHYLAMINE

SYNTHESIS: To a solution of 2.6 g of KOH pellets in 50 mL hot MeOH, there was added a mixture of 6.8 g 2,5-dimethoxythiophenol (see under 2C-T-2 for its preparation) and 5.8 g (s)-butyl bromide. The reaction was exothermic, with the deposition of white solids. This was heated on the steam bath for a few h, the solvent removed under vacuum, and the resulting solids dissolved in 250 mL H_2O. Additional aqueous NaOH was added to bring universal pH paper to a full blue color. This was extracted with 3x40 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. The residue was 2,5-dimethoxyphenyl (s)-butyl sulfide which was a pale yellow oil, weighing 10.12 g. It was sufficiently pure for use in the next reaction without a distillation step.



A mixture of 15.1 g $POCl_3$ and 14.1 g N-methylformanilide was heated for 10 min on the steam bath. To this claret-colored solution was added 9.4 g of 2,5-dimethoxyphenyl (s)-butyl sulfide, and the mixture heated for 35 min on the steam bath. This was then added to 200 mL of well-stirred warm H_2O (pre-heated to 55 °C) and the stirring continued until the oily phase had completely solidified (about 15 min). These light brown solids were removed by filtration, and washed with additional H_2O. After sucking as dry as possible, these solids (12.14 g wet) were ground under an equal weight of MeOH which produced a yellowish crystalline solid with a mp of 76-81 °C. Recrystallization of a 0.4 g sample from an equal weight of boiling MeOH provided 0.27 g of 2,5-dimethoxy-4-(s-butylthio)benzaldehyde as a pale cream-colored crystalline material with a mp of 86-87 °C.

To a solution of 8.0 g of the crude 2,5-dimethoxy-4-(s-butylthio)benzaldehyde in 40 g of nitromethane there was added 0.38 g of anhydrous ammonium acetate, and the mixture was heated on the steam bath for 1 h. The reddish colored solution was decanted from some insoluble tan material and the excess nitromethane removed under vacuum. The heavy red oil that remained was diluted with an equal volume of boiling MeOH, and allowed to return to room temperature. The orange-colored crystals that slowly formed were removed by filtration and, after air drying, weighted 6.24 g. This was again recrystallized from an equal volume of MeOH, yielding 2,5-dimethoxy-4-(s-butylthio)-ß-nitrostyrene as yellow, somewhat beady crystals that weighed (when dry) 3.50 g and which had a mp of 62-65 °C. A small portion of this fraction was crystallized yet again from MeOH to provide an analytical sample that was yellow-orange in color, and had an mp of 68-69 °C. Anal. ($C_{13}H_{17}NO_4S$) C,H.

A solution of LAH (120 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 3.3 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of

8.83 g 2,5-dimethoxy-4-(s-butylthio)-ß-nitrostyrene in 80 mL anhydrous THF dropwise over the course of 2 h. After a few min further stirring, the temperature was brought up to a gentle reflux on the steam bath, and then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 18 mL IPA followed first by 5 mL of 15% NaOH and then by 15 mL of H_2O. The reaction mixture was filtered, and the filter cake washed with THF. The filtrate and washing were combined and stripped of solvent under vacuum providing about 8.5 g of a pale amber oil. Without any further purification, this was distilled at 135-150 °C at 0.4 mm/Hg to give 6.12 g of a clear white oil. This was dissolved in 30 mL IPA, and neutralized with 2.1 mL of concentrated HCl forming crystals immediately. Another 10 mL of IPA was added to allow the solids to be finely dispersed, and then about 100 mL of anhydrous Et_2O were added. The solids were removed by filtration, Et_2O washed, and air dried to constant weight. The product, 2,5-dimethoxy-4-(s)-butylthiophenethylamine hydrochloride (2C-T-17) was obtained as spectacular white crystals, weighing 5.67 g.

DOSAGE: 60 - 100 mg.

DURATION: 10 - 15 h.

QUALITATIVE COMMENTS: (with 60 mg) "This material took fully three hours to get into its maximum effect. I never was at a +++, quite, and I am not sure why it is really active, but I know it is. There does not seem to be any interference with my concentration or mental coordination, but I wouldn't want to drive right now. Good appetite in the evening, for a Chicago-style pizza, and there was no Tomso effects (the rekindling of a psychedelic effect with alcohol) with a glass of wine. An over-all good and instructive ++, no visuals, totally benign. There is no hesitation in doing it again some day."

(with 100 mg) "A small fragment hadn't dissolved when I drank the solution, and it must have stuck to the back of my mouth, because it made a searing spot that burned for 5 minutes. The first central effects were noted at an hour. The plateau stretched from the 3rd to the 7th hour, then tapered off quite quickly. My sleep was fitful, with some hints of nervous sensitivity. I felt that there were some residuals even into the next morning. A truly heavy psychedelic, but with very few explicit sensual changes or unusual perceptions to justify that comment. Why is it heavy? It just is. This dosage is high enough."

EXTENSIONS AND COMMENTARY: An interesting, and quite logical, habit that seems to always pop up when a lot of talk and energy become directed at a specific compound, is the habit of using a nickname for it. The Tweetios are an example, and in the 2C-T-X family I had mentioned the term SESQUI. Here, this compound was called NIMITZ, for the obvious reason that the major freeway from Oakland to San Jose, the Nimitz freeway, was also called State Highway 17. Its

name has been changed to Interstate 880, and I guess it could now only be used as a reference point if efforts were being made for a 2C-T-880.

The reason that 2C-T-17 is of special theoretic interest is that it is one of the very first of the active psychedelic compounds (along with 2C-G-5) to have a potential optically active center on the side of the ring away from the nitrogen atom. One of the oldest and best studied variants of the phenethylamine chain are the alpha-methyl homologues, the substituted amphetamines. Here there is an asymmetric carbon atom right next to the amine group, allowing the molecule to be prepared in either a right-hand way or a left-hand way. The "R" or the "S" isomer. And in the several studies that have looked at such isomers separately, it has always been the "R" isomer that has carried the psychedelic effects. This probably says something about the nitrogen end, the metabolic end, the "north" end of the receptor site that recognizes these compounds, and suggests that there is some intrinsic asymmetry in the area that binds near to the basic nitrogen atom.

But very little is known of the receptor's "south" end, so to speak, the geometry of the area where the opposite end of the molecule has to fit. Here, with 2-C-17, there is a secondary butyl group, and this contains an asymmetric carbon atom. But now this center of asymmetry is clear across the benzene ring from the nitrogen, and should certainly be in some entirely new part of the receptor site. Why not make this compound with the "R" and the "S" forms in this new and unusual location? Why not, indeed! Why not call them the right-lane and the left lane of the Nimitz? Fortunately, both "R" and "S" secondary butyl alcohols were easily obtained, and the synthesis given above for the racemic compound was paralleled for each of these isomers, separately. Is there any chemistry that is different with the specific optical isomers from that which has been reported with the racemic? There certainly is for the first step, since the butyl alcohols rather than the butyl bromides must be used, and this first step must go by inversion, and it cannot be allowed any racemization (loss of the optical purity of the chiral center).

The synthesis of 2C-T-17 "R" required starting with the "S" isomer of secondary butanol. The "S" 2-butanol in petroleum ether gave the lithium salt with butyllithium which was treated with tosyl chloride (freshly crystallized from naphtha, hexane washed, used in toluene solution) and the solvent was removed. The addition of 2,5-dimethoxythiophenol, anhydrous potassium carbonate, and DMF produced "S" 2,5-dimethoxyphenyl s-butyl sulfide. The conversion to "R" 2,5-dimethoxy-4-(s-butyl-thio)benzaldehyde (which melted at 78-79 °C compared to 86-87 °C for the racemic counterpart) and its conversion in turn to the nitrostyrene, "S"-2,5-dimethoxy-4-(s)-butylthio-ß-nitrostyrene which melted at 70-71 °C compared to 68-69 °C for the racemic counterpart, followed the specific recipes above. The preparation of the intermediates to 2C-T-17 "S" follows the above precisely, but starting with "R" 2-butanol instead. And it is at these nitrostyrene stages that this project stands at the moment.

It would be fascinating if one of the two optically active 2C-T-17's carried all of the central activity, and the other, none of it. What is more likely is that the

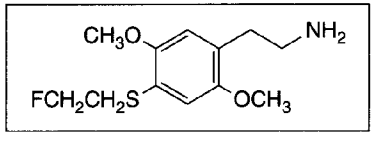
spectrum of effects will be teased apart, with one isomer responsible for some of them and the other isomer responsible for the others. Then, again, maybe the south end of the receptor site in the brain is totally symmetric, and the two optical antipodes will be indistinguishable.

An incidental bit of trivia — yet another bit of evidence that we are all totally asymmetric in our personal body chemistry. "R" and "S" secondary butanols smell different. The "R" has a subtle smell, which is rather fragrant . The "S" is stronger, hits the nasal passages harder, and reminds one of isopropanol more than does the "S" isomer.

#49 2C-T-21; 2,5-DIMETHOXY-4-(2-FLUOROETHYLTHIO)PHENETHYLAMINE

SYNTHESIS: To a solution of 6.9 g of KOH pellets in 100 mL hot MeOH, there was added 13.0 g 2,5-dimethoxythiophenol (see under 2C-T-2 for its preparation) followed by 9.6 g 2-fluoroethyl bromide. The reaction was exothermic, with the immediate deposition of white solids. This was allowed to stand for 2 h, added to 1 L H_2O, and extracted with 3x75 mL CH_2Cl_2. The extracts were pooled and the solvent removed under vacuum. The residue was 2,5-dimethoxyphenyl 2-fluoroethyl sulfide which was a colorless oil and weighed 17.2 g. It was sufficiently pure for use in the next reaction without a distillation step.

A mixture of 26.8 g $POCl_3$ and 24.8 g N-methylformanilide was heated for 10 min on the steam bath. To this claret-colored solution was added 17.0 g of 2,5-dimethoxyphenyl 2-fluoroethyl sulfide, and the mixture heated an additional 25 min on the steam bath. This was then added to 1.5 L of well-stirred warm H_2O (pre-heated to 55 °C) and the oily phase that formed solidified almost immediately. This brown sugar-like product was removed by filtration, and washed with additional H_2O. After sucking as dry as possible, the residual solids (weighing 19.0 g wet) were dissolved in an equal weight of boiling MeOH which, after cooling in an ice-bath, deposited pale ivory colored crystals of 2,5-dimethoxy-4-(2-fluoroethylthio)benzaldehyde. This was air dried to constant weight, which was 15.1 g.



To a solution of 15.0 g 2,5-dimethoxy-(2-fluoroethylthio)benzaldehyde in 75 mL nitromethane there was added 1.35 g of anhydrous ammonium acetate, and the mixture was heated on the steam bath for 70 min (the progress of the reaction must be followed by continuous TLC monitoring). The clear deeply-colored solution was decanted from some insoluble material and the excess nitromethane removed under vacuum. There resulted 17.78 g of almost dry brick-red crystals which were dissolved in 110 mL boiling EtOAc. After cooling overnight in the refrigerator, the crystalline product was removed, washed with EtOAc, and air dried. There was obtained 14.33 g of 2,5-dimethoxy-4-(2-fluoroethylthio)-ß-nitrostyrene as bright orange crystals.

A solution of LAH (140 mL of a 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 3.7 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 8.9 g 2,5-dimethoxy-4-(2-fluoroethylthio)-ß-nitrostyrene in 40 mL of hot anhydrous THF (a heat lamp was needed to keep the nitrostyrene in solution). As the nitrostyrene entered the hydride solution, there was an immediate loss of color. After 1 h stirring at room temperature, the temperature was brought up to a gentle reflux on the steam bath, then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 15 mL IPA and the inorganic solids were made white and filterable by the addition of 15 ml 15% NaOH. The loose cottage-cheesy solids were removed by filtration, and washed with additional THF. The filtrate and washes were pooled and stripped of solvent under vacuum providing 7.39 g of a pale amber oil. This was dissolved in 600 mL dilute H_2SO_4, and washed with 3x50 mL CH_2Cl_2 (which removed the light yellow color). The aqueous phase was made strongly basic with 25% NaOH, extracted with 3x75 mL CH_2Cl_2 and, after pooling, the solvent was removed under vacuum leaving 4.91 g of product as an oil. This was distilled at 145-160 °C at 0.4 mm/Hg giving 3.91 g of a white oil. This was dissolved in 40 mL IPA and neutralized with 35 drops of concentrated HCl. The beautiful white solids that formed were removed by filtration, and washed with IPA. All were suspended in, and ground under, 40 mL anhydrous Et_2O, refiltered and air dried. The final weight of 2,5-dimethoxy-4-(2-fluoroethylthio)phenethylamine hydrochloride (2C-T-21) was 4.07 g of glistening white crystals.

DOSAGE 8 - 12 mg.

DURATION: 7 - 10 h.

QUALITATIVE COMMENTS: (with 6 mg) "I noticed something undefined within five minutes which went away. Within 15 minutes I noticed a definite awareness of activity. There was a progressive increase in awareness of something happening over the next two hours with a plateau of perhaps an hour then occurring. The nature of the happening, as usual, was not clear. During the experience I was more talkative than I usually am. I seemed to be interacting with all others. There was no euphoria but, then, there was no body load or nausea, nor was there any nystagmus. I found a little mental confusion at the peak and there was some searching in my memory bank for the right chips at times. I lost the entire line of one of my conversations at one point during the plateau and had to ask what I was talking about. I tested my visual field on a painting and with sufficient concentration I could get the center part to wiggle a little. I didn't try to observe anything with my eyes closed. I feel that there was something physical about the eyes. In the evening,

after-images were quite intense, and the next day my eyes seemed tired or bothered. What can I say? The material was pleasant and I certainly got the feeling of being high but not getting too much out of it. There were no insights or "ah-hahs." I wonder if periodic and frequent use (say twice a day) at the one or two milligram level would be a positive mood enhancer?"

(with 8 mg) "Comes on very gradually and slowly. Takes about an hour to feel. Reasonably intense in two hours, ++. Very pleasant material, enhancing communication, clear thinking, good feeling. There is a feeling of closeness; the bondedness with the group grows steadily during the day, reaching a highly rewarding level. For me a couple of firsts regarding food. I was hungry only two hours into it. I usually don't want food 'til well down as I usually feel that it interferes with the experience. And, also, I nibbled constantly as I felt that there was nothing in my body. And I enjoyed it thoroughly, feeling only the warmth and energy, with no contrary developments. There was a nice feeling of inner strength and peace."

(with 8 mg) "It was very difficult to fix the times of ascent or descent. Some chilling during onset but not later. And there was some yawning and ear-popping. It is easy on the body, in no way threatening. This time I am very relaxed and somewhat lethargic; the visuals are not too pronounced. Excellent sleep."

(with 10 mg) "I find I can use it if I set my energy in a direction I really want to go in. Otherwise I can just be stoned and self-indulgent. Not out-of-body cosmic at all. But it's good material, an ally, not presenting hidden negatives."

(with 12 mg) "Well ... 12 milligrams is quite enough for a +3, which was established within the first hour and plateau'd by the end of the second. Body felt quite safe, again, but there was considerable push of energy. I did not feel particularly interested in doing anything like writing and in fact preferred to watch television while rocking a bit on the couch, to ease the push. Mood was faintly grim, but not more than faintly. I noted something that I hadn't seen before with this material: time slowing. The first two hours seemed to last a very long time. There was no anorexia. It wasn't until 10 PM [fifth hour] that the idea of writing had any appeal at all. By then, I was still +3 but a lot more at ease. I wrote two letters and enjoyed the process. Sleep was fine. My mood next day was slightly introverted, not very spontaneous for a while. Late in the afternoon, it was a lot better."

EXTENSIONS AND COMMENTARY: This is about as potent a phenethylamine as they come. There are a couple in the 2C-G family that are similar in potency, but they are much longer lived. The motivation for the use of the beta-fluoroethyl group can be seen under the discussion of DOEF, where there was an amalgamation of two lines of reasoning: the imitation of potent serotonin agonists with a need of including an atom (the fluorine) that is potentially labelable with a positron emitter. And the mass-18 isotope of fluorine, with a half-life of just under 2 hours, is ideal for many biological studies. In fact, much of the research work being carried out by the Nuclear Medicine group in Berkeley is based on the analogy between a halogen atom and a beta-fluoroethyl group. There are some similarities in pharmacology so

that if there is a bromine or an iodo atom present in a drug, it is a fair guess that the corresponding beta-fluoroethyl would also be active. In a sense, the cute (and chemically impossible) idea of putting a bromo atom on the sulfur of the 2C-T family is nicely satisfied by using the beta-fluoroethyl group instead (which is chemically completely possible).

A logical extension of 2C-T-21 is the three carbon amphetamine analogue which should be, by comparing structures and activities, a very potent and interesting material in its own rights. This would be 2,5-dimethoxy-4-(2-fluoroethylthio)amphetamine or, following the nomenclature used with the earlier members of this series, ALEPH-21. A solution of 2,5-dimethoxy-4-(2-fluoroethylthio)-benzaldehyde (see earlier in this recipe) in nitroethane with ammonium acetate gave 1-(2,5-dimethoxy-4-(2-fluoroethylthio)phenyl)-2-nitropropene as yellow-orange crystals from MeOH with a melting point of 102-104 °C. And that is where the project now stands. It has not yet been reduced to the amine.

This phenethylamine, 2C-T-21, was the last of the 2C-T's to be completed. A couple of other sulfur analogues have been given numbers, and have been started, but the syntheses are still at some intermediate state.

The (n)-butyl compound, named 2C-T-19, has been taken to the nitrostyrene stage. Reaction between 2,5-dimethoxythiophenol and (n)-butylbromide with KOH gave 2,5-dimethoxyphenyl (n)-butyl sulfide as a colorless oil. This, with phosphorus oxychloride and N-methylformanilide, provided 2,5-dimethoxy-4-(n-butylthio)benzaldehyde as pale orange solids from MeOH, with a melting point of 78-79 °C. This, with nitromethane and ammonium acetate, gave 2,5-dimethoxy-4-(n-butylthio)-ß-nitrostyrene, with a melting point of 133-134 °C from either IPA or acetonitrile.

The 2,2,2-trifluoroethyl compound, which I have named 2C-T-22, has been taken to the benzaldehyde stage. Reaction between 2,5-dimethoxythiophenol and 2,2,2-trifluoroethyliodide with KOH gives 2,5-dimethoxyphenyl 2,2,2-trifluoroethyl sulfide as a very pale amber oil. This, with phosphorus oxychloride and N-methylformanilide provided 2,5-dimethoxy-4-(2,2,2-trifluoroethyl)-benzaldehyde as crystals that proved to be exceedingly difficult to purify. Yellow solids can be obtained from several solvents, and they melt in the 70 °C area. The initially isolated fraction melted at 69-72 °C and showed three major spots by both TLC and GCMS. The largest GC peak was the correct product with a parent peak of 280 m/e, and cracking fragments at 154 and 234 m/e. A small sample was finally obtained from hexane with a melting point of 78-79 °C but I am not sure that even it is particularly pure. Not surprisingly, the reaction of this crude benz-aldehyde with nitromethane and ammonium acetate gave a nitrostyrene product that was a complex mixture. And there that project also rests.

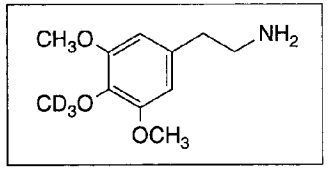
A couple of additional efforts warrant comment. The reaction between trifluoromethyliodide and 2,5-dimethoxythiophenol should have produced 2,5-dimethoxyphenyl trifluoromethyl sulfide, but it didn't produce anything. And one more. What about a bare thio group at the 4-position in this 2C-T-family? Maybe

this can be protected through everything as the disulfide, and be reduced at the last step! The disulfide, 2,5-dimethoxyphenyl disulfide (see under 2C-T-15) was aimed towards the needed bis-aldehyde with phosphorus oxychloride and N-methylformanilide, but all that came out of this were black oils and tars. This has also been abandoned for now.

And it has just occurred to me that there is yet another effort that is certainly worth making, inspired by the observation that 2,2-difluoroethyl iodide is commercially available and not prohibitively expensive. It, with 2,5-dimethoxythiophenol, and following the obvious steps to the aldehyde, the nitrostyrene, and the final amine, would produce 2,5-dimethoxy-4-(2,2-difluoroethylthio)-phenethylamine hydrochloride. It lies exactly half way between the highly potent 2C-T-21 (the mono-fluoro), and the yet to be finished 2C-T-22 (the trifluoro). Let's be weird, and call it 2C-T-21.5. I will wager *mucho* that it will be very potent.

#50 4-D; 3,5-DIMETHOXY-4-TRIDEUTEROMETHOXY-PHENETHYLAMINE

SYNTHESIS: To a solution of 34.0 g homosyringonitrile (3,5-dimethoxy-4-hydroxyphenylacetonitrile, see under ESCALINE for its preparation) in 350 mL acetone containing 0.5 g decyltriethylammonium iodide, there was added 25 g trideuteromethyl iodide followed by 50 g of finely powdered anhydrous K_2CO_3. This mixture was held at reflux on a steam bath for 12 h, added to 2 L of dilute HCl, and extracted with 3x100 mL of CH_2Cl_2. The extracts were washed with 5% NaOH, and the solvent removed under vacuum, yielding 28.0 g yellow solids. These were distilled at 135-150 °C at 0.5 mm/Hg providing 19.4 g 3,5-dimethoxy-4-trideuteromethoxyphenylacetonitrile which melted at 76.5-77.5 °C after crystallization from toluene, or 77-78 °C from methylcyclohexane/$CHCl_3$ 3:1. The mp of the proteo-reference compound, from toluene, was 77-78.5 °C. The OCD_3 stretch in the infra-red occured at 2072 cm^{-1}.



A solution of 275 mL of 1.0 M LAH in THF was cooled under He to 0 °C and treated with 7.25 mL 100% H_2SO_4 added very slowly with vigorous stirring. A solution of 19.3 g 3,5-dimethoxy-4-trideuteromethoxyphenylacetonitrile in 200 mL anhydrous THF was added slowly, and following the addition stirring was continued for 20 min. The reaction mixture was brought to a reflux for 30 min on a steam bath, cooled again to 0 °C, and the excess hydride destroyed with 25 mL IPA. About 15 mL of 15% NaOH was required to convert the solids to a filterable white consistency. These were removed by filtration, the cake washed with IPA, the filtrates and washes were combined, and the solvent removed under vacuum leaving a white oil as residue. This was dissolved in 1.5 L dilute H_2SO_4, washed with

3x75 mL CH_2Cl_2, made basic with aqueous NaOH, and then extracted with 3x75 mL CH_2Cl_2. Removal of the solvent from these extracts under vacuum yielded 18.5 g of a colorless oil which was distilled at 120-150 °C at 0.5 mm/Hg to provide 13.5 g of a white oil. This was dissolved in 70 ml IPA and neutralized with concentrated HCl, producing spontaneous crystals. These were removed by filtration, washed first with IPA then with anhydrous Et_2O. After air drying, the final yield of 3,5-dimethoxy-4-trideuteromethoxyphenethylamine hydrochloride (4-D) was 13.50 g.

DOSAGE: 200 - 400 mg (as the sulfate salt); 178 - 356 mg (as the hydrochloride salt).

DURATION: 12 h.

QUALITATIVE COMMENTS: (with 275 mg) "The onset was smooth and gradual. Within the hour, the slight queasiness I experienced (not as much as with mescaline) completely disappeared. Some visual enhancement, good energy, good communication. It was a very special day for me as I was in a good place pretty much the whole day, and able to communicate clearly without deeper feelings getting in the way. While most enjoyable, and at times remarkable fun, I did not experience the intensity I am familiar with, with mescaline."

(with 300 mg) "The taste was bitter to a moderate degree but faded fast. About 40 minutes later the first stirrings of pleasurable experience came on. It was very mild. Twenty minutes after that an unease of the stomach was apparent, and it stayed with me until I ate some crackers an hour or so later. I got no sharpened visual reactions and no physical instability at any time. I did feel a quickening of thought and verbal flow; again, this was mild and unlike my earlier mescaline patter."

(with 350 mg) "A rapid onset — alert in 20 minutes. Climbed to a plus two in about one hour and stayed there. During the first two hours had a slight queasiness or pre-nausea, and cold hands and feet, but this all disappeared completely and I became very hungry during the whole latter half of the experience. I did not eat much at any one time, but did a lot of snacking and everything tasted good. Very pleasant after the plateau was reached. Pretty good visuals with eyes closed, but not as bright as 2C-B. Very little visuals with eyes open — some movement and flow of objects — pupils dilated. Spent most of the day lying down — had no aversion to conversation but it felt good just to be still. I was in a funny place I can't quite describe — I was in an 'alert lassitude,' a state of 'interested detachment,' or a place of 'vibrating equanimity' or whatever. While trying to recapture the day, it seemed to me that it was a good day, but that nothing much had really transpired. However, upon reflection, I am startled to find that several important shifts took place. It was a day that allowed some peaceful gear-shifting in the mind."

(with 400 mg) "Not a great taste. Some type of awareness at approx. 20

minutes. Considerable nausea peaking at about 1 hr. Some nausea continued through the experience but became quite low. I enjoyed the color show considerably. Trees outside would change color in a wave-like manner. The book-covers upstairs would also change colors and become distorted. Brightly lighted items would undergo the same thing. Believed I could suppress the vision, but concentrating on something would cause it to easily undergo the color and visual changes. Evidently I had little problem following the conversation downstairs, but I remained somewhat quiet. Had an element of confusion that seemed to last for some 4 or 5 hours. Had no problems dropping off to sleep that evening."

EXTENSIONS AND COMMENTARY: The effects of 4-D and ß-D are similar to one-another, both as to dosage and effect. And with both, there is a close parallel to those reported from mescaline. It is reasonable to assume that the human body handles these materials in the same manner, although no metabolic studies have ever been published.

A similar deuterium substitution pattern is of course completely feasible with TMA and related 3,4,5-trimethoxy-substituted analogues. Some studies have supported the idea that the ability to remove methyl groups from such aromatic ethers might be correlated to endogenous schizophrenia. It is possible to imagine that, in such individuals, the effects of substituting trideuteromethyl groups for normal methyl groups might result in psychopharmacological differences of action. Two reports exist that describe metabolic products of mescaline that have lost this methyl group on the 4-position oxygen. It is possible that these might be produced in abnormal quantities in mentally ill subjects. There are also similar reports of the 3-methoxyl group being demethylated in man. Here, studies with 3,5-D (3,5-bis-trideuteromethoxy-4-methoxyphenethylamine) might reveal some differences in quantitative responses in man. These are extremely minor metabolites, however. I suspect that more extensive studies will establish that 4-D, 3,5-D and ß-D all have properties indistinguishable from one-another, at least in healthy subjects.

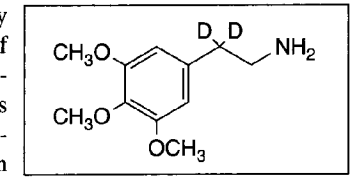
#51 ß-D; 3,4,5-TRIMETHOXY-ß,ß-DIDEUTERO-PHENETHYLAMINE

SYNTHESIS: To a solution of 13.6 g homosyringonitrile (see under ESCALINE for its preparation) in 150 mL acetone containing 200 mg decyltriethylammonium iodide and 30 g of finely powdered anhydrous K_2CO_3, there was added 20 g methyl iodide. The mixture was held at reflux for 18 h in a heating mantle with effective stirring. This was added to 1 L H_2O, acidified with concentrated HCl, and extracted with 3x75 mL CH_2Cl_2. The extracts were pooled, washed with 2x100 mL 5% NaOH, once with dilute HCl, once with saturated brine, and the solvent was

removed under vacuum. The pale yellow residue was distilled at 130-150 °C at 0.3 mm/Hg to yield 12.9 g of 3,4,5-trimethoxyphenylacetonitrile as an off-white solid. Upon crystallization from methylcyclohexane/$CHCl_3$ it was white and had a mp of 77-78 °C. Attempts to prepare this compound by the theoretically appealing route from 3,4,5-trimethoxybenzaldehyde to N,N-dimethyl-3,4,5-tri-methoxy-benzylamine (reductive amination with dimethylamine), to 3,4,5-trimethoxy-N,N,N-trimethylbenzylammonium iodide (methylation with methyl iodide), and then to 3,4,5- trimethoxyphenylacetonitrile (with some source of cyanide ion) gave excellent yields in the first two steps, and no product at all in the last step.

A solution of 20.6 g of 3,4,5-trimethoxphenylacetonitrile in 70 g pyridine was treated with 15 mL 99+% D_2O and held at reflux for 24 h. All volatiles were stripped first under vacuum and finally with a hard vacuum at room temperature in a Kugelrohr apparatus. The dark residue was treated again with another 30 mL pyridine and another 15 mL 99+% D_2O. The flask was protected with a drying tube and held at reflux for another 24 h. Again, all volatiles were stripped, and the residue distilled at 110-130 °C at 0.25 mm/Hg to yield 16.77 g of an almost white solid. The GCMS verified this chemical to be 3,4,5-trimethoxy-ß,ß-dideuterophenylacetonitrile, with a parent peak at m/e 209 and no visible peak at m/e 207.

A solution of 250 mL of 1 M LAH in THF was cooled under He to 0 °C and treated with 6.8 mL 100% H_2SO_4 added very slowly with vigorous stirring. A solution of 18.23 g 3,4,5-trimethoxy-ß,ß-dideuterophenyl-acetonitrile in 200 mL anhydrous THF was added slowly, and following the addition stirring was continued for 20 min. The reaction mixture was brought to a reflux for 30 min on a steam bath, cooled again to 0 °C, and the excess hydride destroyed with 15 mL IPA. About 10 mL of 15% NaOH was required to convert the solids to a filterable white consistency. These were removed by filtration, the cake washed with IPA, the filtrates and washes were combined, and the solvent removed under vacuum leaving 17 g of a white oil as residue. This was dissolved in 2 L dilute H_2SO_4, washed with 3x75 mL CH_2Cl_2, made basic with aqueous NaOH, and then extracted with 3x75 mL CH_2Cl_2. Removal of the solvent from these extracts under vacuum yielded 10.3 g of a colorless oil which was distilled at 120-130 °C at 0.3 mm/Hg to provide 9.2 g of a white oil. This was dissolved in 50 ml IPA and neutralized with concentrated HCl, producing spontaneous crystals. These were diluted with 50 mL anhydrous Et_2O, removed by filtration, washed first with Et_2O/IPA, and then with anhydrous Et_2O. After air drying, the final yield of 3,4,5-trimethoxy-ß,ß-dideuterophenethylamine hydrochloride (ß-D) was 10.0 g of white needles.



DOSAGE: 200 - 400 mg (as the sulfate salt); 178 - 356 mg (as the hydrochloride salt).

DURATION: 12 h.

QUALITATIVE COMMENTS: (with 200 mg) "The onset was very gradual and very gentle. At about an hour and a half I was rather out of my body (at least I wasn't aware of my body, it felt so light). I was listening to Berlioz Requiem, and it took me to the highest realm. I was totally caught up in the magnificence of the music, of the genius it took to compose it, the love it took to complete it, and the devotion of the composer. I felt as though this music had been written for me. What came next is hard to remember because I was so taken with this experience which came only 1 1/2 hours after ingestion. I wondered what time it was and how come I was having a peak experience so soon, because this material was supposed to reach its peak after two hours. Well, now we can revise the records, heh? Incidentally this material is really good for interior work. It was a magnificent experience — one of the best."

(with 275 mg) "I begin to feel it in 15 minutes, stomach getting squeamish. Looking up into the clouds, becoming absorbed in them, watching light grow in intensity, stomach feelings disappeared. Became totally absorbed by the music. Listening to Boito's Prologue to Mephistopheles — exquisitely beautiful, dramatic. Lying on the couch, the music continuing, I was suddenly filled with enormous power. I realized that raw, male power was pouring through me as I had never before experienced it. I was wild, totally self satisfied, and completely oblivious of others and their needs. I wanted to strike out, to win, to conquer. I felt what conquerers have felt in the past, the unbridled passion to vanquish everything. I could see how such misguided power could lead nations to war. Wanting still more power, I was about to find out if God would grant me the power to destroy the world if I wished it, when I felt a gentle kiss on my brow. My wife had leaned over just in time to save the world."

(with 275 mg) "Never had I had such a magnificent appreciation of God. It was clear that if I minded my business and turned to Him to learn as I had been doing today, then I could continue to grow and learn in a most wonderful way. It became crystal clear to me that I didn't have to help anybody or heal anybody, as everyone can turn directly to the source for their needs. An earth-shaking experience."

(with 300 mg) "I had extreme nausea, and vomited. This had a very hard impact on me, and I had to retreat with a paranoia that swept over me without warning. I lay down and let it sweep on, and through this came several very important insights. At least they were important to me. It was about the fourth hour before I could emerge from my retreat, and at that time I knew that I had answered some troublesome personal problems. It was a satisfactory day, but I probably shall not repeat it."

(with 350 mg) "Strong body awareness started within 15 minutes. Visual activity started within half an hour. Visuals were typical kinds, but seemed to arrive earlier. A strong experience of pleasantness started and continued throughout the experience. I tended to internalize to some extent. Ended on a water bed at maybe an hour and a half, pulled covers over me, and went inward with considerable visuals but not much insight. I felt good about where I was. I would not mind being there again, so something was going well. I am not sure how long this continued. The visuals decreased somewhere around the 5th or 6th hour. After 8 or 9 hours, activity considerably decreased. I felt quite clear and reasonably centered. Would I do this again? The answer is yes."

(with 500 mg) "I consumed the material over a period of twenty minutes, and at the 1 hour 45 minute point, haven't had any nausea, but I am still careful not to bounce around. Am absolutely grounded even though I am completely into the experience. No more that state in which it is possible to seriously consider trying to rise two inches above the floor and skim, as I do so expertly in dreams. As a matter of fact I haven't had those dreams for some time now. This material doesn't allow the straddling of realities as does ordinary mescaline. I know where my realities are, and reality is, basically, where my center is. Thus I am grounded in the physical reality even when the doors are open to non-physical levels."

EXTENSIONS AND COMMENTARY: The 4-D and the ß-D are two of five obvious deuterium isomer derivatives of mescaline. The three remaining are: (1) 3,5-D (4-methoxy-3,5-bis-trideuteromethoxyphenethylamine); (2) 2,6-D (2,6-dideutero-3,4,5-trimethoxyphenethylamine); and (3) α–D (α.α-dideutero-3,4,5-trimethoxyphenethylamine). I fully expect both 3,5-D and 2,6-D to be indistinguishable from mescaline in effect, since it is known that not much metabolism takes place in man at these locations of the molecule.

The last compound, α-D, could be quite a different matter. The principal metabolite of mescaline is 3,4,5-trimethoxyphenylacetic acid, and this product requires enzymatic attack at the exact position where the deuteriums will be located. To the extent that they are harder to remove (come off more slowly or to a lesser degree), to that extent the molecule will be more potent in man, and the dosage required for effects will be less. The compound will be easily made by the reduction of 3,4,5-trimethoxyphenylacetonitrile with lithium aluminum deuteride. And if there is a believable difference between α-D and mescaline, it will be necessary to synthesize each of the two optically active α-mono-deutero analogs. That will be quite a challenge.

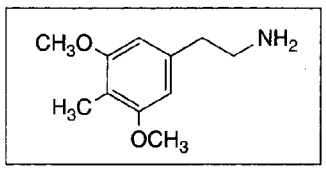
Some years ago I performed a fascinating series of experiments with another isotopically labeled mescaline derivative. This was ß-^{14}C labeled material, which I self-administered on three occasions, at three different levels. One dosage was with 350 milligrams, a second a few weeks later was with 4 milligrams, and a third was a few weeks later yet, with about 60 micrograms. In each case, exactly the same absolute quantity of radioactivity was administered, so the metabolic distribution was equally visible. Only the weight dosage was different. Urinary analysis was run for each experiment for the presence of unchanged mescaline, and for the primary metabolite, 3,4,5-trimethoxyphenylacetic acid. The smaller the

dosage, the proportionately larger amount of mescaline was oxidized to the inactive acetic acid, and the smaller amount was excreted in an unchanged state. It seemed to me that there might be a finite capacity of the body to oxidatively deaminate mescaline, and at larger and larger dosages, this capacity became increasingly depleted. Perhaps this is why mescaline requires such a large dosage to be effective in man.

#52 DESOXY; 3,5-DIMETHOXY-4-METHYLPHENETHYLAMINE

SYNTHESIS: To a well-stirred solution of 31 g 2,6-dimethoxytoluene in 200 mL CH_2Cl_2 there was added 11 mL elemental bromine, a portion at a time. There was a copious evolution of HBr and the color gradually faded from deep red to straw. The reaction mixture was poured into 500 mL H_2O, and the organic layer separated, washed first with dillute NaOH and finally with dilute HCl. The solvent was removed under vacuum, and the residue distilled at 85-90 °C at 0.4 mm/Hg to provide 44 g of 3-bromo-2,6-dimethoxytoluene as a white oil.

A well-stirred solution of 42 mL diisopropylamine in 100 mL petroleum ether was placed in a He atmosphere and cooled to 0 °C with an external ice-water bath. There was then added 120 mL of a 2.5 M solution of n-butyllithium in hexane, producing a clear but viscous solution of the lithium amide. Maintaining this temperature, there was added 100 mL of anhydrous THF, followed by 10 mL dry CH_3CN, which produced an immediate white precipitate. A solution of 23 g of 3-bromo-2,6-dimethoxytoluene in 75 mL anhydrous THF was then added which produced a light red color. The reaction mixture was allowed to come to room temperature. The color became progressively darkened, eventually becoming a deep red-brown. After 0.5 h, the reaction mixture was poured into 500 mL of dilute H_2SO_4, the layers were separated, and the aqueous layer extracted with 2x75 mL CH_2Cl_2. The organics were combined, the solvent removed under vacuum, and the residue distilled. Discarding a first fraction, the cut boiling at 125-165 °C at 0.3 mm/Hg was collected. This light yellow fraction spontaneously crystallized and weighed 11.0 g. Trituration under 20 mL petroleum ether provided 1.72 g of 3,5-dimethoxy-4-methylphenylacetonitrile as a yellowish solid.



A solution of LAH in anhydrous THF under nitrogen (20 mL of a 1.0 M solution) was cooled to 0 °C and vigorously stirred. There was added, dropwise, 0.54 mL 100% H_2SO_4, followed by 1.5 g 3,5-dimethoxy-4-methylphenylacetonitrile as a solid. The reaction mixture was stirred at 0 °C for a few min, then brought to room temperature for 1 h, and finally to a reflux on the steam bath for 30 min. After cooling back to 0 °C there was added IPA until no more hydrogen was evolved, followed by sufficient 15% NaOH to produce a granular texture. The white solids

were removed by filtration, and washed with THF. The filtrate and washes were stripped of solvent under vacuum, the residue added to 150 mL dilute H_2SO_4 and washed with 2x50 mL CH_2Cl_2. The aqueous phase was made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. These extracts were pooled, the solvent removed under vacuum, and the residue distilled at 110-120 °C at 0.45 mm/Hg to give a colorless viscous oil. This was dissolved in 10 mL of IPA, neutralized with 10 drops of concentrated HCl and diluted with 20 mL anhydrous Et_2O. The product was removed by filtration, washed with Et_2O, and air dried to give 0.55 g 3,5-dimethoxy-4-methylphenethylamine (DESOXY) as white crystals.

DOSAGE: 40 - 120 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 40 mg) "Initially I felt very chilled, so I lay down under a blanket. Eyes-closed imagery became very dream-like and my general state was felt as having lost my center. Also, not much in touch with feelings, sense of strangeness, almost alien view of the world. Not through recognizable eyes. Neither pleasant nor unpleasant, just strange. Was able to drift into sleep very easily, or sleep-like trance state, with disconnected, far-out imagery. After 3 hours the nausea was gone, I was able to get up and explore. A little food went down well. No drive, no strong focus in any direction. Feel this was a quite fascinating experience. Completely down by six hours. Would go a bit slowly because of slight hints of neurological sensitivity — the instant chilling and a tendency to dart on going to sleep. The nervous system does not feel over-exposed, but all of a sudden there will be a millisecond of auditory hallucination, or an out-of-the-blue startle. So take it easy going up." [Some 24 hours after this experiment had been completed, and a normal baseline re-established, a complex and psychologically disruptive syndrome occurred, that lasted for the better part of a week. The temporal juxtaposition between the use of desoxy and the subsequent "spiritual crisis" initially suggested some possible connection, but in retrospect the events seem to be unrelated].

(with 40 mg) "I have offered to be a control on an experiment where there had been a close relationship between a trial with desoxy and what might have been a psychotic break, or some kind of so-called spiritual emergency. These two events lay within a day of one another. I was aware of my 40 milligram dosage at about three-quarters of an hour into the experiment, and felt that there was no more intensification at the two-hour point. At that time I felt distinctly spaced but with a very good feeling, and I could see no reason not to increase the dosage at some future time. There was a good and mellow mood, and enjoyment in escapist reading. The only physical oddity that I noted was that there had been no urge to urinate, and only a small amount of quite concentrated urine was passed rather late in the experiment. I was at baseline at the fifth hour, and there was nothing unusual at any time during

the following week."

(with 100 mg) "The stuff has a sweet taste! There was a slight heart-push in the early awareness period, with a pulse up to 100 and a feeling of pressure in the chest. There were no apparent visual enhancements, but the eyes-closed imagery to music was noteworthy. Thinking skills and conversation seemed to be fully under control, if not enhanced. There was none of the colorful psychedelic world of mescaline, but this might be just around the corner; perhaps with a larger dose. This is a comfortable in-between level. Sleep was not possible at the sixth hour, but two hours later, it was easy and very restful. There was no negative price to pay the next day."

EXTENSIONS AND COMMENTARY: All substituents that are involved with the several drugs being discussed in this writing are really things that are stuck like warts on the benzene ring that is central to every phenethylamine. Some of these warts are things attached with a oxygen atom; there are some of these in every single compound in this story. No oxygen atom, no psychedelic effect. Without them, one has stimulants or, more frequently, no effects at all.

But the removal of an oxygen atom (in those cases where there is more than one) can radically change the nature of the effects seen. This is the exact meaning of the term "desoxy." "Des", without, and "oxy", the oxygen. Since this drug is simply the structure of mescaline with the oxygen at the 4-position plucked out of the picture, the first impulse was to abbreviate this compound as DOM for desoxymescaline. However, a long, long time ago, in a universe far, far away, a compound was synthesized that had a methoxy group replaced by a methyl, and it was already named DOM. This was the first of the STP analogs, and the initials stood for desoxy (DO, losing an oxygen) and methyl (M, having it replaced with a methyl group). These are two different worlds. One M stands for Mescaline, and the other M stands for Methyl. Let's call it 4-desoxymescaline, or simply DESOXY, and be exact.

This drug is a prime example of a pharmacological challenge directed to the metabolic attack at the 4-position as a mechanism for the expression of biological activity. A methoxy group there would allow easy removal of the methyl group from the oxygen by some demethylation process, but a bare methyl group there cannot be removed by any simple process. It must be removed by a very difficult oxidation.

This is not the first time that oxygen atoms have been removed from the mescaline molecule. Both the 3,5-dideoxymescaline (3,5-dimethyl-4-methoxyphenethylamine) and 3,4,5-trideoxymescaline (also called desoxymescaline in the literature, but really tri-desoxymescaline or 3,4,5-trimethylphenethylamine) have been studied in the cat, and have shown extraordinary pharmacological profiles of CNS action. The trimethyl compound showed behavior that was interpreted as being intense mental turmoil, accompanied by a startling rise in body temperature. The significance is hard to determine, in that LSD gave similar

responses in the cat, but mescaline was without effects at all. No human studies have been made on these compounds, just animal studies. But they might prove upon trial in man to be most revealing. They would have to be performed with exceptional care.

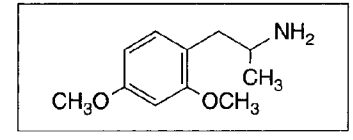
The 3-carbon chain amphetamines that correspond to these mescaline look-alikes with one or more methoxy groups replaced with methyl groups, are largely untested and would require independent and novel syntheses. The 3,4,5-trimethylamphetamine is known, and is known to be very hard on experimental cats.

A mescaline analogue with a bromo atom in place of the 4-methoxyl group is an analogue of mescaline in exactly the same way that DOB (a very potent amphetamine) is an analog of TMA-2 (the original trisubstituted amphetamine). This analogue, 3,5-dimethoxy-4-bromoamphetamine, has been found to be a most effective serotonin agonist, and it is a possibility that it could be a most potent phenethylamine. But, as of the present time, it has never been assayed in man.

#53 2,4-DMA; 2,4-DIMETHOXYAMPHETAMINE

SYNTHESIS: To a solution of 10 g 2,4-dimethoxybenzaldehyde in 50 mL nitroethane there was added 0.5 g anhydrous ammonium acetate, and the mixture was heated on the steam bath for 2 h. The excess solvent/reagent was removed under vacuum, and the residue oil dissolved in 25 mL boiling MeOH. On cooling, this deposited yellow crystals of 1-(2,4-dimethoxyphenyl)-2-nitropropene that, after filtering, MeOH washing, and air drying, weighed 10.2 g and had a mp of 78-79 °C.

A magnetically stirred suspension of 6.0 g LAH in 300 mL anhydrous Et_2O was brought up to a gentle reflux under a He atmosphere. A total of 8.5 g 1-(2,4-dimethoxyphenyl)-2-nitropropene was introduced into the reaction mixture by allowing the condensed Et_2O to leach it from a modified Soxhlet condenser. After the addition was complete, the reaction was held at reflux for an additional 24 h. After cooling with an external ice bath, the excess hydride was destroyed by the cautious addition of H_2O. When the exothermic reaction had subsided, there was added 500 mL H_2O, 150 g potassium sodium tartrate, and sufficient base to bring the pH above 9. The phases were separated, the organic phase dried over anhydrous $MgSO_4$, the drying agent removed by filtration, and the clear filtrate then saturated with anhydrous HCl gas to produce white crystals of 2,4-dimethoxyamphetamine hydrochloride (2,4-DMA) with a mp of 146-147 °C.



DOSAGE: greater than 60 mg.

DURATION: short.

QUALITATIVE COMMENTS: (with 60 mg) "This is definitely threshold, or even a bit more. There is a lot of amphetamine-like component, and a certain blush of euphoria. There is also a diffusion of association, so it's more than just amphetamine, no question about it. At the three-hour point, it is definitely quieting down."

EXTENSIONS AND COMMENTARY: What can one say as to the active dosage of 2,4-DMA? Nothing. What can one say as to the duration? Probably short. The 60 milligram report given above is the highest level that I personally know of having been tried in man, and there is no hint as to what might be found at a fully active dose, or just where that dose might be. It might be fully speedy. It might be fully psychedelic. It might give a cardiovascular push that would be scary. Studies of 2,4-DMA on vascular strips (associated with serotonin action) were not impressive in comparison with structurally related psychedelics, and it seems as if its action might involve norepinephrine release. It is a reasonable guess that there would be cardiovascular activity at higher levels. But it will only be with human trials, someday, that the answer will be known for sure.

The meta-orientation of the two methoxyl groups does, however, greatly increase the susceptibility of the aromatic ring to electrophilic attack. This is one of the three possible meta-dimethoxy substituted amphetamines, and it is the best studied one in the pursuit of potential radio-halogen substituted brain blood-flow agents. This strategy is discussed under IDNNA; the other two meta-compounds are discussed under 3,4-DMA.

The homologues of 2,4-DMA that were iodinated (or occasionally fluorinated) were mono- or di-alkylated on the nitrogen, and the precursor that was common to all was the corresponding acetone. The above nitrostyrene, 1-(2,4-dimethoxyphenyl)-2-nitropropene, was reduced in acetic acid with elemental iron, and the base-washed extracts stripped of solvent and distilled (125-145 °C at 0.5 mm/Hg) to give 2,4-dimethoxyphenylacetone as a water-white oil. The principal reductive amination product of this, the one that was most thoroughly explored with various halogenation schemes, was obtained by the reaction of 2,4-dimethoxyphenylacetone with dimethylamine and sodium cyanoborohydride. This product, 2,4-dimethoxy-N,N-dimethylamphetamine or 2,4-DNNA, distilled at 105-115 °C at 0.4 mm/Hg and formed a perchlorate salt that melted at 98-98.5 °C. This could be iodinated with the radio-iodide anion, when oxidized with chloramine-T in buffered sulfuric acid, to give the iodinated analogue (2,4-dimethoxy-N,N-dimethyl-5-iodoamphetamine) in an excellent yield. Radio-fluorination with acetyl hypofluorite gave the 5-fluoroanalogue (2,4-dimethoxy-N,N-dimethyl-5-fluoroamphetamine) in an acceptable yield. Both compounds went into a rat's brain to a pretty good extent, but both of them washed out too rapidly to be clinically interesting.

A large family of other N-substituted homologues of 2,4-DMA were similarly prepared from the above ketone and sodium cyanoborohydride. Methylamine, ethylamine, propylamine, isopropylamine and hexylamine gave the corresponding N-alkyl homologues. The N,N-diethyl homologue was made from the primary amine, 2,4-DMA itself, with acetaldehyde and sodium cyanoborohydride but the product, N,N-diethyl-2,4-dimethoxyamphetamine, could not be converted into a crystalline hydrochloride salt.

Yet another variation on these structures was launched, again with the design of making radio-iodination targets which are not psychedelic and thus might be useful clinically. In this variation, the nitrogen atom substitution pattern was held constant, with two methyl groups, as were the ring locations of the two oxygen atoms. But the identities of the alkyl groups on these oxygen atoms were varied. The synthetic procedure followed was to make the appropriate 2,4-dialkoxybenzaldehyde, convert it to the nitrostyrene with nitroethane, reduce this to the phenylacetone with elemental iron, and then reductively aminate this ketone with dimethylamine. Following this reaction scheme, five amphetamine homologues of 2,4-DMA were made, three with the 4-methoxy group maintained but the 2-position extended, and two with both groups extended symmetrically. These are: (1) N,N-dimethyl-2-ethoxy-4-methoxyamphetamine; (2) 2-(n)-butyloxy-N,N-dimethyl-4-methoxyamphetamine; (3) 2-(n)-decyloxy-N,N-dimethylamphetamine; (4) 2,4-diethoxy-N,N-dimethylamphetamine; and (5) N,N-dimethyl-2,4-di-(i)-propoxyamphetamine. I believe that most of these have been iodinated and assayed in rats, and several of them appear quite promising. But none of them have been assayed in man, yet. The bromination product of 2,4-DMA (5-bromo-2,4-dimethoxyamphetamine, 5-Br-2,4-DMA) is way down in activity (see its recipe, separately). Since all iodo analogues are of about the same potency as the bromo counterparts, and since the addition of two methyl groups on the nitrogen does not appear to enhance central activity, I feel the iodination products of these N,N-dialkyl-dialkoxyamphetamines would not have any interesting psychopharmacology.

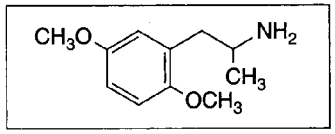
There is something vaguely counterproductive, in my evaluation of things, when the goal of a research project is to avoid activity rather than to create it. Although this chemistry was completely fascinating and could have produced the world's best positron-emitting, brain-scanning diagnostic compound, I feel it quite unlikely that it would have produced the world's best insight-revealing, empathy-enhancing psychedelic, so this research direction never totally caught my fancy. I went on to other things.

#54 2,5-DMA; DMA; 2,5-DIMETHOXYAMPHETAMINE

SYNTHESIS: A solution of 10.0 g 2,5-dimethoxybenzaldehyde in 50 mL glacial acetic acid was treated with 6.8 g of nitroethane and 4.0 g of anhydrous ammonium acetate. This mixture was heated on the steam bath for 3 h and then the reagent/solvent was removed under vacuum. The residue was suspended in H_2O and extracted with $CHCl_3$. Removal of the solvent from the pooled extracts yielded 11.2 g of an impure 1-(2,5-dimethoxyphenyl)-2-nitropropene which, on recrystalliza-

tion from 75 mL boiling MeOH, gave 6.7 g of product with a mp of 73-75 °C. Anal. ($C_{11}H_{13}NO_4$) C,H,N. This nitrostyrene has been periodically available commercially from a number of sources.

A solution of 17.0 g of 1-(2,5-dimethoxyphenyl)-2-nitropropene was prepared in 500 mL anhydrous Et_2O. This solution was added slowly to a well-stirred suspension of 12.0 g LAH in 700 mL anhydrous Et_2O. The mixture was then brought up to a reflux and maintained there for 20 h, cooled with an external ice bath, and the excess hydride destroyed by the cautious addition of H_2O. Finally, a total of 500 mL H_2O was added, followed by the addition of 300 g potassium sodium tartrate, and sufficient aqueous NaOH to bring the pH above 9. The two phases were separated, and the ether phase dried by the addition of anhydrous $MgSO_4$. The drying agent was removed by filtration, and the clear filtrate saturated with a stream of anhydrous HCl gas. The formed crystals of 2,5-dimethoxyamphetamine hydrochloride (2,5-DMA) were removed by filtration, washed with anhydrous Et_2O, and dried to constant weight of 16.3 g. Recrystallization from EtOH gave an analytical sample with a mp of 114-116 °C. The hydrobromide salt is reported to melt at 129-131 °C.



DOSAGE: 80 - 160 mg.

DURATION: 6 - 8 h.

EXTENSIONS AND COMMENTARY: The qualitative information on 2,5-DMA is very sparse. I was up to a 1+ with 80 milligrams of the hydrochloride, and since it appeared to be totally a physical trip with tremors and some cardiovascular push and nothing of a sensory nature, I chose to explore it no further. A report from South America found the intoxication to be largely pleasant (this, at 75 milligrams), with an enhanced interest in one's surroundings, but no perceptual changes, no overt stimulation, and no gross physiological effects other than a slight mydriasis (dilation of the pupils). I have also been told of a single trial of 250 milligrams of the tartrate (this is equivalent to somewhere in the 150-200 milligram range of the hydrochloride salt, depending upon the acid/base ratio of the tartrate salt) with some "speedy" effects but still no sensory changes. A seizure of capsules reported by the drug law enforcement authorities some 20 years ago found that each contained some 200 milligrams of the hydrobromide salt. This is equivalent to 170 milligrams of the hydrochloride salt, and suggests that level may be an effective dosage.

An intriguing, but little studied, analogue of 2,5-DMA is the compound with methyls in place of the methoxyls. 2,5-Dimethylamphetamine has been looked at, in man, as a potential anorexic, but there is little effect even at 150 milligrams. The 3,4-isomer, 3,4-dimethylamphetamine or xylopropamine, is an adrenergic agent and it has been found to be an analgesic in man at as little as 10 milligrams.

This was assayed, rather remarkably, by attaching electrodes to the tooth fillings of the experimental subjects. But with this base, cardiovascular effects were not observed until doses of about 100 milligrams were administered, and toxic effects (nausea and vomiting) were reported at 150 milligrams. There was no suggestion of anything psychedelic.

All three isomers of monomethylamphetamine have also been looked at in man. The ortho- and meta-isomers, 2-methyl- (and 3-methyl-) amphetamine are weak anorexics. At doses of up to 150 milligrams orally, there were signs of stimulation noted — talkativeness and loss of appetite. The para-isomer, 4-methylamphetamine or Aptrol, is more potent. At 75 milligrams (orally, in man) there is clear adrenergic stimulation, and at twice this dosage there are signs of mild toxicity such as salivation, coughing and vomiting.

There is a mystery, at least to me, concerning the commercial production of 2,5-DMA. At regular intervals, there is a public announcement of the production quotas that are requested or allowed by the Drug Enforcement Administration, for drugs that have been placed in Schedules I or II. In the Schedule I category there are usually listed amounts such as a gram of this, and a few grams of that. These are probably for analytical purposes, since there are no medical uses, by definition, for drugs in this Schedule. But there is a staggering quantity of 2,5-DMA requested, regularly. Quantities in the many tens of millions of grams, quantities that vie with medical mainstays such as codeine and morphine. I have heard that this material is used in the photographic industry, but I have no facts. Somewhere I am sure that there is someone who has to keep a lot of very careful books!

In the area of psychedelic drugs, the value of 2,5-DMA is mainly in its role as a precursor to the preparation of materials that can come from a direct electrophilic attack on the activated 4-position. These uses can be found under things such as DOB and DOI and DON. The radio-halogenation of N-substituted homologues of 2,5-DMA with hypoiodite or hypofluorite is part of an extensive study underway in the search for radio-labeled brain blood flow agents. The rationale for this work is to be found in the commentary under IDNNA. In essence it has been found that the N-substitution or N,N-disubstitution of 2,5-DMA where the 4-position is unsubstituted and thus available for the introduction of a radioactive nucleus can give rise to potentially useful drugs. Most of these 2,5-dimethoxy exploratory compounds were made by the reductive alkylation of 2,5-dimethoxy-4-(radio)-iodophenylacetone, using various mono or dialkyl amines. This, too, is described under IDNNA.

However, the study of various direct iodinations and fluoridations that would have the N,N-dimethyl substitution on the amphetamine nitrogen atom, would require the 4-proteo- analogue, and this was made from the above nitrostyrene. A solution of the above nitrostyrene, 22.3 g 1-(2,5-dimethoxyphenyl)-2-nitropropene in 100 mL acetic acid was added to a suspension of elemental iron in acetic acid (45 g in 250 mL) and worked up with water and base washing to give, after distillation at 92-106 °C at 0.35 mm/Hg, 13.8 g 2,5-dimethoxyphenylacetone as a pale yellow

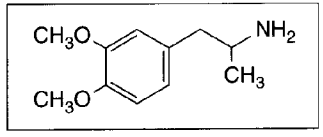
oil. This underwent reductive amination with dimethylamine hydrochloride in MeOH solution, using sodium cyanoborohydride, to give the target compound 2,5-dimethoxy-N,N-dimethylamphetamine oxalate with a melting point of 133-134 °C (4.6 g ketone gave 1.38 g of salt). Anal. ($C_{15}H_{23}NO_6$) C,H. It has also been prepared by the N,N-dimethylation of 2,5-DMA directly, with formaldehyde and formic acid. This has been called 2,5-DNNA, or IDNNA without the "I." This intermediate, 2,5-DNNA, underwent direct radioiodination with labeled iodine monochloride in the presence of perchloric acid to give IDNNA with a 40% incorporation of isotope. Reaction with labeled acetyl hypofluorite, on the other hand, gave only a 2% in-corporation of the radio-isotope. This latter compound is, chemically, 4-fluoro-2,5-dimethoxy-N,N-dimethylamphetamine and, using the reasoning suggested above and with IDNNA, might best be encoded FDNNA.

The 2,5-dimethylamphetamine analogue mentioned above was also explored in this IDNNA concept. The commercially available 2,5-dimethylbenzaldehyde was converted to the nitrostyrene with nitroethane (1-(2,5-dimethylphenyl)-2-nitropropene, yellow crystals with a melting point of 24.5-25.5 °C) which reacted with elemental iron in acetic acid to give the ketone 2,5-dimethylphenylacetone (boiling at 140-150 °C at 0.4 mm/Hg). Reductive amination with dimethylamine and sodium cyanoborohydride gave 2,5-DMNNA (2,5,N,N-tetramethylamphetamine) as a clear oil with a boiling point of 115-125 °C at 0.35 mm/Hg. It gave poor yields of the 4-fluoro analogue with acetyl hypofluorite.

All of these latter materials remain unevaluated in man.

#55 3,4-DMA; 3,4-DIMETHOXYAMPHETAMINE

SYNTHESIS: A solution of 33.2 g of veratraldehyde in 15.0 g nitroethane was treated with 0.9 g of n-amylamine and placed in a dark place at room temperature. In a day or so, separated H_2O was apparent and, after a couple of weeks, the mixture completely solidified. The addition of 50 mL EtOH and heating effected complete solution and, on cooling, this provided 1-(3,4-dimethoxyphenyl)-2-nitropropene as yellow crystals, 29.0 g, with mp of 70-71 °C. The more conventional reaction scheme, 6 h heating of a solution of the aldehyde and nitroethane in acetic acid with ammonium acetate as catalyst, gave a much inferior yield of product (33.2 g gave 14.8 g) of the same purity. Recrystallization from MeOH increased the mp to 72-73 °C.



To a refluxing suspension of 7 g LAH in 600 mL anhydrous Et_2O, stirred and under an inert atmosphere, there was added 7.5 g 1-(3,4-dimethoxyphenyl)-2-nitropropene by allowing the returning condensed ether to leach out the material as a warm solution from a Soxhlet thimble. Following the completion of the addition of the nitrostyrene, refluxing was maintained for 24 h, and the reaction mixture allowed to stand several days at room temperature. The

excess hydride was destroyed by the cautious addition of 500 mL H_2O containing 40 g H_2SO_4, and the phases were separated. The aqueous phase was washed with both Et_2O and CH_2Cl_2. There was then added 200 g potassium sodium tartrate, and the pH brought above 9 by the addition of aqueous NaOH. This clear solution was extracted with 3x150 mL CH_2Cl_2, the extracts were pooled, and the solvent removed under vacuum to give a residual oil. This was dissolved in Et_2O, saturated with anhydrous HCl gas, and the resulting solids removed by filtration. Recrystallization from 10 mL acetone gave 1.35 g 3,4-dimethoxyamphetamine hydrochloride (3,4-DMA) as beautiful white crystals with a mp of 144-145 °C.

DOSAGE: a few hundred milligrams.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 70 mg i.v.) [One patient received 0.004 mM/Kg of the hydrochloride salt intravenously and exhibited only slight increase in psychiatric symptoms; a comparable dosage in a second individual also elicited only insignificant changes.]

(with 700 mg i.v.) [When one of these patients was reinjected at a later date with approximately 0.04 mM/Kg of 3,4-DMA a definite 'mescaline-like' state was induced. The symptoms included colored hallucinations of geometric figures and occasional structured forms. The other individual experienced visual distortions, notable after-imagery, feelings of unreality, and paranoid ideas. Marked mydriasis and gross body tremors also occurred but apparently no hallucinations were experienced.]

EXTENSIONS AND COMMENTARY: These "Qualitative Comments" are not explicit quotations from people who had taken 3,4-DMA. They are written descriptions by the observers who had given 3,4-DMA to psychiatric patients. This is one of the most outrageous chapters in the books on military medicine. The chemical warfare group within the U.S. Army explored many potential psychedelics by administering them to innocent patients with not even a thought of obtaining informed consent. These experiments took place at the New York State Psychiatric Institute (amongst other places) in the early 1960's. The Edgewood Arsenal code name for 3,4-DMA was EA-1316. A few non-military studies have indicated that 3,4-DMA is orally active at 160 milligrams, and so probably its potency by this more conventional route would fall midway between that of mescaline and of MDA. The 3-methoxy-4-other-than-methoxy things (such as hydroxy, ethoxy, allyloxy and methyl) are mentioned in the recipe for MEPEA. The alpha-ethyl homologue of 3,4-DMA, 2-amino-1-(3,4-dimethoxyphenyl)butane, and of other DMA's are discussed under the recipe for ARIADNE.

There are a total of six possible amphetamine molecules with two methoxyl groups attached. The 3,4-orientation has always been the most appealing to the life

scientists as this is the positional substitution pattern found in the natural neurochemicals dopamine, norepinephrine and epinephrine. These latter two are called noradrenalin and adrenalin in England. Two adjacent hydroxy groups represent the catechol in the well known word catecholamines. You might read in a textbook, "This is where nature placed the groups when she put the compounds in our brains. So that is where the groups might be the most interesting in a psychedelic." Why? I have never understood this kind of reasoning. If a possible psychedelic has just the exact oxygen positioning of a neurotransmitter, then, voila, that's why it is active. And if a possible psychedelic has some positioning of these oxygen atoms that is different than that of a neurotransmitter? Then voila again. That's why it is active. Both sound equally reasonable to me, and neither one even begins to address the fundamental question, how do the psychedelic drugs do what they do? A study in the human animal of the intimate effects of one of these neurotransmitter analogues might bring us a little bit closer to answering this fundamental question. But maybe it wouldn't, after all. Nothing has made much sense so far! Anyway, 3,4-DMA is one of the ten essential amphetamines that can, in theory, arise from the ten essential oils of the spice and herb trade. In this case, the origins are methyl eugenol and methyl isoeugenol.

Two of these "different" isomers, 2,4-DMA and 2,5-DMA, have already been discussed in their own separate recipes. And the remaining three of the six possible DMA's that are "different" have been made and studied pharmacologically in animals but not in man. These are the 2,3-DMA, 2,6-DMA and the 3,5-DMA isomers. The products of their reaction with elemental bromine are discussed under META-DOB.

Both the 2,6- and the 3,5-isomers, as the N,N-dimethyl homologues, have been looked at as potential radio-halogen recipients in the search for positron-emitting brain blood-flow indicators, as discussed in the recipe for IDNNA. Both were made from the appropriate nitrostyrene via the corresponding phenylacetone.

The 2,6-isomer was derived from 2,6-dimethoxybenzaldehyde. This, in nitroethane and ammonium acetate, gave the nitrostyrene as canary-yellow crystals from MeOH that melted at 101.5-102.5 °C. Elemental iron in acetic acid converted this nitrostyrene to 2,6-dimethoxyphenylacetone (a water-white oil with boiling point of 95-105 °C at 0.4 mm/Hg. Anal. ($C_{11}H_{14}O_3$) C,H) and reductive amination with dimethylamine and sodium cyanoborohydride gave 2,6-dimethoxy-N,N-dimethylamphetamine perchlorate (2,6-DNNA) with a melting point of 109-110 °C. This base was readily fluorinated with ^{18}F acetylhypofluorite and iodinated with chloramine-T-oxidized ^{122}I iodide ion. It was also halogenated with (non-radioactive) bromine and iodine monochloride to give the corresponding 3-bromo-(and 3-iodo)-2,6-dimethoxy-N,N-dimethylamphetamines but these, in turn, did not react with radioactive acetyl hypofluorite.

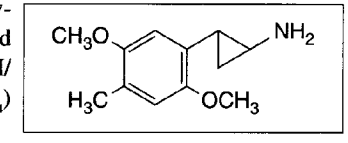
The 3,5-isomer followed precisely the same flow sheet. 3,5-Dimethoxybenzaldehyde gave the nitrostyrene (with a melting point of 87-88 °C), the phenylacetone (with a boiling point of 110-130 °C at 0.3 mm/Hg) and the product 3,5-dimethoxy-N,N-dimethylamphetamine perchlorate (3,5-DNNA) with a melting point of 100-101 °C. This also reacted readily with ^{18}F acetylhypofluorite and ^{122}I-hypoiodite. Several alpha-ethyl homologues of these compounds have also been discussed in the recipe for ARIADNE.

#56 DMCPA; 2-(2,5-DIMETHOXY-4-METHYLPHENYL)CYCLOPROPYLAMINE

SYNTHESIS: To a solution of 25 g 2,5-dimethoxy-4-methylbenzaldehyde (see the recipe for 2C-D for the preparation) and 29.2 g malonic acid in 50 mL anhydrous pyridine, there was added 2 mL piperidine and this was heated on the steam bath for several h. The mixture was added to a solution of 125 mL concentrated HCl in 500 mL H_2O at 0 °C, and the solid product that was formed was removed by filtration, and washed with H_2O. Recrystallization from aqueous EtOH yielded 31 g 2,5-dimethoxy-4-methylcinnamic acid with a mp of 163-166 °C. Anal. ($C_{12}H_{14}O_4$) C,H.

In a cooled high-pressure reaction vessel there was placed a suspension of 30 g 2,5-dimethoxy-4-methylcinnamic acid in 150 mL liquid isobutene. This was treated dropwise with 0.6 mL concentrated H_2SO_4, then sealed and brought to room temperature. After 48 h shaking, the vessel was cooled again to -10 °C, opened, and poured into 200 mL of 10% Na_2CO_3. This was extracted with hexane, the pooled extracts washed with H_2O, and the solvent removed to yield 17.0 g of (t)-butyl 2,5-dimethoxy-4-methylcinnamate as an amber oil. Anal. ($C_{16}H_{22}O_4$) C,H.

The cyclopropane ester was prepared by the reaction between 16 g (t)-butyl 2,5-dimethoxy-4-methylcinnamate and dimethylsulfoxonium methylide, prepared as described in the Kaiser reference in the acknowledgements. Hydrolysis of this ester gave 53% trans-2-(2,5-dimethoxy-4-methylphenyl)cyclopropanecarboxylic acid which, after recrystallization from a MeOH/H_2O mixture, had a mp of 136 °C. Anal. ($C_{13}H_{16}O_4$) C,H.



A suspension of 4 g of trans-2-(2,5-dimethoxy-4-methylphenyl)-cyclopropanecarboxylic acid in an equal volume of H_2O, was treated with sufficient acetone to effect complete solution. This was cooled to 0 °C and there was added, first, 2.0 g triethylamine in 35 mL acetone, followed by the slow addition of 2.5 g ethyl chloroformate in 10 mL acetone. This was stirred for 0.5 h, and then there was added a solution of 1.7 g NaN_3 in 6 mL H_2O, dropwise. After 1 h stirring at 0 °C, the mixture was quenched by pouring into H_2O at 0 °C. The separated oil was extracted with Et_2O, and extracts dried with anhydrous $MgSO_4$. Removal of the solvent under vacuum gave a residue of the azide, which was dissolved in 10 mL anhydrous toluene. This solution was heated on the steam bath until the nitrogen evolution was complete, and the removal of the solvent under vacuum gave a residue of crude isocyanate as an amber oil. This intermediate isocyanate was

dissolved in 5.4 g benzyl alcohol and the reaction mixture was heated on the steam bath for 6 h. The excess benzyl alcohol was removed by distillation, yielding trans-2-(2,5-dimethoxy-4-methylphenyl)carbobenzoxyamidocyclopropane as a crystalline residue. This was recrystallized from an EtOAc/hexane mixture to give 6.13 g of a crystalline product with a mp of 107-108 °C. Anal. ($C_{20}H_{23}NO_4$) C,H,N.

A solution of 1.5 g trans-2-(2,5-dimethoxy-4-methylphenyl)carbobenzoxyamidocyclopropane in 120 mL MeOH containing 200 mg 10% Pd/C was shaken under hydrogen gas at 35 psig for 45 min. The solution was filtered through celite, and a sufficient amount of a solution of 5% HCl in EtOH was added to the filtrate to make it acidic. Removal of all volatiles under vacuum gave a solid residue that was recrystallized from an EtOH/ether mixture to give 0.98 g of trans-2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine hydrochloride (DMCPA) as white crystals with a mp of 210-211 °C.

DOSAGE: 15 - 20 mg.

DURATION: 4 - 8 h.

QUALITATIVE COMMENTS: (with 10 mg) "The effects were quite real at an hour, but very hard to define. Nothing left at four hours, but my sleep was filled with bizarre and colorful dreams. Something was still working somewhere, at some level."

(with 20 mg) "I found myself lightheaded, and the thinness seemed to be, rather remarkably, on the left side of my brain. The experience was flighty. I was reminded of the aura that has been described preceding a convulsion. I was decoupled from my experience and from my environment. Not all of the control is there, and I am uncomfortable. But in an hour, there is complete control again, and I can relax my conscious guard which allows an easy plus three. With this, there was easy fantasy, erotic, quite a bit of movement in the visual field, and mild anorexia. The residual hyperreflexive thinness is largely gone, and not at all worrisome. This stuff is complicated, with a little too much of the physical. The next day was without any residues at all."

EXTENSIONS AND COMMENTARY: Most of the human trials took place in the fifteen to twenty milligram range. Several reports describe some muscular tremor, especially in the earliest part of the experience, but this never seemed to be a concern. The efforts to lock imagery to music were not too successful. All of these clinical studies were conducted on the trans-compound, but on the racemic mixture. This has been resolved into the two optical isomers, but they have not been compared in man. The cis-mixture is unknown.

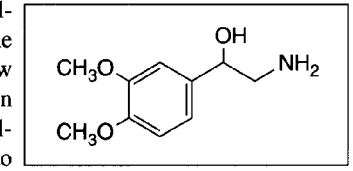
This material is intimately related to tranylcypromine, a clinically proven antidepressant. This drug is a known monoamine oxidase inhibitor, and it is certainly possible that some of this pharmacological property might be found in

DMCPA if it were to be looked for. The hints of physical toxicity at the higher doses assayed might suggest some such activity.

This compound, DMCPA, was modeled directly after the structure of DOM, with the 2,5-dimethoxy-4-methyl substitution pattern. Another analogue of tranylcypromine, similarly modeled, is 3,4,5-trimethoxytranylcypromine, or trans-2-(3,4,5-trimethoxyphenyl)cyclopropylamine (TMT). It has been evaluated at levels of only 13 milligrams orally, and at this dose there were no hints of central activity.

#57 DME; 3,4-DIMETHOXY-ß-HYDROXYPHENETHYLAMINE

SYNTHESIS: To a solution of 10.2 g 3,4-dimethoxybenzaldehyde in 10 mL EtOH, cooled to 0 °C, there was added a solution of 4.2 g KCN in 40 mL H_2O. With good stirring, there was slowly added 10 mL concentrated HCl (caution: HCN is evolved) and the two-phase reaction mixture was allowed to continue stirring until there was the spontaneous formation of crystals. After a few days standing, these were removed by filtration and well washed with H_2O. All was recrystallized from 75 mL of 50% MeOH and air dried to provide 6.95 g of the cyanohydrin 3,4-dimethoxy-α-hydroxyphenylacetonitrile. The mp was 104-106 °C, which can be increased to 109 °C by recrystallization from benzene.



A well-stirred suspension of 4.7 g LAH in 500 mL anhydrous Et_2O was brought up to a gentle reflux, and 4.7 g 3,4-dimethoxy-α-hydroxyphenylacetonitrile was leached in from a Soxhlet thimble, over the course of 3 h. The color of the ether solution progressed from yellow to green, to an eventual blue. The reflux was maintained for 16 h. After cooling again, there was added (carefully) a solution of 27 g H_2SO_4 in 500 mL H_2O. The completely clear two-phase mixture was separated, and the aqueous phase treated with 87 g potassium sodium tartrate. The addition of 25% NaOH brought the pH >9, and this phase was extracted with 4x100 mL CH_2Cl_2. Removal of all the organic solvents under vacuum gave a residue that was part oil and part solid. This was extracted with 4x50 mL boiling Et_2O, the extracts pooled, and saturated with anhydrous HCl gas. The 0.95 g of pale-yellow crystals that formed were removed by filtration, and finely ground under 5 mL CH_3CN. There remained, after refiltration and air drying, 0.85 g of 3,4-dimethoxy-ß-hydroxyphenethylamine hydrochloride, DME, with a mp of 170-172 °C.

DOSAGE: greater than 115 mg.

DURATION: unknown.

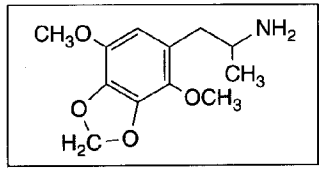
QUALITATIVE COMMENTS: (with 115 mg) "I was faintly nauseous about an hour after taking the compound, and perhaps I was more alert than usual in the evening. Substantially no effects."

EXTENSIONS AND COMMENTARY: The rationale for exploring the beta-hydroxylated phenethylamines, especially those with oxygens at the biologically important 3- and 4-positions, has already been presented. Norepinephrine is a ß-hydroxylated phenethylamine with oxygens at these two ring positions. With DME, these are masked as two methyl ethers, and the initials DME stand for 3,4-dimethoxyphenyl-ß-ethanolamine. This is an alternate name for 3,4-dimethoxy-ß-hydroxyphenethylamine.

An exactly analogous compound is 3,4-methylenedioxy-ß-ethanolamine, where the masking is done with the biologically more fragile methylenedioxy ether. Originally I had called this compound MDE (methylenedioxyethanolamine) but that code has been, since 1975, used exclusively for 3,4-methylenedioxy-N-ethylamphetamine, which is a recipe all by itself. Under the discussion of members of the BOX series, there is a methylenedioxyphenethylamine with a methoxyl group at the ß-position, and it is called BOH (q.v.). There, a reasonable code name for this specific compound is given, namely BOHH. "BO" stands for the beta-oxygen function on a phenethylamine; this is the heart of the BOX family. The "H" which is the third letter of BOHH stands for the free hydroxyl group. And the final "H" is for homopiperonylamine (which is the trivial name for the compound without the hydroxyl group). BOHH, or 3,4-methylenedioxy-ß-hydroxyphenethylamine, or 3,4-methylenedioxy-ß-ethanolamine, has also be assayed in man at up to 100 milligrams without any effects, and must be considered, as of now, to be inactive centrally. The possible toxic roles of ß-ethanolamines as potential adrenolytic agents, have been discussed in the BOHD recipe. And beware of the use of the code name MDE in the very old literature. It might be this BOHH compound.

#58 DMMDA; 2,5-DIMETHOXY-3,4-METHYLENEDIOXY-AMPHETAMINE

SYNTHESIS: Apiole, as the crystalline essential oil 1-allyl-2,5-dimethoxy-3,4-methylenedioxybenzene, is isolated directly from commercial Oil of Parsley, by



careful fractional distillation. It is the fraction that boils at 165-167 °C at 27 mm/Hg. A solution of 19.8 g apiole in a mixture of 43 g KOH and 60 mL hot EtOH was heated in the steam bath for 24 h. With vigorous stirring, it was diluted with H_2O, at a rate which the crystals that formed spontaneously could accumulate from the turbidity that was generated. When no more H_2O could be added (there was persistent oiling out of material) the reaction mixture was filtered to give 12.1 g of an amber solid material. This was recrystallized from 20 mL boiling hexane, which was filtered while hot to remove insolubles. From the cooled filtrate, there was obtained 9.3 g of 2,5-dimethoxy-3,4-methylenedioxy-1-propenylbenzene, isoapiole, as pale cream-colored solids.

A stirred solution of 8.8 g 2,5-dimethoxy-3,4-methylenedioxy-1-propenylbenzene and 3.9 g pyridine in 45 mL acetone was cooled to ice-bath temperatures, and treated with 7.9 g tetranitromethane. This extremely dark reaction was stirred at 0 °C for 5 min, then quenched with a solution of 2.6 g KOH in 45 mL H_2O. With continued stirring, there appeared yellow crystals of 1-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-2-nitropropene which, after filtering, washing with 50% acetone and air drying, weighed 8.0 g and had a mp of 110-111 °C.

To a well-stirred and gently refluxing suspension of 6.3 g LAH in 500 mL anhydrous Et_2O, under an inert atmosphere, there was added 7.5 g 1-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-2-nitropropene by leaching out the nitrostyrene from a thimble in a modified Soxhlet condenser apparatus. The addition took 1.5 h, and the refluxing was maintained for an additional 3 h. After cooling, the excess hydride was destroyed by the cautious addition of 300 mL of 1.5 N H_2SO_4. The aqueous phase was brought to a pH of 6 with Na_2CO_3. This was heated to 80 °C and clarified by filtration though paper. The addition of a stochiometric amount of picric acid in boiling EtOH gave rise to precipitation of the product picrate as globs that did not crystallize. These were washed with cold H_2O, then dissolved in 30 mL 5% NaOH. Extraction with 2x75 mL Et_2O, and the stripping of the solvent from the pooled extracts, gave 3.1 g of an oily residue which, upon dissolving in 250 mL Et_2O and saturation with anhydrous HCl gas, gave white crystals. These were removed by filtration, Et_2O-washed, and air dried, to give 2.9 g of 2,5-dimethoxy-3,4-methylenedioxyamphetamine hydrochloride (DMMDA) that melted in the 165-175 °C range.

DOSAGE: 30 - 75 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 25 mg) "The intoxication was there at an hour and a quarter, and I was hit with nausea with no particular warning. I am shaky, a little dilated in the eyes, and there is a modest depersonalization (reminding me of LSD). Time might be slightly slowed, and there is a mild ataxia in the legs. A couple of hours later, all effects are going away fast. I ate an apple, but maybe my mouth didn't work quite right. The apple was incredibly noisy."

(with 32 mg) "I am up to a 2 1/2 plus at something after two hours, with no apparent visuals, no push, no erotic. And a few hours later it is quietly slipping away. It felt completely safe, and without any conspicuous psychedelic action, at least at this level."

(with 50 mg) "I took graded doses of 10 milligrams every thirty minutes for a total of 50 milligrams, and there were no effects at all."

(with 50 mg) "In the middle of this all, I found myself getting into abstract thinking, and maybe some imagery as well. The effects were disappointingly light."

(with 75 mg) "This was equal to somewhere between 75 and 100 micrograms of LSD. I was caught up with the imagery, and there was an overriding religious aspect to the day. The experience had an esthetic value. I liked it."

EXTENSIONS AND COMMENTARY: DMMDA was the first of the tetraoxygenated amphetamine derivatives that was ever explored in man, back in 1962. And it is not easy to find an acceptable single phrase to describe its action or an acceptable number to describe its potency. I have put the value of 10 mescaline units (M.U.) into the literature and this would imply that maybe 30 milligrams was an active dose. This is probably too low, and some day I would like to run an experiment with the entire research group with this compound to see just what it really does.

The essential oil that corresponds to DMMDA is, of course, apiole from the Oil of Parsley, which again ties together the spice world and the amphetamine world. And there is isoapiole, also a natural thing. This pair represents the ring-substitution pattern of one of the ten essential oils and DMMDA is one of the ten essential amphetamines.

Several people have asked me what I thought about the potential activity of a compound with a methyl group added to DMMDA. One of these possibilities would be the N-methylated derivative, 2,5-dimethoxy-N-methyl-3,4-methylenedioxyamphetamine, or METHYL-DMMDA (or DMMDMA for the dimethoxymethylenedioxy-methamphetamine nomenclature). It is a MDMA analogue, and is described in the recipe for METHYL-MMDA-2.

The placement of an added methyl group onto the ß-position of DMMDA, rather than on the nitrogen atom, produces a pair of stereoisomeric homologues. These are the threo- (or-trans-) and erythro- (or cis)-2,5-dimethoxy-ß-methyl-3,4-methylenedioxyamphetamines. They have never been assigned trivial names (my original codes for them were S-1495 and S-1496 which is not too intuitively informative). Their chemically proper names would have the 2-amino-3-substituted phenylbutane form. The synthesis of these DMMDA homologues started with the reduction of the nitrosyrene to the ketone (see under METHYL-MMDA-2 for this preparation), followed by methylation with fresh sodium isopropoxide and methyl iodide, to give the beta-methyl product. This formed the two possible oximes, one with a mp of 120 °C, and the other from MeOH with a mp of 146 °C. The 120 °C oxime, with fresh sodium ethoxide gave threo-2-amino-3-(2,5-dimethoxy-3,4-methylenedioxyphenyl)butane hydrochloride. This salt had a mp of 247-249 °C. The 146 °C oxime gave erythro-2-amino-3-(2,5-dimethoxy-3,4-methylenedioxyphenyl)butane hydrochloride with a mp of 188-189 °C. The threo-isomer showed a possible threshold effect at 80 milligrams, with hyperventilation and perhaps some mental muddiness. The erythro-isomer showed no effects, but it had

been taken up only to 10 milligrams.

The only other ß-methyl homologue of an active material that was explored chemically, was related to MDA. The ketone (3,4-piperonylacetone, see under MDMA) was methylated with sodium isopropoxide and methyl iodide, and a crystalline oxime was obtained. Reduction with Zn dust gave what appeared to be 2-amino-3-(3,4-methylenedioxyphenyl)butane hydrochloride, but there were sufficient uncertainties (possible dimethylation, only one oxime isolated, the need of strong reducing conditions) that the entire project was placed in, and still is in, an indefinite holding pattern. The similar analogues for DOM are the two Classic Ladies, DAPHNE and ELVIRA, and they, too, are for some time in the future.

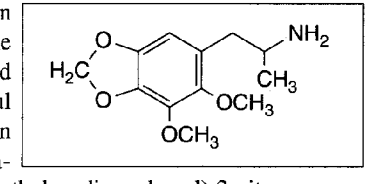
#59 DMMDA-2; 2,3-DIMETHOXY-4,5-METHYLENEDIOXY-AMPHETAMINE

DOSAGE: about 50 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 50 mg) "I am into it; it is much like MDA."

EXTENSIONS AND COMMENTARY: This is pretty sparse information upon which to build a picture of biological activity. First, the synthesis was done by someone else and, as I have not been able to find where the notes are, this will be the one recipe in the footnote without explicit directions incorporated. The procedure used was exactly the same as that described for DMMDA, except that the starting material was dillapiole rather than apiole. The dillapiole was obtained by the careful fractionation of Oil of Dill (as opposed to the isolation of apiole from the careful fractionation of Oil of Parsley). Isomerization to isodillapiole, nitration with tetranitromethane to give 1-(2,3-dimethoxy-4,5-methylenedioxyphenyl)-2-nitropropene, and its reduction with LAH in ether to give 2,3-dimethoxy-4,5-methylenedioxyamphetamine hydrochloride (DMMDA-2) proceeded in a precisely analogous manner to the preparation of DMMDA.



And the pharmacological part is rather thin as well. I was not the taster, and can only quote what I had been given. This same observer found a threshold at 28 milligrams. Under other circumstances, this comment on DMMDA-2 would have been tucked into the commentary on DMMDA where it belongs, but the activity level was called for in a large review article, and on the basis of the above, both its initials and the value of 5x the potency of mescaline were permanently

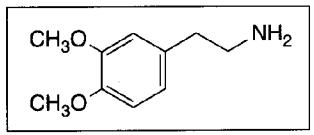
enshrined in the published literature. What is it really like? I don't know. Its structure is an appealing amalgamation of that of MMDA and MMDA-2, and it might be quite a winner if the dosage and the duration were known. It is, after all, one of the ten essential amphetamines, since dillapiole is one of the ten essential oils.

At the time that DMMDA and DMMDA-2 were synthesized, I had visions of doing the same thorough study with these as I had set up with the TMA's (six possible, six done) and the MMDA's (six possible, five done). Here, too, with a pair of methoxy groups on an amphetamine skeleton, with a methylenedioxy ring thrown in, six isomers are possible but only these two have been prepared. The unknown ones will certainly be called DMMDA-3, -4, -5 and -6, but the assignments of code to structure haven't even been thought out yet. The remarkable and totally unexpected activity of DOM was discovered at about this time and it was a much more tempting direction to follow. The remaining four possible DMMDA's have been left to that famous time, a future "rainy day."

#60 DMPEA; 3,4-DIMETHOXYPHENETHYLAMINE

SYNTHESIS: A solution [illegible] 3,4-dimethoxybenzaldehyde in 140 mL acetic acid was treated with 23 mL [illegible]methane and 12.5 g anhydrous ammonium acetate, and heated on the steam bath for 45 min. To this there was slowly added, with good stirring, 300 mL H_2O, and the resulting solids were removed by filtration. The product was finely ground under a small amount of MeOH, filtered again, and air dried to give 13.5 g 3,4-dimethoxy-ß-nitrostyrene with a mp of 142-143 °C.

To a stirred suspension of 12.0 g LAH in 500 mL anhydrous Et_2O that was at a gentle reflux and under an inert atmosphere, there was added 11.45 g 3,4-dimethoxy-ß-nitrostyrene by leaching it from a thimble in a modified Soxhlet condenser. The addition took 2 h and the refluxing was maintained for another 16 h. After cooling to room temperature, the excess hydride was destroyed by the cautious addition of 500 mL 1.5 N H_2SO_4. The phases were separated, and to the aqueous phase there was added 250 g potassium sodium tartrate. The pH was brought to >9, and the clear solution was extracted with 3x100 mL CH_2Cl_2. Removal of the solvent from the combined extracts under vacuum gave 5.2 g of a pale yellow oil. This was dissolved in 300 mL anhydrous Et_2O and saturated with anhydrous HCl gas, giving 5.0 g of a slightly sticky off-white solid. This was recrystallized from 75 mL of boiling CH_3CN to give 3.3 g 3,4-dimethoxyphenethylamine hydrochloride (DMPEA) as beautiful white crystals.



DOSAGE: greater than 1000 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 500 mg) "Nothing."
(with 1000 mg) "Nothing."
(with 10 mg i.v.) "Nothing."
(with 1000 mg of 3,4-dimethoxyphenylacetic acid, a major human metabolite of DMPEA) "Nothing."
(with 500 mg of N-acetyl-3,4-dimethoxyphenethylamine, a major human metabolite of DMPEA) "Nothing."

EXTENSIONS AND COMMENTARY: Why all the interest? Why keep pursuing a compound that is so obviously without activity? Or a metabolite that is also without activity? The answer is that these are totally fascinating compounds *just because* they have no activity! By the way, in this instance, I actually made up most of the quotations. I am not sure that the subjects actually said, "Nothing," but they did report that there were no effects. In my own experiments, my notes record the phrase, "No effects whatsoever."

A little background: one of the transmitter heavyweights in the brain is dopamine. Dopamine is called dopamine because it is an amine that comes from an amino acid that is 3,4-dihydroxyphenylalanine and this, in German, is Di-Oxo-Phenyl-Alanine, or DOPA. The levo-optical (or L-) isomer of DOPA has rather cutely been called the punch-drunk Spanish matador, or El Dopa. But that is not part of the story.

The story is really about the "Pink Spot of Schizophrenia." Many years ago, an observation was made in a biochemical laboratory on the East Coast that stirred up a rolling controversy. It had been found that if the urines of schizophrenic patients (sloppily called "schizophrenic urines") were extracted in such and such a way, and the extracts chromatographed, a pink spot would develop at a particular place on the chromatogram. Well, if this proved to be true with urines of a sick population, and were this proved to be different from the urines of a healthy population, it would constitute an objective diagnosis of schizophrenia. A simple chemical test to confirm a pathology that had defied all efforts to achieve consensus amongst the psychiatrists of the world.

The literature was suddenly filled with dozens of papers. Researcher A confirmed that the pink spot was found with schizophrenics, and not with normal controls. Researcher B found the pink spot in all urines, regardless of pathology. Researcher C found it in no urines at all. Researcher D argued that it was a factor from the hospital diet. Researcher E found that the pink spot reflected the time of day that the urine sample was collected. Researcher F drew a conclusion about where truth might lie by tallying the number of papers that supported argument A, B, C, D, or E.

The only confirmable fact that endured was that the pink spot was due to DMPEA. So a bright spotlight was directed towards its possible role in mental illness. And this expressed itself in the simple question: would it produce schizophrenia in a normal subject? No. And in a way I am comforted that that did

not evolve into a simple litmus test for a schizophrenic diagnosis. There are so many cultural, political, and social factors that come to bear on the assignment of a diagnosis of mental illness, that I would have been forever skeptical of a neat biochemical marker.

A chemical modification of DMPEA that has been explored in this question of pink spots, mental pathology, and diagnostic markers, is the corresponding acetamide. One of the metabolites of DMPEA was found to be the N-acetyl derivative, N-acetyl-3,4- dimethoxyphenethylamine. It was found to be demethylated in man, and to have pharmacological activity in animals. Maybe this was the active compound that could be involved in the schizophrenic process. But human trials with it, as with the principal metabolite 3,4-dimethoxyphenylacetic acid, showed nothing at all in man.

Another chemical modification is the beta-hydroxy analogue of DMPEA. It has been explored separately, and is the subject of its own recipe, in its own rights. See DME.

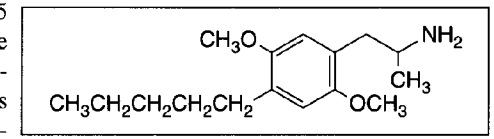
Pink was not the only colorful spot associated with schizophrenia. Somewhere at about this same time, a research paper from Canada reported the observation of a mauve spot in the chromatographic analysis of urines of schizophrenic patients. This had nothing to do with DMPEA. I was working closely with a researcher at the psychiatric institute and we were fascinated by, again, a possible diagnostic marker. We assayed the urines of the next 10 patients being admitted as acute schizophrenics. No trace of mauve. We wrote to Canada, and verified the analytical procedure. We were told that the whatzis should have been added after, rather than before, the whosey, and that we should have heated for 30, not 10 minutes. Okay. We assayed the urines of the next 10 patients being admitted using these new directions. No trace of mauve. Another call to Canada, and we were informed that we still weren't doing it right. They were consistently batting a 100% positive correlation between mauve spots and schizophrenics, and 0% with healthy controls. In fact, they actually gave this positive test the name of a disease, Malvaria.

Then, that little burst of insight! Aha! What if, just what if, they had been seeing something given to their schizophrenics? Chlorpromazine was the popular treatment of the day. We took a whopping dose of chlorpromazine, and over the next couple of days did manage (barely) to collect our urine samples. Both of us were positive Malvarians! And three days later, we were again negative. We were most likely seeing a metabolite of chlorpromazine. One last call to Canada with the ultimate question — had you given any medication to your schizophrenics before your urine analysis? Of course (came the answer) — it would not be ethical to leave them untreated. Another color down the drain, and still no objective measure for mental illness.

By the way, I cannot say I like the chlorpromazine trip. There is no real communication either with others or with yourself, with that stuff. You are a zombie, but if you are both schizophrenic and a zombie, you cannot possibly be troublesome for anybody in the emergency room.

#61 DOAM; 2,5-DIMETHOXY-4-(n)-AMYLAMPHETAMINE

SYNTHESIS: A solution of 110 g p-dimethoxybenzene and 102 g valeric acid in 168 g polyphosphoric acid was heated on the steam bath for 3 h, giving a deep red homogeneous solution. This was poured into 1 L H_2O with good stirring. The strongly acidic, cloudy suspension was extracted with 3x200 mL CH_2Cl_2, the extracts pooled, washed with 4x150 mL 5% NaOH, and finally once with dilute HCl. The solvent was removed under vacuum, and the residual amber oil cooled overnight at 0 °C. Some 30 g of crystalline, unreacted dimethoxybenzene were removed by filtration, and the 85 g of residual oil distilled at the water pump. Another 15 g of dimethoxybenzene came over as an early cut, but the fraction boiling at 184-192 °C (mostly 188-192 °C) weighed 53.0 g and was reasonably pure 2,5-dimethoxyamylophenone. The reaction of the acid chloride of valeric acid with p-dimethoxybenzene and anhydrous $AlCl_3$ in CH_2Cl_2 (parallel to the preparation of the butyrophenone analog, see DOBU) gave an inferior yield (23.2 g from 92 g dimethoxybenzene), but did provide a sizeable sample (12.2 g) of 2-hydroxy-5-methoxyamylophenone from the basic washes of the crude reaction mixture. This pale yellow solid, after recrystallization from MeOH, had a mp of 62-62.5 °C. Anal. ($C_{12}H_{16}O_3$) C,H.



To 360 g mossy zinc there was added a solution of 7.2 g mercuric chloride in 200 mL warm H_2O, and this was swirled periodically for 2 h. The H_2O was drained off, and the amalgamated zinc added to a 2 L three-neck round-bottomed flask, treated with 200 mL concentrated HCl, and heated with an electric mantle. A solution of 53.0 g of 2,5-dimethoxyamylophenone in 107 mL EtOH containing 30 mL concentrated HCl was added drop-wise over the course of 4 h accompanied by 330 mL of concentrated HCl added batchwise over this same period. The mixture was held at reflux overnight and, after cooling, diluted with sufficient H_2O to allowed CH_2Cl_2 to be the lower phase. The phases were separated, and the aqueous phase was extracted with 2x200 mL additional CH_2Cl_2. These organic phases were combined, washed first with 5% NaOH and then with H_2O, and the solvent removed under vacuum. Distillation at the water pump yielded two fractions. The first distilled from about 100-130 °C, weighed 8.8 g, had a faint smell of apples and fennel, and was free of a carbonyl group in the infra-red. It proved to be only 50% pure by GC, however, and was discarded. The major fraction was a pale amber oil distilling between 152-170 °C and was substantially free of smell. It weighed 18.9 g, and was (by GC) 90% pure 2,5-dimethoxy-(n)-amylbenzene.

A mixture of 36.3 g $POCl_3$ and 40.9 g N-methylformanilide was allowed to incubate for 0.5 h. To this there was then added 18.5 g of 2,5-dimethoxy-(n)-amylbenzene and the mixture heated on the steam bath for 2 h. This mixture was poured into a large quantity of H_2O and stirred overnight. The black oily product

was extracted with 3x100 mL CH_2Cl_2, and the extracts combined and stripped of solvent under vacuum. The black residue was distilled at 180-205 °C at 20 mm/Hg to give 12.5 g of a pale amber oil that slowly set up to a crystalline mass. An analytical sample was recrystallized from MeOH to provide 2,5-dimethoxy-4-(n)-amylbenzaldehyde with a mp of 25-26 °C. Anal. ($C_{14}H_{20}O_3$) H; C: calcd, 71.16: found, 71.92, 71.74.

A solution of 12.3 g 2,5-dimethoxy-4-(n)-amylbenzaldehyde in 50 mL acetic acid was treated with 4.0 g anhydrous ammonium acetate and 12 mL nitroethane. This mixture was heated on the steam bath for 4 h, then poured into a large quantity of H_2O. This was extracted with 3x200 mL CH_2Cl_2, the extracts washed with H_2O, and the solvent removed to give a deep red oil that, on standing in the refrigerator, slowly set to a crystalline mass weighing 13.5 g. An analytical sample was recrystallized from MeOH to provide 1-(2,5-dimethoxy-4-(n)-amylphenyl)-2-nitropropene as fine yellow microcrystals with a mp of 44 °C sharp. Anal. ($C_{16}H_{23}NO_4$) C,H,N.

To a gently refluxing suspension of 10 g LAH in 500 mL anhydrous Et_2O under a He atmosphere, there was added by 13.2 g 1-(2,5-dimethoxy-4-(n)-butyl-phenyl)-2-nitropropene by allowing the condensing ether drip into a Soxhlet thimble containing the nitrostyrene which effectively added a warm saturated solution of it dropwise to the reaction mixture. Refluxing was maintained for 18 h, and the cooled reaction flask stirred for several additional days. The excess hydride was destroyed by the cautious addition of 1 L 8% H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated, and the aqueous layer was washed with an additional 2x100 mL Et_2O. Removal of the solvent from the organic phase and washings provided 4.7 g of a thick red oil that was discarded. The aqueous phase was then extracted with 2x200 mL CH_2Cl_2 which actually removed the product as the sulfate salt. This organic phase was washed with 2x100 mL 5% K_2CO_3 (removing the H_2SO_4) and with the evaporation of the solvent there was obtained 6.2 g of an oily amber residue. This was dissolved in 200 mL Et_2O and saturated with anhydrous HCl gas. Fine white crystals of 2,5-dimethoxy-4-(n)-amylamphetamine hydrochloride (DOAM) separated, were removed by filtration, Et_2O-washed and air dried, and weighed 5.2 g. The mp of 136-139 °C was increased to 145-146 °C by recrystallization from CH_3CN. Anal. ($C_{16}H_{28}ClNO_2$) C,H,N.

DOSAGE: greater than 10 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 10 mg) "There was a clear threshold that in no way interfered with my day's activities. I was quite gay and voluble at lunch and bubbled on into the afternoon with puns and high spirits. There may have been a little motor incoordination as noted in handwriting, and there was a strange tenseness during driving. There were no sequelae, there was no trouble sleeping, and with this potency way down from the lower homologues, I have no pressing desire to take this compound to a higher dose."

EXTENSIONS AND COMMENTARY: The actual procedure that was published for the isolation of this final amine was a different one, one that would certainly work, but which was based on the procedures tried and proven with the lower homologues. The process described above is just a bit bizarre (a sulfate salt extracting into methylene chloride) but it was the actual thing that was done. The work was started towards two additional compounds but these never got past the first "ketone and phenol" stage. p-Dimethoxybenzene was brought into reaction with n-caproic acid with polyphosphoric acid (aiming towards 2,5-dimethoxy-4-(n)-hexylamphetamine, DOHE) but this was dropped when DOAM proved to be down in potency. And the reaction between p-dimethoxybenzene and benzoyl chloride with anh. aluminum chloride went well (aiming towards 2,5-dimethoxy-4-benzylamphetamine, DOBZ). A goodly amount of the phenol (2-hydroxy-5-methoxybenzophenone) was obtained as fine yellow crystals, but this line of inquiry was also dropped.

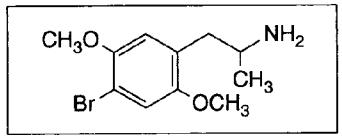
The preparation of DOAM was, as a matter of fact, the last of the homologous series of compounds actually completed, which stemmed from the original discovery of DOM. The "Ten Classic Ladies" concept was mentioned under ARIADNE, and the adding of a methyl group in the place of a hydrogen atom at the 4-position-methyl led to the synthesis of Ms. HECATE and gave rise to DOET. The whole series of methyl-ethyl-propyl-butyl-amyl compounds was appealing to me, in that the potency seemed to increase initially as the chain got longer, and then it abruptly dropped off. Wouldn't it be nice, I thought, if I could interest some pharmacologist in looking at this tight set of drugs with some animal model, to see if there is some neurotransmitter activity that would show a parallel action.

I learned of a curious young researcher in Washington who had an elegant procedure for measuring serotonin agonist action using the (otherwise) discarded sheep umbilical artery strips. These become available each year at lambing time, do not cost the life of anything, and require very little compound. He assayed my compounds and, lo and behold, the serotonin activity also went through a maximum in the middle of this series. We published a short paper to this effect, which served as a excellent vehicle to get the cogent human data into the scientific literature.

I have never understood the reasons that there might be connection between the twitching of a umbilical artery in a sheep and the appearance of an insight in the mind of man. And, I have never personally met this pharmacologist. Some day, I hope to do both.

#62 DOB; 2,5-DIMETHOXY-4-BROMOAMPHETAMINE

SYNTHESIS: To a well-stirred solution of 1.95 g of the free base of 2,5-dimethoxyamphetamine (2,5-DMA) in 12 mL glacial acetic acid, there was added 1.8 g elemental bromine dissolved in 4 mL acetic acid over the course of 5 min. The slightly exothermic reaction was allowed to stir for 3 h, and then added to about 200 mL H_2O. The cloudy solution was washed with 2x100 Et_2O, made basic with aqueous NaOH, and extracted with 3x100 mL CH_2Cl_2. Evaporation of the solvent from the pooled extracts gave about 3 mL of a pale amber oil which was dissolved in 250 mL anhydrous Et_2O and saturated with anhydrous HCl gas. The fine white crystals of 2,5-dimethoxy-4-bromoamphetamine hydrochloride, DOB, were removed by filtration, Et_2O washed, and air dried. These weighed 1.7 g and had a mp of 195-196 °C. Recrystallization from IPA brought this up to 207-208 °C. Proton NMR spectroscopy of the hydrochloride salt in D_2O gave confidence that the bromine atom had uniquely entered the 4-position, in that there were only two unsplit aromatic hydrogen atoms present, at 6.97 and at 7.20 ppm downfield from external TMS.



DOSAGE: 1.0 - 3.0 mg.

DURATION: 18 - 30 h.

QUALITATIVE COMMENTS: (with 0.4 mg) "There was a distinct enhancement of visual perception, and some strengthening of colors. A clean, cold feeling of wind on the skin. I felt an enriched emotional affect, a comfortable and good feeling, and easy sleeping with colorful and important dreams."

(with 2.0 mg) "There was a continuous tremor at the physical level, and an incredible Moebius strip representation of reality at the intellectual level. I was able to enter into personal problems easily, and get out again when I chose to. During the next day, there were brief lapses of attention, or little fugue states, and it was not until the following evening that I was completely myself again."

(with 2.8 mg) "About three hours into this I had a severe cramp, and had a near fainting response to the pain, and yet there was no pain! I felt that I was very near a loss of consciousness, and this was most disturbing. There were flashes of depersonalization. I saw rings around the moon with prismatic colors, and there were long-lasting "after-images" following any viewings of points of light. I was still a good plus 1 at 14 hours, but did manage to sleep. It was the next day before I was again at baseline."

(with 3.0 mg) "This was a complex, but a very good day. It involved making a large pot of chicken-vegetable soup, and listening to H.L., my favorite Saturday morning fundamentalist Christian radio preacher, bless 'im. The Democrats are not exactly all anti-American dupes of Moscow (or the Devil), but to H.L., they are practically, almost, next-door to it. The Rapture is supposed to happen tomorrow according to a certain book, newly published (just in time, looks like) and he is busy softening the possible disappointment of those who may find themselves unchanged Monday morning. Wunnerful. It's been one heck of a good experiment, and I can't understand why we waited nine years to try this gorgeous stuff. Without going into the cosmic and delicious details, let's just say it's a great material and a good level."

(with 0.5 mg of the "R" isomer) "I am underway, and this is a smooth intoxication. I am completely functional, but still really a plus two. I would not choose to drive a car. Not very far. I felt a rather quick dropping to a plus-one at the fifth hour, but there is a residual stimulation still the following morning."

(with 1.0 mg of the "R" isomer) "By the fourth hour I am absolutely a +++ and am searching the kitchen for food. But what I eat is only so-so. There is not the introspection or intensity of 2.0 milligrams of the racemate material, but this is a rewarding place nonethless. At the 18th hour, there was some fitful sleep, with bizarre dreams. The next day I was still hungry for altered spaces, and successfully challenged the residual plus one with LSD and, as is usually the case, acid cut right through the detritus and allowed a direct shot up to a +++ again."

(with 1.5 mg of the "R" isomer) "This is a +++ but it is vaguely irrational. I feel a heavy body load, but then the temperature outside is over a hundred degrees and I may not be in the best of all physical environments. I would not wish any higher dosage. There were cat-naps at the twelth hour, but most symptoms were still there at the 18th hour. A good experience. It would be interesting to compare this, some day, with 3.0 milligrams of the racemate."

(with 0.5 mg of the "S" isomer) "There are no effects at all."

(with 1.0 mg of the "S" isomer) "There is something warm and nice at a couple of hours into this, but I am no more than threshold, and the effects are very slight. By the fifth hour there are no longer any effects."

EXTENSIONS AND COMMENTARY: The stars had clearly lined up in favor of making DOB and exploring its biological activity. This preparation had been completed in 1967 and the report of this compound and its unprecedently high potency published in 1971. And very shortly, two additional papers appeared completely independently. One described DOB made via a different route, and describing high activity in rats. The other described DOB and a couple of closely related brominated amphetamines and their action in man.

This is one of the last of the experimental compounds within the phenethylamine family on which any animal toxicity studies were performed by me prior to human studies. A mouse injected with 50 mg/Kg (ip) showed considerable twitching and was irritable. Another, at 100 mg/Kg (ip), had overt shaking at 20 minutes, which evolved into persistent hyperactivity that lasted several hours. Yet another, at 125 mg/Kg (ip), lost much of her righting reflex within 15 minutes,

entered into convulsions at 50 minutes, and was dead a half hour later. A fourth mouse, at 150 mg/Kg (ip), entered into spontaneous convulsions within 10 minutes, and expired in what looked like an uncomfortable death at 22 minutes following injection. What was learned? That the LD/50 was somewhere between 100 and 125 mg/Kg for the mouse. And an effective dose in man of maybe 2 mg (for an 80 Kg man) is equivalent to 25 ug/Kg. Therefore the index of safety (the therapeutic index, the lethal dose divided by the effective dose) is well over a thousand. I feel that two mice were killed without anything of value having been received in return.

Actually, it is very likely that the damaging, if not lethal, level of DOB in man is a lot lower than this ratio would imply. There was a report of a death of a young lady following the snorting of an amount of DOB so massive, there was the actual recovery of over nine milligrams of the drug from her body tissues in the post-mortem examination. It was said that she and her companion had thought that the drug they were using was MDA and, taking a dosage appropriate for this, effectively overdosed themselves. He survived, following convulsions and an extended period (several weeks) of being in a comatose state. Tragic examples have been reported that involve arterial vascular spasm. But in most overdose cases ascribed to DOB, the identity of the drug has remained unestablished.

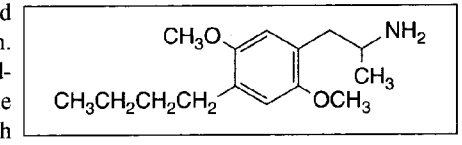
As with DOI, the presence of a heavy atom, the bromine atom, in DOB makes the radioactive isotope labelled material a powerful research tool. Studies with DOB labelled with either ^{82}Br or ^{77}Br have been used in human subjects to follow the distribution of the drug. The use of a whole body scanner permits the imaging of the intact body, with the travelings of the radioactivity easily followed from outside. A fascinating finding is that DOB goes first and foremost to the human lung where it accumulates for a couple of hours. It is only afterwards that the brain level builds up. There is a strong implication that some metabolic conversion occurs in the lung, and it is only after this that the truly active metabolite is available for central action. This is consistent with the relatively slow onset of effect, and the very long duration of action.

As with all the other psychedelics which can and have been studied as their optical isomers, it is the "R" isomer of DOB that is the more active than the racemic mixture, and the "S" is certainly much less active, but it has never been run up to fully active levels. The alpha-ethyl homologue of DOB is mentioned under ARIADNE. The positionally rearranged isomers of DOB are discussed under META-DOB.

#63 DOBU; 2,5-DIMETHOXY-4-(n)-BUTYLAMPHETAMINE

SYNTHESIS: A well stirred suspension of 140 g anhydrous $AlCl_3$ in 400 mL CH_2Cl_2 was treated with 102 g butyryl chloride. This mixture was added in small portions, over the course of 20 min, to a well-stirred solution of 110.4 g p-dimethoxybenzene in 300 mL CH_2Cl_2. After an additional 1 h stirring, the mixture was poured into 1 L H_2O, and the two phases separated. The aqueous phase was extracted with 2x100 mL CH_2Cl_2, and the organic fractions pooled. These were washed with 4x125 mL 5% NaOH which removed both unreacted butyric acid as well as a small amount of 2-hydroxy-4-methoxybutyrophenone. Removal of the CH_2Cl_2 under vacuum gave 156.7 g of a residue that was distilled at 170-178 °C at the water pump. The isolated 2,5-dimethoxybutyrophenone was a pale yellow oil that weighed 146 g and was about 85% pure by GC analysis. The principal impurity was unreacted dimethoxybenzene. The identical preparation with CS_2 as a solvent, rather than CH_2Cl_2 gave a somewhat smaller yield of product.

To 150 g mossy zinc there was added a solution of 3 g mercuric chloride in 60 mL H_2O, and this was swirled periodically for 2 h. The H_2O was drained off, and the amalgamated zinc added to a 1 L three-neck round-bottomed flask, treated with 80 mL concentrated HCl, and heated on the steam bath. A solution of 20.8 g of 2,5-dimethoxybutyrophenone in 45 mL EtOH containing 10 mL concentrated HCl was added in increments over a 4 h period. During this period an additional 140 mL of concentrated HCl was added periodically to the ketone solution. Heating was maintained for an additional 4 h. After cooling, the aqueous filtrate was extracted with 3x100 mL CH_2Cl_2 and these pooled extracts washed with 2x200 mL 5% NaOH to remove a small amount of phenolic impurity. After removal of the solvent under vacuum, the residual 16.1 g of clear oil was distilled over the 100-160 °C range (largely at 141-145 °C) at the water pump to give 10 g of 2,5-dimethoxy-(n)-butylbenzene as a white oil. This was about 90% pure by GC analysis, and was used without further purification in the next step.



A mixture of 98 mL $POCl_3$ and 108 mL N-methylformanilide was allowed to incubate for 0.5 h. To this there was then added 47.3 g of 2,5-dimethoxy-(n)-butylbenzene and the mixture heated on the steam bath for 1.5 h. This mixture was poured into 1 L H_2O and stirred overnight. The H_2O was drained from the extremely gooey black crystals that were formed, and extracted with 2x100 mL portions of hexane. The black residue was diluted with these extracts and, on slow evaporation there was deposited 26.4 g of oily amber crystals. Filtering these through a medium porous funnel and sucking the oily phase away from the solids yielded 14.8 g of yellow crystals that could be recrystallized from 50 mL MeOH to give, after filtration and air drying to constant weight, 6.4 g of 2,5-dimethoxy-4-(n)-butylbenzaldehyde as pale yellow crystals with a mp of 47-48 °C. The recovery of all organic soluble things from the above process gave, after removal of the extraction solvents and making boiling hexane extractions of the residues, a second crop of aldehyde of equal weight and of identical mp. An analytical sample, from hexane, had the same mp. Anal. ($C_{13}H_{18}O_3$) C,H.

A solution of 13.2 g 2,5-dimethoxy-4-(n)-butylbenzaldehyde in 50 mL acetic acid was treated with 4.0 g anhydrous ammonium acetate and 10 mL

nitroethane. This mixture was heated on the steam bath for 4 h, then poured into a large quantity of H_2O. This was extracted with 2x200 mL CH_2Cl_2, the extracts washed with H_2O, and the solvent removed to give 19 g of a deep red oil. This was dissolved in 35 mL hot MeOH and slowly cooled, depositing yellow-orange crystals. These were removed by filtration, washed with cold MeOH, and air-dried to constant weight. Thus there was obtained 11.8 g of 1-(2,5-dimethoxy-4-(n)-butylphenyl)-2-nitropropene with a mp of 54-56 °C. Recrystallization of an analytical sample from MeOH tightened the mp to 55-56 °C. Anal. ($C_{15}H_{21}NO_4$) C,H,N.

To a gently refluxing suspension of 8.5 g LAH in 300 mL anhydrous Et_2O under a He atmosphere, there was added 11.0 g 1-(2,5-dimethoxy-4-(n)-butylphenyl)-2-nitropropene by allowing the condensing ether to drip into a Soxhlet thimble containing the nitrostyrene, thus effectively adding a warm saturated solution of it dropwise. Refluxing was maintained overnight, and the cooled reaction flask stirred for several additional days. The excess hydride was destroyed by the cautious addition of 600 mL H_2O containing 55 g H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated, and 250 g of potassium sodium tartrate was dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was above 9, and this was then extracted with 3x200 mL CH_2Cl_2. Evaporation of the solvent produced 12 g of an amber oil that gelatinized to a waxy, amorphous mass. This was leached as thoroughly as possible with anhydrous Et_2O which was clarified by filtration, then saturated with anhydrous HCl gas. After a few minutes delay, there commenced the separation of fine white crystals of 2,5-dimethoxy-4-(n)-butylamphetamine hydrochloride (DOBU). These weighed, after filtration, Et_2O washing, and air drying to constant weight, 5.8 g. Recrystallization from boiling CH_3CN (this is an unusually exothermic crystallization) yielded 5.4 g of a fluffy white product with mp 151-152 °C. Anal. ($C_{15}H_{26}ClNO_2$) C,H,N.

DOSAGE: uncertain.

DURATION: very long.

QUALITATIVE COMMENTS: (with 2.2 mg) "It was almost the fourth hour before I noticed something. Then I felt an increasing manic intoxication, winding up tighter and tighter. Sleep was impossible until some 18 hours after the start of the trial. There was some paresthesia, but no mydriasis. This might be a stimulant, but it is not a psychedelic, at least at this level. Go up slowly."

(with 2.8 mg) "Nothing for over seven hours. Then there was what seemed to be an irritability and shortness of temper. Mentally I am completely clear, but no more alert than usual. There was no sleep that evening, and the next day there was a feeling of overall depression. Perhaps that was due to the lack of sleep, but there were no signs of residual sleepiness."

EXTENSIONS AND COMMENTARY: It is not possible to give a dosage range

for DOBU. There is no question but that whatever is occurring is slow of onset, and very long lived. In general, the effects resemble stimulation more that anything else.

A butyl group has four carbons, and they can be interconnected in four ways (as long as you don't connect them in rings). If all four of them are in a straight chain, you have the so-called normal butyl (or n-butyl) group, and this is the exact arrangement that is found in the DOBU. The atoms can be numbered #1 through #4, going outwards from the point of attachment. The chain can, however, be only three carbons long, and the fourth or extra carbon attached on the #2 carbon atom; this is called the iso-butyl (or i-butyl) group. Or the extra left-over carbon can be attached to the #1 carbon atom; this is called the secondary butyl (or sec-butyl or s-butyl) group. Or lastly, the atoms can be all scrunched up, with the chain only two carbons long, and the other two left-over methyl carbons attached to the #1 carbon atom. This isomer is called the tertiary butyl (or tert-butyl or t-butyl) group. In animal studies, and in preliminary human studies, the activity of these compounds drops as the butyl group gets more and more scrunched.

The isomer with the iso-butyl group has been synthesized by the Friedel-Crafts reaction of isobutyryl chloride with p-dimethoxybenzene, followed by reduction of the ketone to an alcohol, dehydration to a dimethylstyrene, and final hydrogenation to a hydrocarbon. The formation of the benzaldehyde, reaction with nitroethane, and final lithium aluminum hydride reduction to 2,5-dimethoxy-4-(2-methylpropyl)-amphetamine hydrochloride (DOIB, mp 164-166 °C) were completely conventional. In drug discrimination studies in rats, DOIB was only a third as active as DOM, and in humans the activity falls in the 10 to 15 milligram area. The isomer with the sec-butyl group was made in a somewhat similar manner, from 2,5-dimethoxyacetophenone. The addition of ethyl magnesium bromide gave an alcohol which with dehydration yielded a pair of dimethylstyrenes isomeric to the compound mentioned above. From there an identical sequence of steps (hydrogenation, benzaldehyde synthesis, nitrostyrene, and lithium aluminum hydride reduction) produced 2,5-dimethoxy-4-(1-methylpropyl)amphetamine hydrochloride (DOSB, mp 168-170 °C.). In the rat studies it was only a twelfth the potency of DOM, and in man the active dose is in the 25 to 30 milligram area. As with the normal butyl compound, there is a strong stimulation factor, with real and long-lasting sleep disturbance.

The last of the butyl isomers, the tert-butyl compound, was made from a much more obvious starting material. This is the commercially available tert-butyl hydroquinone. It was methylated in sodium hydroxide with methyl iodide, and then carried through the above sequence (benzaldehyde. mp 124 °C from cyclohexane, nitrostyrene, yellow crystals from methanol, mp 95-96.5 °C, and lithium aluminum hydride reduction) to give 2,5-dimethoxy-4-(1,1-dimethylethyl)amphetamine hydrochloride (DOTB, mp 168 °C). Rats trained in a process called the Sidman Avoidance Schedule gave behavior that suggested that DOTB had no activity at all, and in human trials, doses of up to 25 milligrams were totally without effect.

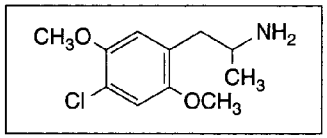
An effort was made to prepare a butyl analogue containing a ring, but it was

never completed. This was the cyclopropylmethyl isomer, 2,5-dimethoxy-4-cyclopropylmethylamphetamine hydrochloride, DOCPM. Only the first step of its synthesis was complete (the reaction of cyclopropylcarboxylic acid chloride with p-dimethoxybenzene) and even it went badly. The desired ketone (2,5-dimethoxyphenyl cyclopropyl ketone) was most difficult to separate from the recovered starting ether. A promising approach would be the isolation of the phenol (2-hydroxy-5-methoxyphenyl cyclopropyl ketone) which is a beautiful yellow solid with a melting point of 99-100 °C from methanol. Anal. ($C_{11}H_{12}O_3$) C,H. It then could be methylated to the wanted intermediate. It is the major product when the reaction is conducted with anhydrous aluminum chloride in methylene chloride.

The 2-carbon phenethylamine homologues of these compounds could all, in principle be easily made by using nitromethane instead of nitroethane with the intermediary benzaldehydes. But, as of the present time, none of them have been made, so their pharmacology remains completely unknown.

#64 DOC; 2,5-DIMETHOXY-4-CHLOROAMPHETAMINE

SYNTHESIS: A solution of 6.96 g 2,5-dimethoxyamphetamine hydrochloride (2,5-DMA) in 250 mL H_2O was made basic with aqueous NaOH and extracted with 3x75 mL CH_2Cl_2. After removal of the solvent from the pooled extracts under vacuum, the residual free base was dissolved in 36 g glacial acetic acid and, with good stirring, cooled to 0 °C with an external ice bath. There was then added, with a Pasteur pipette, 3 mL of liquid chlorine. The generation of HCl was evident, and the reaction was allowed to stir for an additional 3 h. The mixture was then poured into 300 mL H_2O and washed with 3x100 mL Et_2O. The aqueous phase was made basic with NaOH and extracted with 3x150 mL CH_2Cl_2. After removal of the solvent from the pooled extracts, the residue was dissolved in Et_2O and saturated with anhydrous HCl gas. There was the formation of a heavy oily precipitate. The ether supernatent was decanted, and the residue was intimately mixed with 200 mL of fresh anhydrous Et_2O. Everything set up as an off-white crystalline mass weighing 2.3 g. This was dissolved in 12 mL of boiling MeOH and diluted with 230 mL boiling Et_2O. The clear solution was quickly filtered to give a clear, pale amber mother liquor, which soon started depositing lustrous white crystals. After filtering, Et_2O washing, and air drying to constant weight, there was obtained 1.4 g of 2,5-dimethoxy-4-chloroamphetamine hydrochloride (DOC) From the mother liquors (from the original HCl saturation) an equal amount of product could be obtained by exploiting the acetone insolubility of the hydrochloride salt of the product. The published mp of this salt, from acetone/EtOH, is 187-188 °C. A sample of this hydrochloride salt, prepared from the amino analogue via diazotization and eventual hydrolysis of an acetylated precursor, was recrystallized from EtOH/ether and had a mp of 193-194.5 °C.



DOSAGE: 1.5 - 3.0 mg.

DURATION: 12 - 24 h.

QUALITATIVE COMMENTS: (with 1.6 mg) "I was hit with a slightly light head; the effects were quite real. I was disconnected, and somehow spacey, but this was a favorable spacey which was kind of fun. Somewhere at about the sixth hour I realized that I was beginning to drop off a bit, but six hours later yet, there was still a lot of memory. This is a long thing."

(with 2.4 mg) "This is what I might call an archetypical psychedelic. Everything is there in spades, with few if any of the subtle graces, the 'gentle images' and 'gentle fantasies' of the 2-carbon phenethylamines. This is the works. There are visuals, and there are interpretive problems with knowing just where you really are. The place where nothing makes sense, and yet everything makes sense. I have just slept for a few hours, and now I am awake and it has been eighteen hours, and there is a lot still going on, although I have a relaxed, good feeling. Anyone who uses this had better have 24 hours at their disposal."

(with 2.4 mg) "Here I am at the sixth hour, and I am still roaring along at a full plus three. I have established that this material is neither anti-erotic nor anorexic. The body is very comfortable, and so is the mind. There is an interesting aspect, perhaps peculiar only to this experiment and under these conditions. With my eyes closed the fantasy is a completely dark screen, lovely and seductive, subtle, and yet light must be deliberately brought in. This is not in any way negative for being in the dark, but is just unusual. I will have to try this in the daylight next time, to see what the eyes-closed brings to the mind-screen. At 24 hours, I have found that my sleep was not too great. My dreams were tight, and I kept defending against trouble; the nervous system was too alert. I was in a good humor, though, and I still am. This is excellent stuff, but start early in the day."

EXTENSIONS AND COMMENTARY: It is clear that the three halo-amphetamine derivatives, DOI, DOB and DOC, are all pretty much of the same potency. And all of them very long lived. The difference between the various halogen atoms was brought up under the 2C-C discussion. DOC is clearly a long-lasting, dyed-in-the-wool psychedelic.

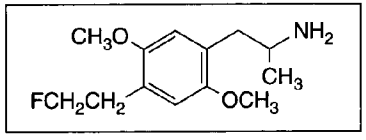
In the making of this, by the procedures that have been followed in Canada, there are two chemical intermediates which might, some day, be looked at as potential psychedelics under their own colors. Reduction of the compound that is called DON in this Book II (2,5-dimethoxy-4-nitroamphetamine hydrochloride) with Pd/charcoal and hydrogen, gives the 4-amino derivative. This is 2,5-dimethoxy-4-aminoamphetamine dihydrochloride, DOA, which melts at 248-250

°C. And the reduction of an oxime intermediate gives rise to the acetamido analogue, 2,5-dimethoxy-4-acetamidoamphetamine hydrochloride, DOAA, with a mp of 249-250 °C. Neither compound has been tasted, but someday this omission will be corrected. DOA and DOAA have a sinister ring to them, however, and some changes of terminology might be needed. DOA, in the coroner's vocabulary, means Dead-On-Arrival. But then, AMA (the American Medical Association) just happens to also mean (in the jargon of emergency medicine) Against-Medical-Advice. Everything averages out, somehow. Remember that the amyl homolog (amyl at the 4-position) follows the 4-letter convention of all of the DOM homologues, and has the code name of DOAM. Thus, DOA, amino; DOAA, acetamido, and DOAM, amyl.

One must learn to keep one's sense of humor. The immortal humorist Wavy Gravy once said, "If you can't laugh at life, it just isn't funny anymore." The code name of this compound, 2,5-dimethoxy-4-chloroamphetamine is, after, all, DOC. This should certainly appeal to some physicians.

#65 DOEF; 2,5-DIMETHOXY-4-(2-FLUOROETHYL)-AMPHETAMINE

SYNTHESIS: A well-stirred solution of 0.45 g free base DOB in 2 mL CH_2Cl_2 was treated with 0.37 g triethylamine, cooled to 0 °C, and there was then added a solution of 0.39 g 1,1,4,4-tetramethyl-1,4-dichlorodisilylethylene in 2 mL CH_2Cl_2. The reaction mixture was allowed to return to room temperature, with stirring continued for 2 h. The solvent was removed under vacuum, the residue suspended in hexane, and the insoluble by-products removed by filtration through celite. Removal of the solvent under vacuum gave 0.60 g 1-(4-bromo-2,5-dimethoxyphenyl)-2-(1-aza-2,5-disila-2,2,5,5-tetramethylcyclopentyl)propane as a gold-colored impure semi-solid mass which was used without further purification.



To a solution of 0.60 g 1-(4-bromo-2,5-dimethoxyphenyl)-2-(1-aza-2,5-disila-2,2,5,5-tetramethylcyclopentyl)propane in 10 mL anhydrous Et_2O under an inert atmosphere and cooled to -78 °C there was added 1.8 mL of a 1.7 M solution of t-butyl lithium in hexane. The resulting yellow solution was stirred for 20 min, and then treated with 1.65 mL of a 1.4 M solution of ethylene oxide in Et_2O, the stirring was continued for 40 min, then the reaction mixture allowed to come to room temperature over an additional 40 min. There was added 20 mL hexane, and the temperature increased to 50 °C for an additional 2 h. The reaction mixture was treated with 3 mL H_2O and diluted with 60 mL Et_2O. The organic phase was washed with saturated NH_4Cl, dried over anhydrous $MgSO_4$, and after filtering off the in-

organic drying agent, the organic solvents were removed under vacuum. The gold-colored residual oil was dissolved in 10 mL MeOH and treated with a 10% KOH. This mixture was heated for 30 min on the steam bath, returned to room temperature, and the volatiles removed under vacuum. The residue was dissolved in 3% H_2SO_4, washed twice with CH_2Cl_2, brought to pH 12 with 25% NaOH, and extracted with 3x50 mL CH_2Cl_2. The pooled extracts were combined, dried with anhydrous Na_2SO_4, and the solvent removed under vacuum to give 0.24 g of 2,5-dimethoxy-4-(2-hydroxyethyl)amphetamine (DOEH) as a white solid with a mp of 102-104 °C.

To a suspension of 0.94 g DOEH in ice-cold anhydrous Et_2O containing 1.4 g triethylamine, there was added 2.4 g trifluoroacetic anhydride dropwise over the course of 10 min. The reaction mixture was brought to reflux temperature, and held there with stirring for 1 h. After cooling, 60 mL of CH_2Cl_2 was added, and the organic phase washed with saturated $NaHCO_3$. The solvent was removed under vacuum, providing a gold-colored solid as a residue. This was dissolved in 50 mL MeOH, diluted with 30 mL H_2O and, following the addition of 0.76 g solid $NaHCO_3$ the reaction mixture was stirred at room temperature for 3 h. The excess MeOH was removed under vacuum, and the remaining solids were suspended in CH_2Cl_2 and washed with H_2O. After drying the organic phase with anhydrous Na_2SO_4 and removal of the solvent under vacuum, there was obtained 1.34 g 1-(2,5-dimethoxy-4-(2-hydroxyethyl)phenyl)-2-(2,2,2-trifluoroacetamido)propane as white solid with a mp of 129-131 °C. Anal. ($C_{15}H_{20}F_3NO_4$) C,H.

A well-stirred solution of 0.09 g 1-(2,5-dimethoxy-4-(2-hydroxyethyl)phenyl)-2-(2,2,2-trifluoroacetamido)propane in 15 mL CH_2Cl_2 was cooled to -78 °C and treated with 0.05 g diethylaminosulfur trifluoride (DAST) added dropwise. The pale yellow reaction solution was stirred an additional 5 min and then brought up to room temperature and stirred for 1 h. There was then added (cautiously) 3 mL H_2O followed by additional CH_2Cl_2. The phases were separated, the organic phase washed with H_2O, dried with anhydrous Na_2SO_4 and, after filtering off the drying agent, stripped of solvent under vacuum. There was thus obtained 0.088 g of 1-[2,5-dimethoxy-4-(2-fluoroethyl)phenyl]-2-(2,2,2-trifluoroacetamido)propane as a white solid with a mp of 102-104 °C.

A solution of 0.12 g 1-[2,5-dimethoxy-4-(2-hydroxyethyl)phenyl]-2-(2,2,2-trifluoroacetamido)propane in a mixture of 5 mL CH_2Cl_2 and 5 mL IPA was treated with 0.2 mL 2 N KOH, heated on the steam bath for 30 min, and then stripped of solvents under vacuum. The residue was suspended in CH_2Cl_2 and washed with 20% NaOH. The organic phase was dried with anhydrous Na_2SO_4 which was removed by filtration, and the combined filtrate and washings stripped of solvent under vacuum. The residual glass (0.08 g) was dissolved in IPA, neutralized with concentrated HCl and diluted with anhydrous Et_2O to provide 2,5-dimethoxy-4-(2-fluoroethyl)amphetamine hydrochloride (DOEF) as a white crystalline solid with a mp of 205-208 °C. Anal. ($C_{13}H_{21}ClFNO_2$) C,H.

DOSAGE: 2 - 3.5 mg.

DURATION: 12 - 16 h.

QUALITATIVE COMMENTS: (with 2.2 mg) "Somewhere between the first and second hour, I grew into a world that was slightly unworldly. Why? That is hard to say, as there was no appreciable visual component. I just knew that the place I was in was not completely familiar, and it was not necessarily friendly. But it was fascinating, and the music around me was magical. Time was moving slowly. I had to drive across the bay at about ten hours into this, and I was comfortable. That evening I slept well, but my dreams were pointless."

(with 3.0 mg) "It took almost three hours to full activity. The first signs of effects were felt within a half hour, but from then on the progress was slow and easy, without any discernible jumps. There was absolutely no body discomfort at all. Completely comfortable. There was a general humorousness about my state of mind which is always a good sign. We went to the bedroom at the two and a half hour point, and proceeded to establish that the material is far from anti-erotic. Beautiful response, without a mention of any feeling of risk at orgasm. I myself was not able to reach orgasm until about 5th to 6th hour, and then it was full and exceptionally delicious. So was the second one, a couple of hours later, if I remember correctly. All systems intact, body, mind and emotion. Gentle. Good for writing. No dark corners apparent at all. For me, not highly visual. Would take again, higher."

(with 3.0 mg) "There was no body threat at any time — very comfortable. Good eyes closed, with complex imagery to music, but not too much with eyes-open. My attention span is relatively short, and easily diverted into new directions — all quite reminiscent of DOI both as to dosage and effect. At 13 hours, I am still too alert to sleep, but a couple of hours later, OK. In the morning there is still a trace of something going on. This was a valid +++."

EXTENSIONS AND COMMENTARY: I was asked by a student of mine a while ago, when I told him of this material, just why would anyone just happen to place a fluorine atom at the end of the 4-ethyl group of DOET? It wasn't the sort of thing that someone would just happen to do. If there were a rationale, then that's fine. But by capricious impulse, no. But there is a rationale of sorts, which I just hinted at in the discussion under 2C-T-21.

This argument of reason goes as follows. Assume that I would like to put a fluorine atom into a drug that does not normally have one. Why would I want to? Because I want to have the molecule carry a radioactive fluorine atom into some inner recess of the brain. Why? Because by using a positron-emitting fluorine I could possibly visualize the area of the brain that the drug went to. And if it went there in some abnormal way, the exact measure of that abnormality might give some clue as to potential brain misfunctioning.

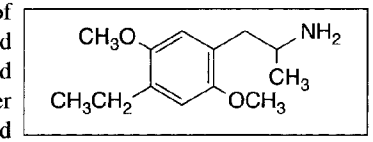
But, if you put a fluorine atom on a drug, it becomes a totally new drug and, quite reasonably, a pharmacologically different drug. However, a body of evidence

is being accumulated that if a halogen, such as a bromine or an iodine atom, is replaced by a beta-fluoroethyl group, the electronic and polar properties of the drug can be pretty much the same. So, what psychedelics have a bromo or an iodo group? Obviously, DOB and DOI. Thus, DOEF is a natural candidate for fluorine-18 positron emission tomography, and also a natural candidate for clinical trials. And, voila, it is an active material.

And I'll bet you dollars to doughnuts, that if one were to make the two-carbon analog 2,5-dimethoxy-4-(2-fluoroethyl)-phenethylamine, it would be every bit as much a treasure and ally as is 2C-B or 2C-I. In fact, I am sure enough about this prediction that I am willing to name the stuff 2C-EF. It will be easily made from 2C-B by the same reaction scheme that was used above for DOEF. And I will even guess that its activity level will be in the 20-30 milligram area.

#66 DOET; HECATE; 2,5-DIMETHOXY-4-ETHYL-AMPHETAMINE

SYNTHESIS: To a solution of 19.7 g 2,5-dimethoxy-4-ethylbenzaldehyde (see the recipe for 2C-E for its preparation) in 72 g glacial acetic acid there was added 6.5 g anhydrous ammonium acetate and 10.2 g nitroethane. After heating for 1.75 h on the steam bath, the reaction mixture was cooled in a wet ice bath, diluted with 10 mL H_2O, and seeded with a small crystal of product. The yellow crystals were removed by filtration (7.6 g wet with acetic acid) and another 2.25 g was obtained from the mother liquors with additional H_2O. The combined fractions were recrystallized from 25 mL boiling MeOH, to give 6.5 g fine yellow crystals of 1-(2,5-dimethoxy-4-ethyl)-2-nitropropene, with a mp of 67.5-68.5 °C. Anal. ($C_{13}H_{17}NO_4$) C,H,N.



A suspension of 6.5 g LAH in 500 mL well stirred anhydrous Et_2O was held at reflux under an inert atmosphere, with the return of the condensed solvent passing through a Soxhlet thimble containing 6.5 g 1-(2,5-dimethoxy-4-ethylphenyl)-2-nitropropene. After the addition of the nitrostyrene was complete, the stirred suspension was maintained at reflux for an additional 18 h, then cooled to room temperature. The excess hydride was destroyed with 500 mL 8% H_2SO_4, added cautiously until the hydrogen evolution ceased, then at a speed that allowed the formed solids to disperse. The phases were separated, the aqueous phase washed once with Et_2O, treated with 150 g potassium sodium tartrate, and finally made basic (pH >9) with 5% NaOH. This was extracted with 3x100 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. The residue, 7.9 g of a clear oil, was dissolved in 100 mL anhydrous Et_2O and saturated with anhydrous HCl gas. After standing at room temperature for 2 h, the crystalline 2,5-dimethoxy-4-

ethylamphetamine hydrochloride (DOET) was removed by filtration, washed with Et_2O, and air dried to constant weight. There was obtained 5.9 g of lustrous white crystal with a mp of 190-191 °C. Recrystallization from CH_3CN or EtOAc increased the mp to 194-195 °C. Anal. ($C_{13}H_{22}ClNO_2$) C,H,N.

DOSAGE: 2 - 6 mg.

DURATION: 14 - 20 h.

QUALITATIVE COMMENTS: (with 1.0 mg) "This was a very gentle, relaxing level, but there were no psychedelic effects that were apparent. Easy, and relaxed, and I am in no way intoxicated or turned on. But I was in the throes of my menstrual period, and the cramps (and the accompanying irritability) were completely knocked out. Perhaps this is why I felt so relaxed and at peace."

(with 2.5 mg) "There is much, too much, movement with my eyes closed. And an awful lot there with my eyes open. The movement on the concrete floor in the basement when I went downstairs for wood for the fireplace, was too much. I felt almost sea-sick. And I am having reality problems — I cannot seem to find my centering point of reference. There has to be a place to pin myself down to, and it is not findable anywhere I look. And my legs are twitching, and feeling as if they are falling asleep, and I had a crawling sensation on my body, so the body is not at peace either. In the morning I was still ++, but there is a clear indication that I am repairing. Anyway, I survived the experience. This is definitely not my thing."

(with 4 mg) "Just after an hour into the experiment, I was surprised by the awareness of some effects — I had forgotten that I had taken something. At the second hour, it was real, but subtle. As a psychotomimetic or STP-like thing, there is very little there. But as a mood energizer, it is really a ++ or more. The clinical literature is right — none of the hallucinogenic effects, but one brings into play whatever one wants to. Worked at cleaning up the office until 11 PM. I slept well. This has none of the LSD or STP seriousness."

(with 6 mg) "The onset was slow, and subtle. But the effects are fully there in about three or so hours. Everything I smelled was vivid, as are all the colors and shapes; they are clean, beautiful, serenely self-contained. No visual movement. The eyes-closed fantasy images tend to take off on their own, however, and they are extremely rich. I don't see any dark corners. I believe it might well be possible to be creative with this, and there is no suggestion of body depletion, of body load."

(with 7 mg) "A hot day. Unbelievably lovely erotic-to-divine, deep loving, open, not much visual, eyes-closed form-image-symbol. Sleep attempts very shallow, slight 'thinness', with an anticipation of darts. Intellect and feeling-emotion area intact and functioning at all times. Next morning still at a plus one. Incredible material. Perhaps best at 6 to 7 milligrams, no higher due to body load."

EXTENSIONS AND COMMENTARY: The original code for this compound was

DOE, which was completely logical based on DOM being the methyl member of this series (DO for the removal of the oxygen, desoxy, and M for putting a methyl in its place). And the putting of the ethyl thence should be DOE. This was fine until it was pointed out to me by a close colleague that DOE was a classic abbreviation for desoxyephedrine, a synonym for methamphetamine. The pressure to add the "T" of the "ET" of the ethyl was heightened by looking ahead to other members of the series. DOA became DOAM, DOE became DOET, but DOM was already too firmly set in popular usage. And, anyway, DOME really looked strange.

The original publications of the action of DOM clearly documented the compound as being a psychedelic and one with a sizeable measure of potential abuse. And, it is not a surprise that it was quickly shuffled into a legal classification that effectively precluded any further study of it. So, when this immediate homologue of DOM was studied and discussed in the literature, all reported dosages were those that were at the lowest levels, and no disturbing hints of abusability were mentioned. And this particular homologue has so far escaped the attention and restrictive action of the drug enforcement agencies, although the specific wording of the Controlled Substance Analogue Enforcement Act of 1986 might make this point moot, at least as far as human trials are concerned. At modest levels, DOET has the reputation of being a cognitive enhancer and is largely free of those sensory distortions that would catch the attention of the authorities who cannot tolerate drugs that distort the senses. The higher levels mentioned here have never been put into the published literature. It must be noted that there is a considerable variation of individual responses to this material and some people have had very negative experiences with as little as five milligrams. Some people are quite sensitive. Our Classic Lady HECATE can be quite capricious.

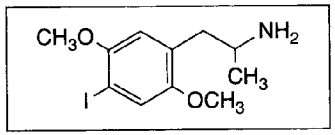
The young experimental subject who had the dramatic relief from menstrual cramps at the one milligram dose tried the compound again the following month, and again had complete relief. But another volunteer, also plagued with severe cramping at that particular time of month, found no relief at all. A 50% success rate. No one else has, to my knowledge, explored this particular property.

#67 DOI; 2,5-DIMETHOXY-4-IODOAMPHETAMINE

SYNTHESIS: A mixture of 14.8 g phthalic anhydride and 19.5 g of 2,5-dimethoxyamphetamine (2,5-DMA) as the free base was heated gradually to about 150 °C with an open flame. A single clear phase was formed with the loss of H_2O. After the hot melt remained quiet for a few moments, it was allowed to cool to about 50 °C and then diluted with 100 mL of hot MeOH. The solution was stirred until homogenous, seeded with product, and then cooled in an ice bath to complete the crystallization. After removal of the product by filtration, washing sparingly with MeOH, and air drying, there was obtained 24.6 g of N-(1-(2,5-dimethoxyphenyl)-

2-propyl)phthalimide as off-white crystals, with a mp of 105-106 °C. Anal. ($C_{19}H_{19}NO_4$) C,H,N.

To a solution of 2.0 g N-(1-(2,5-dimethoxyphenyl)-2-propyl)phthalimide in 15 mL warm acetic acid which was being vigorously stirred, there was added a solution of 1.2 g iodine monochloride in 3 mL acetic acid. This was stirred for 2 h at about 40 °C during which time there was a definite lightening of color, but no solids formed. The reaction mixture was poured into 600 mL H_2O which produced a reddish glob floating in a yellow-orange opaque aqueous phase. The glob was physically removed, dissolved in 30 mL boiling MeOH which, on cooling in an ice bath, deposited off-white crystals. These were removed by filtration, washed with MeOH, and air dried to give 1.5 g of N-[1-(2,5-dimethoxy-4-iodophenyl)-2-propyl]phthalimide as fine white crystals with a slight purple cast. The mp was 103-105.5 °C and the mixed mp with the starting non-iodinated phthalimide (mp 105-106 °C) was depressed (85-98 °C). Extraction of the aqueous phase, after alkalinification, provided an additional 0.15 g product. Anal. ($C_{19}H_{18}NO_4$) C,H,N.



A solution of 0.75 g N-(1-(2,5-dimethoxy-4-iodophenyl)-2-propyl)-phthalimide in 10 mL EtOH was treated with 0.3 mL of hydrazine hydrate, and the clear solution was held at reflux on the steam bath overnight. After cooling, there was a crystallization of 1,4-dihydroxyphthalizine that started as small beads but finally became extensive and quite curdy. These solids were removed by filtration and had a mp of about 340 °C (reference samples melted over a five to ten degree range in the area of 335-350 °C). The filtrate was dissolved in 100 mL CH_2Cl_2 and extracted with 2x150 mL 0.1 N HCl. The aqueous extracts were washed once with CH_2Cl_2, made basic with 5% NaOH, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent under vacuum gave 0.5 g of a colorless oil which was dissolved in 300 mL anhydrous Et_2O and saturated with anhydrous HCl gas. There was obtained, after filtration, and air drying, 0.35 g of 2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) as white crystals that melted at 200.5-201.5 °C. This value did not improved with recrystallization. Anal. ($C_{11}H_{17}ClINO_2$) C,H,N.

DOSAGE: 1.5 - 3.0 mg.

DURATION: 16 - 30 h.

QUALITATIVE COMMENTS: (with 0.6 mg) "There was a nice spacey light-headedness for a few hours, and time seemed to move quite slowly. Then a generic sadness came over me, as I reminisced about earlier days (recalling pleasures now gone) and wondered if I would be allowed to be here on the Farm when I am old and not important. There is so much to be done, and I cannot do it all, and no one else cares. My mood became present-day and healthy by about the seventh hour."

(with 1.6 mg) "The general nature of the experience was depressing, with a sad view of life. There was no way I could connect with my emotions. Even my sadness was vague. At about the ninth hour I decided that enough was enough, and this strangely disappointing about-plus-two was aborted with 125 micrograms of LSD. The emotions became present and living within a half hour. I was greatly relieved. The erotic was not a mechanical attempt but a deeply involved feeling with an archetype of orgasm easily available. It was shaped like a flower, richly colored, with an unusual "S" shape to it. This was a lovely end to a difficult day."

(with 3.0 mg) "This is a clear, clean psychedelic. The eyes-closed imagery is excellent, with clearly delineated patterns, pictures, and colors. Perfect for an artist, and next time I'll devote some time to painting. Total ease for the body, but no help for my smoking problem. I still want to smoke. And at sixteen hours into this I am still at 1.5+ but I'll try to go to bed anyway, and sleep."

(with 3.5 mg) "I was at a full crashing +++ for about three or four hours. There was none of the LSD sparkle, but there were moments of 'light-headedness' where one could move sideways with reality. I could leave where I was right over there, and come over here and get a strange but authentic view of where the 'there' was that I had left. It would be out-of-body, except that the body came over here with me rather than staying there. This doesn't make sense now, but it sure did then. There was no trace of body impact, and I slept late that evening, but with some guardedness due to the intense imagery. This was no more intense than with 3.0 milligrams, but it was a little bit more to the unreal side."

(with 1.0 mg of the "R" isomer) "There was a clear ++ from the second to the eighth hour, but somehow there was not quite the elegance or the push of the racemate. I was sensible, and managed to do several technical chores in a reasonable way. Easy sleep at 15 hours into it."

(with 2.3 mg of the "R" isomer) "The water solution of the hydrochloride salt has a slightly sweetish taste! I was at a +++ without question, but there was a slight down mood towards the end. And it lasted a really long time; I was distinctly aware of residual stuff going on, well into the next day."

(with 6.3 mg of the "S" isomer) "I was at a benign one-and-a-half plus at about two hours, and finally flattened out at a ++. Would I double this dose? Probably not, but half again (to 9 or 10 milligrams) would feel safe for a plus 3. By evening I was near enough baseline to drive into town for a social obligation, but even when trying to sleep later that night there was some residue of imagery; remarkably, it was all in slow motion. The fantasies were slow-paced and sluggish. It would have been interesting to have explored eyes-closed during the day."

EXTENSIONS AND COMMENTARY: Again, as with every other psychedelic amphetamine analogue which has a chiral center and has been explored as the individual optical isomers, it is the "R" isomer that is the more potent. And again, the other isomer, the "S" isomer, still shows some activity. The same was true with DOB, and DOM, and MDA. The only exception was MDMA, but then that is more

of a stimulant, and there is virtually no psychedelic component to its action. Rat studies, where there is a measure of the discrimination of a test compound from saline, have shown the "R" isomer to have about twice the potency of the "S" isomer. That the "R" is more potent is certain, but the above reports would suggest that the factor would be closer to times-four rather than times-two.

A number of studies with DOI in animal models have shown it to have an extremely high binding capacity to what are called the 5-HT_2 receptors. Serotonin is a vital neurotransmitter in the brain, and is strongly implicated in the action of all of the phenethylamine psychedelics. The place where it acts, at the molecular level, is called its receptor site. As an outgrowth of the cooperative studies of the medicinal chemists working closely with the neuropharmacologists, a number of compounds have emerged that interact with these sites. But this one interacts with these sites and not those, and that one interacts with those sites and not these. So, there has developed a collection of sub-divisions and sub-subdivisions of receptor sites, all related to serotonin, but each defined by the particular compound that interacts most tightly with it.

Thus, there were serotonin "1" receptors, and then there were "1" and "2" receptors, and then "1a and "1b" and "2a" and "2b" receptors, and on and on. These are called 5-HT receptors, since the chemical name for serotonin is 5-hydroxytryptamine, and the scientist would never want to let the layman know just what he is talking about. DOI has been synthesized with a variety of radioactive iodine isotopes in it, and these tools have been of considerable value in mapping out its brain distribution. And by extrapolation, the possible localization of other psychedelic compounds that cannot be so easily labelled. A small neurochemical research company on the East Coast picked up on these properties of DOI, and offered it as a commercial item for research experiments. But I doubt that they are completely innocent of the fact that DOI is an extremely potent psychedelic and that it is still unrecognized by the Federal drug laws since, in their most recent catalog, the price had almost doubled and a note had been added to the effect that telephone orders cannot be accepted for this compound.

The four-carbon butylamine homologue (the ARIADNE analogue) of DOI has been synthesized. A mixture of the free base of 1-(2,5-dimethoxyphenyl)-2-aminobutane (see preparation under DOB) and phthalic anhydride was fused, cooled, and recrystallized from either methanol or cyclohexane to give crystals of N-[1-(2,5-dimethoxyphenyl)-2-butyl]phthalimide with a melting point of 76-77 °C and an analysis ($C_{20}H_{21}NO_4$) C,H,N. This was iodinated with iodine monochloride in acetic acid to give N-[1-(2,5-dimethoxy-4-iodophenyl)-2-butyl]phthalimide which was chromatographically distinct from the uniodinated starting material (silica gel, CH_2Cl_2), but which did not crystallize. This was treated with hydrazine hydrate in ethanol to provide 1-(2,5-dimethoxy-4-iodophenyl)-2-aminobutane hydrochloride which was crystallized from CH_3CN/EtOH to give white crystals with a mp of 217-218.5 °C and an analysis ($C_{12}H_{19}ClNO_2$) C,H,N. This butyl homolog of DOI has been assayed at up to four milligrams, and is without any central

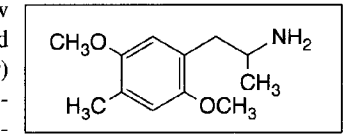
effects whatsoever. An experiment with 12.4 microcuries of ^{131}I labelled material with the whole body scanner showed most of it accumulating in the gut and liver, with almost none to the brain.

For those who find such statistics interesting, the parent compound DOI vies with DOB as probably the most potent of the phenethylamine psychedelics as of the moment, and certainly one of the most long lived.

A very important, centrally pivotal, and completely paradoxical compound in this area, is the N,N-dimethyl homologue of DOI, or 2,5-dimethoxy-N,N-dimethyl-4-iodoamphetamine (IDNNA). This compound was the starting point of the study of a large number of homologues and it deserves, and has received, a separate recipe.

#68 DOM; STP; 2,5-DIMETHOXY-4-METHYLAMPHETAMINE

SYNTHESIS: To a solution of 54.9 g 2,5-dimethoxy-4-methylbenzaldehyde (see the recipe for 2C-D for its preparation) in 215 g glacial acetic acid there was added 19.5 g anhydrous ammonium acetate and 30.6 g nitroethane. This mixture was heated for 3 h on the steam bath, the reaction mixture was cooled in a wet ice bath, allowing the spontaneous formation of yellow crystals. As much H_2O as possible was added (just short of a persistant cloudy oily character) and after a few additional h standing, the crystalline 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene was removed by filtration and recrystallized from boiling acetic acid. The yield, after drying to constant weight, was 28.3 g and the mp was 87-88 °C. Anal. ($C_{12}H_{15}NO_4$) C,H,N.



A suspension of 9.5 g LAH in 750 mL well stirred anhydrous Et_2O was held at reflux under an inert atmosphere, with the return of the condensed solvent passing through a Soxhlet thimble containing 9.5 g 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene. After the addition of the nitrostyrene was complete, the stirred suspension was maintained at reflux for an additional 4 h, then cooled to room temperature and allowed to continue stirring overnight. The excess hydride was destroyed by the addition of 750 mL 8% H_2SO_4, cautiously, until the hydrogen evolution ceased, then at a speed that allowed the formed solids to disperse. The phases were separated, the aqueous phase washed once with Et_2O, treated with 225 g potassium sodium tartrate, and finally made basic (pH >9) with 5% NaOH. This was extracted with 3x150 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. The residue was 9.6 g of a clear oil which spontaneously formed crystals with a mp of 60.5-61 °C from hexane. These solids were dissolved in 150 mL anhydrous Et_2O, and saturated with anhydrous HCl gas. After standing at room temperature for 2 h, the crystalline 2,5-dimethoxy-4-methylamphetamine hydro-

chloride (DOM) was removed by filtration, washed with Et_2O, and air dried to constant weight. There was obtained 8.25 g of glistening white crystals that had a mp of 190.5-191.5 °C. The sulfate had a mp of 131 °C. Anal. ($C_{12}H_{20}ClNO_2$) C,H,N.

The above nitrostyrene may also be converted to the final amine product through the intermediary of the corresponding phenylacetone. To a well stirred suspension of 10.4 g powdered iron in 20 mL glacial acetic acid held at reflux temperature, there was added 4.9 g 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene as a solid. Refluxing was continued for 2 h and then all was filtered through wet Celite. After washing with 300 mL H_2O followed by 300 mL Et_2O, the combined filtrate and washes were separated, and the aqueous phase extracted with 2x100 mL Et_2O. The organic phase and extracts were combined and washed with 2x100 mL saturated K_2CO_3 and the solvent was removed under vacuum yielding a reddish oil weighing 3.3 g. This was distilled at 111-115 °C at 0.5 mm/Hg to give a pale green solid. After recrystallization from benzene, there was obtained 2.8 g 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone as white crystals with a mp of 57-59 °C. This ketone has also been described as a pale-yellow oil with a bp of 115-118 °C at 0.4 mm/Hg. A solution of 0.7 g 1-(2,5-dimethoxyphenyl-4-methyl)-2-propanone in 20 mL MeOH was treated with 6.0 g ammonium acetate, 0.3 g sodium cyanoborohydride, and 3 g Linde 3 A molecular sieves. The mixture was stirred overnight, the solids removed by filtration, and the filtrate dissolved in 100 mL H_2O. The solution was acidified with dilute H_2SO_4, and washed with 2x25 mL CH_2Cl_2. The aqueous phase was made basic with aqueous NaOH, and the product extracted with 2x25 mL CH_2Cl_2. The solvent was removed under vacuum, and the residue distilled (at 160 °C at 0.2 mm/Hg) to give colorless product which was dissolved in 3 mL IPA, neutralized with concentrated HCl, and diluted with 50 mL anhydrous Et_2O. There was obtained 0.18 g of 2,5-dimethoxy-4-methylamphetamine hydrochloride (DOM) as a white solid with a mp of 187-188 °C.

The optical isomers of DOM have been prepared in two ways. The racemic base has been resolved as the ortho-nitrotartranilic acid salt by recrystallization from EtOH. The (+) acid provides the (+) or "S" isomer of DOM preferentially. Also, the above-mentioned 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone can be reductively aminated with optically active alpha-methyl benzylamine with Raney Nickel. This amine is isolated and purified by recrystallization of the hydrochloride salt. When optically pure, the benzyl group was removed by hydrogenolysis with palladium on carbon. The mp of either of the optical isomers, as the hydrochloride salts, was 204-205 °C.

DOSAGE: 3 - 10 mg.

DURATION: 14 - 20 h.

QUALITATIVE COMMENTS: (with 1.0 mg) "There is almost certainly an effect. Physically there is a slight dryness in the mouth, and my eyes are noticeably dilated. There is an eerie feeling overall."

(with 2.3 mg) "Mood elevation at 2-3 hrs. After 3 hours, emotional effects become more pronounced, enhancement of color also. Very little distortion of perception, no disorientation, no creeping or flowing, but color enhancement considerable. The emotional content and empathy for others was closer to mescaline than to amphetamine, a welcome change. No suggestion of nausea at any time. Unable to sleep at ten hours, so I took 3/4 grain Seconal. Headache and listlessness next morning, probably due to the Seconal."

(with 3 mg) "In the middle of the experience I found that I was able to separate components of complex things so as to evaluate them separately. There is no need to respect their normal purpose. The sharpness of observation is enhanced, but one can focus at every different depth of a thing or a concept. Colors are not just brighter; there are more of them. There is a profoundness of meaning inherent in anything that moves. A line of thought or a bit of personal history ties the thinker to the objects that had been thought of, or once experienced. It is this relationship that will prove productive. Not like in a movie which is circular in its totalness, but as in true life where the future is the result of your own involvement with everything about you."

(with 4 mg) "The first four hours were largely directed to the body. There was a shuddering, and a tight jaw, and I am not particularly motivated to talk to anyone. It is more arousing (like amphetamine) than depressing (like phenobarb). I am feeling just a little sick at the three hour point, but a bit of regurgitation clears this up. Then at the fourth hour, it went totally outside of me. I saw the clouds towards the west. THE CLOUDS!!! No visual experience has ever been like this. The meaning of color has just changed completely, there are pulsations, and pastels are extremely pastel. And now the oranges are coming into play. It is a beautiful experience. Of all past joys, LSD, mescaline, cannabis, peyote, this ranks number one. Normally I have no color effects with mescaline. A dynamic experience. Feels good, too."

(with 5 mg) "There was the magnification of light, color and odors. It was all very pleasant and beautiful, except that I had an overwhelmingly negative feeling. This at times grew to considerable intensity, and I feel it was clearly due to anger. At times the negativity disappeared completely, and I broke into the most enjoyable, even hilarious experiences. I alternated about 50-50 between joy and discomfort. As the evening drew on, I became withdrawn and pensive. It seemed clear that I had made all the wrong decisions — choice of partner, place to live, isolation, no meaningful activity. The greatest shocker was that my practice of meditation, which is one of my central focuses, and which I thought had brought me much peace and understanding, seemed to be a delusional solution to my unhappiness and isolation. The experience continued unabated throughout the night with much tension and discomfort. I was unable to get any sleep. I hallucinated quite freely during the night, but could stop them at will. While I never felt threatened, I felt I knew what it was like to look across the brink to insanity."

(with 8 mg) "The very quiet development picks up speed betweeen the first and second hour. There is a rich curly-imaged eyes-closed show that interlocks closely with music. It is occasionally an off-beat fantasy and not directly knit together, and even occasionally unenjoyable. But always intense and completely appropriate to the music. There is a continuous thirst, and little urine. Napping seems OK at 16 hours, but real sleep must wait until the 20 hour point. Overall a rolling +++, and I am looking forward to a repeat some day."

(with 10 mg) "If on this page I shall have expressed it to you then it is true that DOM has the glory and the doom sealed up in it. All that's needed to unseal it is to surround it with a warm living human for a few hours. For that human for those hours all the dark things are made clear."

(with 12 mg) "The first awareness was at 30 minutes and it was in the tummy. The development was extremely rapid, something more like LSD than previously remembered. The body tremor feels like poisoning, there is no escaping the feeling of being disabilitated, but at least there is no nausea. This transition ended and the trauma cleared completely at about the second hour. The music was exceptional, the erotic was exceptional, the fantasy was exceptional. Listz's "A Christmas Cantata #1," part 1, with eyes closed was an experience without precedent. There were some residual effects still noted the next day. This may be a bit much for me."

(with 0.3 mg of the "R" isomer) "Maybe slightly wiry? No effects."

(with 0.5 mg of the "R" isomer) "There is a real effect, and it is significant that the first effects of the racemate were noted at 1.0 milligram. There is a trace of time slowing and in general a pretty full manic state. There is some mydriasis. Everything had pretty much cleared up by evening."

(with 2.0 mg of the"S" isomer) "No effects. There was an unexpected slight tachycardia at the two hour point, but nothing suggesting psychotropic action."

(with 2.6 mg of the "S" isomer) "There are signs of both pulse increase and blood pressure increase. There is some teeth-rubbiness, but still no psychological turn on at all."

EXTENSIONS AND COMMENTARY: The rationale for the design and making of DOM has already been discussed. One could predict that it could have been, theoretically, a totally inactive compound and maybe an effective blocker for whatever receptor sites are being occupied by other psychoactive drugs and even for strange things that some unbalanced people might actually make within their bodies, using their own personal chemistry. On the other hand, it could have been a potent psychedelic in its own rights, and if so, probably long lived. The latter "could have been" proved to be so.

The very modest amount of study of the individual optical isomers clearly indicates that the "R" isomer is the more active. The sparse comments suggest that some of the heavier physical aspects of the racemate might be due to contributions

from the "inactive" "S" isomer. It is, after all, the "S" isomer of amphetamine that carries the major punch of that stimulant. Maybe if that isomer were removed, and one were to explore the pure "R" isomer of DOM, the dramatic visual aspects of the larger dosages might not be complicated with a troublesome physical component.

This compound, unbeknownst to me, was scattered widely and plentifully in the heyday of the Haight-Ashbury in San Francisco, in mid-1967. It was distributed under the name STP, which was said to stand for Serenity, Tranquility, and Peace. It was also claimed to represent Super Terrific Psychedelic, or Stop The Police. The police called it: Too Stupid to Puke. Actually, the name was taken from the initials of a motor additive which was completely unrelated chemically. Incredibly, and sadly, one of the avowed experts in the area of the "sensuous drugs" actually stated that STP, the motor oil additive, was really one and the same as STP, the highly dangerous psychedelic. The motor oil additive, he wrote in a book of his, had properties somewhat related to those of LSD, mescaline, and the amphetamines. How fortunate that the love children of the time didn't do much reading, for they might have gotten into yet deeper pharmacological troubles with drug raids on the local gasoline stations.

Two complications became apparent during this first appearance and they led to serious difficulties. One, there was no equation made between STP and DOM. No one knew what this drug was which had been distributed in a cavalier way throughout the city. There could be no educated guess as to the best treatment of overdose emergencies. And secondly, the initial tablets that had been distributed apparently contained 20 milligrams of DOM per tablet; later, it was dropped to 10 milligrams. Either of these, in retrospect, is now known to be a thoroughly whopping dose. The overdose situation was aggravated by the slow onset of DOM. The user may be aware of some initial effects at the half-hour point, there will be what might be called a + or ++ at the end of the first hour, and the full impact of the drug is not appreciated until some two hours have elapsed. But many of the recipients of the free handouts of DOM were familiar with LSD which can show its alert in 15 to 20 minutes, or even sooner with a large dose, and there is already a deep and compelling intoxication felt at the half-hour point. They, quite reasonably, expected this familiar activity pattern with STP and assumed, when there was little if any activity noted at the half-hour point, that the potency was less than expected. They took one or even two additional dosage units. Thus, some of the overdose victims of that period may well have taken as much as 30 mg of DOM. The slow onset of action, coupled with the remarkably long duration, caught many innocent users unprepared.

Clinical studies have documented the rapid tolerance development from repeated exposures to DOM. Five volunteers were given 6 milligrams daily for three days. Objectively, psychological tests showed a decrease in responses. Subjectively, all found extremely intense effects on the first day, and all but one found it unpleasant. By the third exposure on the third day, all had diminished responses, ranging from only "moderately strong" to "felt absolutely nothing." One

actually slept during the experience on the third day.

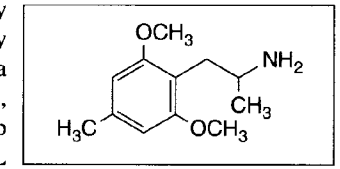
The hexadeutero-analogue (deuterium atoms on the two methoxyl groups) has been prepared as an internal standard for analytical work, but there are no reports of its human pharmacology. A study with this sort of derivative would be a fine companion to the studies already underway with the mescaline analogues that are similarly substituted. A difference exists, however. With mescaline, it is believed that the loss of a methoxyl group is a step towards the inactivation of the compound, whereas with DOM this loss may be associated with the formation of an active metabolite. The several fascinating questions raised by possible differences in both the rates and the degree of demethylation of these two compounds are well worth trying to answer.

A number of compounds related to DOM had been synthesized and studied at the University of California at San Francisco, at about this time. Two of these were simply the juggling of the two methoxyl groups and the methyl group on the ring, still maintaining the 2,4,5-ness relative to the amphetamine chain. These are 2,4-dimethoxy-5-methylamphetamine and 4,5-dimethoxy-2-methylamphetamine. Since the slang name for DOM in and about the medical center was STP, and since STP was the name of a motor oil additive, it is not unreasonable that the first of these to be synthesized, the 2,4-dimethoxy-5-methyl isomer, was referred to by the name of another motor oil additive popular at that time, F-310. The Vilsmeier reaction between 2,4-dimethoxytoluene and the Vilsmeier complex of $POCl_3$ and N-methylformanilide gave the benzaldehyde (mp 117-118 °C) with a yellow malononitrile derivative from EtOH with a mp of 193-194 °C. The nitrostyrene from this and nitroethane formed yellow crystals from CH_3CN, with a mp 138-139 °C. The amine formed easily with LAH in ether, and the product F-310 (or 5-DOM) gave white crystals from CH_3CN with a mp of 182-183 °C.

And the other isomer, the 4,5-dimethoxy-2-methyl counterpart, became known familiarly as F-320, or sometimes simply 2-DOM. Its preparation followed an identical procedure, starting from 3,4-dimethoxytoluene. I have been told that F-310 is not active even at 20 milligrams in man, which would make it several times less potent than DOM (STP). I know of no trials with F-320. The use of the letter "F" does not imply any relationship between these two compounds and the series described elsewhere with the "F" code followed by other numbers, such as F-2 and F-22. These latter are F's because they are furans, not motor oil additives. And yet another oil additive, well known at the time as Z-7, became associated with the synthesis of the DOM (STP) isomer with its groups in the 2,4,6-positions. This is entered separately under ψ-DOM.

#69 Ψ-DOM; Z-7; 2,6-DIMETHOXY-4-METHYLAMPHETAMINE

SYNTHESIS: To a solution of 2,6-dimethoxy-4-methylbenzaldehyde (mp 92-93 °C from the lithiation of 3,5-dimethoxytoluene followed by reaction with N-methylformanilide) in 10 mL nitroethane, there was added 0.1 g anhydrous ammonium acetate and the mixture was heated on the steam bath for 16 h. Removal of the solvent under vacuum gave a slightly oily red-orange crystalline mass which was finely ground under 1 mL of MeOH. Filtration and a sparing wash with MeOH gave, after air drying, 0.8 g of a light yellow crystalline solid with a mp of 121-122.5 °C. Recrystallization from 4 mL boiling absolute EtOH gave 0.6 g of 1-(2,6-dimethoxy-4-methylphenyl)-2-nitropropene as very light yellow platelets, which melted at 123-124 °C.



To a solution of 0.25 g LAH in 25 mL refluxing THF, well stirred and under He, there was added a solution of 0.3 g 1-(2,6-dimethoxy-4-methylphenyl)-2-nitropropene in 5 mL dry THF. Upon the completion of the addition, the reaction mixture was held at reflux for 48 h. After cooling with an external ice bath there was added, in sequence, 0.5 mL H_2O, 0.5 mL 15% NaOH, and finally 1.5 mL H_2O. The inorganic solids were removed by filtration, and the filter cake washed with THF. The solvent from the combined filtrate and washings was removed under vacuum, and the residue (0.3 g) was a crystal clear colorless oil with a high refractive index. This was dissolved in 2 mL IPA, neutralized with concentrated HCl, and diluted with 35 mL of anhydrous Et_2O. After a minute's standing, the solution became turbid, followed by the slow deposition of very fine white crystals. After standing 1 h at room temperature, these were removed by filtration, Et_2O washed, and air dried to constant weight. There was thus obtained 0.3 g 2,6-dimethoxy-4-methylamphetamine hydrochloride (ψ-DOM) with a mp of 203 °C. sharp.

DOSAGE: 15 - 25 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 14 mg) "I am really quite spacey. I can go from a train of thought straight up into thin air. Then, to get to another one there must be a careful choice of words. Logic has nothing to do with any of it. There is no trace of the MDMA-like magic. This is an interpretive drug, not simply an ASC [*altered state of consciousness*] opening."

(with 18 mg) "There is a light-headedness, and a somewhat starry-eyed stoned state. Nothing visual, and no body concern except for what seems to be a very fine inner tremor. I think that with a little more, things might very well begin to move in the visual field. But I have no feeling of great concern about taking a somewhat higher dosage."

(with 25 mg) "I was at a +++ for about three hours, and it was a very weird place. There were some visuals, but they were not at all commensurate with the degree to which I was simply stoned. The erotic does not knit, and it's hard to get involved with music. It is as if you were going down some totally unknown street in a completely familiar city. You know the territory, but yet it is strangely all new. Eyes closed fantasy and shaped imagery was quite remarkable. But some heart arrhythmias and a pretty constant diarrhea made the experience less than totally ideal. My sleep was good and with good dreams."

EXTENSIONS AND COMMENTARY: I can't remember the exact names of the companies that went with the oil additives. STP was, I believe, it's own thing, and originally stood for Scientifically Treated Petroleum. And F-310 was, I believe, a Chevron Oil product. F-320 was, of course, the product of the wild and happy chemists at the Pharmaceutical Chemistry Department at the University of California in San Francisco, playing with what they fondly called "funny drugs." And when the 2,4,6-orientation became an obvious positional isomer, the Pennzoil Oil Company's additive, Z-7, was a natural to have its name volunteered to the cause. There was one additional isomer possible, with the methyl in the 2-position and the methoxyl groups at the 4- and 6-positions. This followed the more conventional aldehyde made from 3,5-dimethoxytoluene via the Vilsmeier process, with $POCl_3$ and N-methylformanilide. This material (2,4-dimethoxy-6-methylbenzaldehyde with mp 64-65 °C from cyclohexane or from MeOH) is completely distinct from the isomer used above (2,6-dimethoxy-4-methylbenzaldehyde with a mp of 92-93 °C from MeOH). The amphetamine from this isomer is 2,4-dimethoxy-6-methylamphetamine, and had been christened by the chemistry crowd as Z-7.1.

Much effort had been put forth in research by this medical school group of graduate students and graduate advisors, to try to explain the biological activity of the 2,4,5-things such as TMA-2 and DOM (STP). And a considerable investment had been made in the attempt to tie together the amphetamine world of psychedelics with the indole world of psychedelics. The convenience of having two methoxy groups para to one another was a clear invitation to speculate upon the formation of a benzoquinone intermediate of some kind, and this would require the loss of the methyl groups which were already known to be metabolically labile. This "quinone-like" intermediate was the cornerstone of a "hydroquinone hypothesis," as it allowed further condensation within the molecule itself involving the primary amine group, to form something called an indolene which, with some arcane electron pushing and removal, could eventually become an indole. There. We now have a tie-in to the tryptamine world, and to serotonin, and that entire neurotransmitter magic.

There was only one small fly in the ointment. No matter how the 2,4,5-things were explained, none of the proposed mechanisms could allow for the 2,4,6-things to also be active.

How can one accommodate such blasphemy? The first and obvious approach was the simplest. Denial. The 2,4,6-things aren't really active at all. Placebo stuff. There is a commonly used phrase, "bad science" which is an infamous term used to belittle findings that do not fit with one's theories or purposes. But that simply didn't wash, because I knew, as did a few others who chose not to identify themselves too publicly, that TMA-2 and TMA-6 were both fully active in the 40 to 50 milligram area. And although not as potent as DOM, the compound of this recipe, ψ-DOM or Z-7, was certainly an active one. So, since approach number one didn't work, try approach number two. Make the shoe fit the wearer, without respect to the size of his foot. One single size shoe fits all. One single mechanistic hypothesis explains all. It was obvious that for the "hydroquinone" hypothesis to survive, Z-7 would have to undergo some metabolic oxidation — phenol formation — in the 3-position.

And guess who was actually euchred into embarking onto the synthesis of this hypothetical metabolic Lucy [that's the anthropological-type, not the LSD-type Lucy]? Moi! On to a new methoxylated amphetamine which would be called Z-7.2. Oxidation of the above 2,4-dimethoxy-6-methylbenzaldehyde with meta-chloroperoxybenzoic acid gave 2,4-dimethoxy-6-methylphenol which smoothly methylated (KOH, CH_3I) to give 2,3,5-trimethoxytoluene as a white oil, bp 59-62 °C at 0.1 mm/Hg. This formed the anion between the meta-methoxy groups with butyllithium, and N-methylformanilide gave the new compound 2,3,6-trimethoxy-4-methylbenzaldehyde, also an oil (bp 130-140 °C at 0.7 mm/Hg) with an excellent NMR spectrum. This formed the 3-carbon nitrostyrene with nitroethane, as bright yellow crystals from methanol with a mp 67-68.5 °C (and excellent NMR and microanalysis, C,H,N). Lithium aluminum hydride reduction gave rise to what I was assuming would be the target amphetamine, 4-methyl-2,3,6-trimethoxy-amphetamine or Z-7.2. This formed a hydrochloride salt which, although analytically excellent, insisted in remaining as an ether and chloroform-soluble oil which had an excellent NMR spectrum. This was certainly MY target compound, but it was not THEIR target compound. The upper echelons who were running the show were serious about this hydroquinone thing. Therefore, this product Z-7.2, that should have been entered into human evaluation, was instead processed further by the substitution of a t-BOC on the amine group, oxidation to the quinone with ceric ammonium nitrate, reduction to the hydroquinone with dithionite, and finally deprotection of the blocking t-BOC group by hydrochloric acid. The final product, 2,5-dihydroxy-6-methoxy-4-methylamphetamine hydrochloride, was an extremely light-sensitive solid which was looked at by NMR (excellent spectrum in D_2O) and by cyclic voltimetry (destructive and uninformative) but which would have been totally worthless to have tasted.

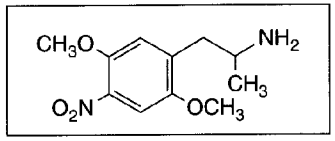
In fact, the whole 2,4,6 substitution concept is just now beginning to explode. Fully half of the drugs described in this Book II are of the classical 2,4,5-trisubstitution pattern, and it is becoming evident that every one of them will have a 2,4,6-trisubstituted counterpart that bids fair to be an active psychedelic. Diligence could thus easily double the number of known psychedelics. The nickname

"pseudo" is really the Greek letter "psi" which looks like a candelabrum standing on the table holding up three candles. If I can find the type in some font, I will simply precede each known drug with this letter, to indicate that the 2,4,5-ness has become a 2,4,6-ness. Therefore, Z-7 is also pseudo-DOM.

Z-7.2 might have been an interesting compound to taste. But the academic climate was not appropriate at that time (early 1977) for such honesty. The "hydroquinone hypothesis" is now not much more than a minor bit of history. And anyhow, it was just about this time that I had uncovered a slick way of getting a sulfur atom into the amphetamine molecule. I quickly lost interest in the pursuit of other people's hypotheses that didn't seem to lead anywhere. Maybe, someday, some single earth-shaking mechanism will emerge to explain everything. But in the meantime, the best contribution I can make to this "grand unified theory of psychedelic activity" is to continue to make new and unexpected things which, if they are active, will effectively destroy any hypothesis that just happens to be popular at the moment. It is a lot more exciting, too.

#70 DON; 2,5-DIMETHOXY-4-NITROAMPHETAMINE

SYNTHESIS: A solution of 8.4 g 2,5-dimethoxyamphetamine base in 40 mL acetic acid was added dropwise over the course of 0.5 h to 43 mL of 50% nitric acid which was well stirred and cooled with an external ice bath. The resulting solution was quenched with ice water, made basic with aqueous NaOH, and extracted with a benzene-ether mixture. The residue that remained after the removal of the solvent was dissolved in dilute HCl which, upon evaporation of the H_2O, yielded a nearly colorless residue. Recrystallization from an ethanol/ether mixture gave, after drying, 10.5 g of 2,5-dimethoxy-4-nitroamphetamine hydrochloride (DON) with a mp of 206-207 °C. The acetamide derivative melted at 166-168 °C. The formamide derivative was easily hydrolyzed with 3N HCl. And the R-isomer of DON hydrochloride had a mp of 231-232 °C.



DOSAGE: 3.0 - 4.5 mg.

DURATION: 8 - 15 h.

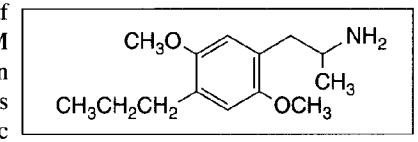
QUALITATIVE COMMENTS: (with 3.0 mg) "There was an amphetamine-like stimulation that was apparent an hour into it, and considerable anxiety. I had stomach cramps, but there were indications that there might be something hallucinogenic at a higher dose."

(with 4.5 mg) "An enhancement of color perception, and some auditory distortion, that was still noticeable some eight hours into the experience. The visual changes were intense. I felt I was running a slight fever, and was restless, but there was almost no physical malaise. I was still somewhat wound up even at the 14th hour."

EXTENSIONS AND COMMENTARY: These qualitative comments are not true quotations, but have been reconstructed from the published summaries of the human trials reported by several South American researchers. I have personally never tasted DON and have only these fragments from which to create a portrait of activity. A brief quotation, from a note published by these researchers in a bulletin that is restricted to forensic scientists serving law enforcement agencies, is certainly subject to a number of interpretations. It reads as follows: "This action [a strong stimulant action reminiscent of amphetamine] seems to reduce the incidence of insightful, and therefore potentially unpleasant experiences, and thus [DON seems likely] to appear on the market as an illicit recreational drug." I must admit that I have tried, and I am still not able, to interpret this quotation.

#71 DOPR; 2,5-DIMETHOXY-4-(n)-PROPYLAMPHETAMINE

SYNTHESIS: A suspension of 285 g mossy zinc in 285 mL H_2O containing 5.7 g mercuric chloride was treated with 285 mL concentrated HCl and shaken as needed to effect amalgamation. The H_2O was then drained off, the zinc washed with fresh water and drained again. There was added a solution of 74 g 2,5-dimethoxypropiophenone (from the reaction of propionic acid and p-dimethoxybenzene in the presence of polyphosphoric acid, see under DOAM for an effective general procedure) in 140 g EtOH. The reaction mixture was held at reflux for 24 h with the periodic addition of concentrated HCl. It was then cooled, diluted with H_2O and CH_2Cl_2, and the organic phase separated. The aqueous phase was extracted with 2x100 mL additional CH_2Cl_2. The combined organic phases were washed with 5% NaOH until the washes remained basic, once with H_2O, and then the solvent was removed under vacuum. The residue was distilled at the water pump, giving an early fraction quite rich in starting p-dimethoxybenzene, and a second fraction (61 g, bp 140-160 °C) which was free of carbonyl group by infra-red, and which was largely 2,5-dimethoxypropylbenzene. It was used without further purification in the following aldehyde synthetic step.



A mixture of 124 g N-methylformanilide and 140 g $POCl_3$ was allowed to stand until there was the development of a strong red color. There was then added 60 g of the above 2,5-dimethoxypropylbenzene and the mixture was held on the

steam bath for 2 h. The mixture was added to 2 L H_2O and stirred until the excess acid chloride had completely decomposed. The mixture was extracted with 3x100 mL CH_2Cl_2 and, after the removal of the solvent from the combined extracts, the residue was extracted with 3x100 mL boiling hexane. Removal of the solvent gave the product 2,5-dimethoxy-4-propylbenzaldehyde as an oil, 23 g, which was characterized as its malononitrile derivative. Equal weights of the product and malononitrile in EtOH with a catalytic amount of triethylamine gave yellow crystals which, on recrystallization from toluene, had a mp of 113-114 °C.

A solution of 21.5 g of the above crude 2,5-dimethoxy-4-propylbenzaldehyde in 75 g acetic acid, was treated with 10.4 g nitroethane and 6.6 g anhydrous ammonium acetate. This was heated on the steam bath for 1.75 h, then cooled and diluted with H_2O to the point of turbidity. With long standing and scratching, there finally was the deposition of crystals which were removed by filtration and sucked as dry as possible. This 23 g of crude product cake was triturated under MeOH, filtered again, and air dried to give 11 g of dull orange crystals. Recrystallization from boiling MeOH gave 1-(2,5-dimethoxy-4-(n)-propylphenyl)-2-nitropropene as fine orange crystals which weighed, after filtering, washing, and drying, 7.4 g, and which had a mp of 94-96 °C.

To a suspension of 6.0 g LAH in 500 mL anhydrous Et_2O, which was being stirred and also held at a gentle reflux, there was added a saturated solution of the above (2,5-dimethoxy-4-(n)-propylphenyl)-2-nitropropene in warm THF. The reaction mixture was held at reflux for 24 h, then cooled to room temperature. The excess hydride was destroyed by the cautious addition of 500 mL dilute H_2SO_4. The phases were separated, and the aqueous phase washed with additional Et_2O. There was then added 150 g potassium sodium tartrate, and the pH was brought to >9 with aqueous NaOH. The product was extracted with Et_2O and, after removal of the solvent, the residue was dissolved in 200 mL anhydrous Et_2O and saturated with anhydrous HCl gas. The solids that formed were removed by filtration, giving 6.15 g 2,5-dimethoxy-4-(n)-propylamphetamine hydrochloride (DOPR) as an electrostatic, white crystalline powder, with a mp of 182.5-183 °C. This was not improved by recrystallization from either IPA or CH_3CN.

DOSAGE: 2.5 - 5.0 mg.

DURATION: 20 - 30 h.

QUALITATIVE COMMENTS: (with 2.0 mg) "The onset is slower than any other thing I can think of. There was nothing at all at the end of an hour, and only a threshold a half hour later. By the middle of the third hour, I was up to 1+, and that seemed to be about as high as it intended to take me. Attempts to sleep at the ninth hour were not successful, as there were strange patterns of not-quite logical thinking going on. Stuff like: 'The block events (like a baby's rectangular building blocks) that were gotten, along with other things, from the full octaves of the left hand in Listz's Hungarian Rhapsody, events that allowed an easy recognition of the odds of achieving successful re-entry from any of several erotic codes.' Clearly this was not a baseline state. After six hours of successful sleep, I was still off-baseline , and on into the following day. Go on up with curiosity but with caution."

(with 3.6 mg) "Imagery that was constructed in response to the music turned out to be necessary to organize and contain it. The trio is the nucleus that transforms the written to the heard, but it has created its own bubble without connections to the real world, and must play on and on and on to keep itself afloat and never touching the stage again."

(with 5.0 mg) "I am now at midnight, and still strongly +++. This is certainly maximum dosage, at least for a long time. There are faint intimations of nervous system scrungies. You know, the kind of thing that makes you figure it's going to be a while before you'll try to relax into sleep. This material, like all the other DO's, is a heavy duty psychedelic, the kind that says to you, 'Forget all that stuff about screening out visuals,' and then proceeds to prove it. Sort of indole-like in that way. Your body as well as your mind tells you you're into it, baby, and better relax and enjoy the trip, because you've left the shore way behind. When it was time for bed, I got to sleep with surprising ease, and slept for only about six hours. My dreams were excellent, balancing, and good humored. But the next day I realized I was still carrying the DOPR in me, and that baseline was definitely not there. But it was OK. No problems except for sleepiness. The next evening I went to bed at unheard-of hour of 9 PM and slept for 13 hours, give or take. Fascinating compound, but I won't go out of my way to take it again soon."

EXTENSIONS AND COMMENTARY: There is a thread of disconnection and of inconsistent reference that pervades most of the reports that I have received concerning the use of DOPR. The word that comes to mind is hypnogogic. There is a drifting into that place that lies between a not-quite-awake and a not-quite-asleep state seems to characterize this compound. There is no question but that it is very potent, and that it is very long-lived. But there is a nagging suggestion of the out-of-body, out-of-center character that is the hallmark of the anesthetic and delusional drugs such as scopolamine or ketamine. With them, the psychedelic effects become clouded with touches of amnesia. If DOPR shows this with it's three carbon alkyl group, thereis every reason to pay close attention as the chain becomes longer.

There had been quite a bit of speculation in the literature that the metabolic attack on DOM was at the 4-position, and this was an oxidation process. In a moment of inspiration, I decided to explore a similar oxidation step in DOPR, since it is probably the most potent of the DO-series. Why not make the compound which would be the first step in this oxidation, the 1-hydroxypropyl analogue? This I did, by using the phthalimide derivative of 2,5-dimethoxyamphetamine (described in the synthesis of DOI) and making the propiophenone using propionic acid as both reagent and solvent, and polyphosphoric acid as the condensing agent. The ketone product (a white crystalline solid from methanol) was dissolved in warm methanol

and reduced to the alcohol with sodium borohydride. This product, also a white crystalline solid, was stripped of the phthalimide blocking group with overnight refluxing with hydrazine in ethanol. The product, 2,5-dimethoxy-4-(1-hydroxy-propyl)-amphetamine (hydroxy-DOPR) had a mp of 148-150 °C from IPA. Its activity is not yet known, but there were no effects at all at trials, orally, of up to 200 micrograms.

But this is all with the normal-propyl compound. There is a rich collection of misinformation and potential discovery that is associated with the isopropyl isomer. This structural isomer, 2,5-dimethoxyl-4-(i)-propylamphetamine is properly called DOIP for des-oxy-iso-propyl. It has been synthesized and explored in animals and, to a modest extent, in man. The synthesis has proceeded from 2,5-dimethoxyacetophenone by the addition of a methyl group to the carbonyl followed by reduction to the hydrocarbon. Aldehyde formation, nitropropene synthesis with nitroethane, and lithium aluminum hydride reduction are uneventful, providing the hydrochloride salt DOIP, which has a mp of 183-184 °C as an analytical sample. Animal tests (such as rabbit hyperthermia assays), have indicated that the isopropyl compound DOIP is less potent than the propyl prototype, DOPR, by between one and two orders of magnitude. In man, a dose of four milligrams, a rousing dose of DOPR, is without any effects. At 10 milligrams, there is some disturbance but substantially no effects. I have been told that with doses in the 20 to 30 milligram range there are valid changes in mental state, but I have not been told the nature of these changes.

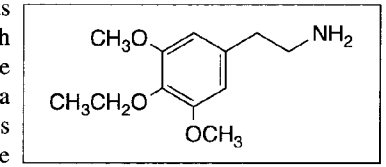
A fascinating red herring had been drawn across all of these exacting lines by a strange visitor to this research project. An olive-faced M.D., Ph.D., passed through this confusing scene briefly, and when he left, a small supply of DOPR left with him. He promptly published in an obscure journal some animal behavioral responses which he ascribed to the isopropyl analogue, DOIP. But what he had studied could only have been DOPR since DOIP, at that time, had not yet been synthesized either by me, or by either of the other two active synthesists of that moment. It was not yet a known material. We all made it some time later, but by that time our olive-face had disappeared. There is a magnificent French phrase that applies here as nowhere else; *Il a foutu le camp*. Its idiomatic meaning is equivalent to our, "He took off," or "He split the scene," but the literal translation is, "He fucked the camp."

#72 E; ESCALINE; 3,5-DIMETHOXY-4-ETHOXYPHENETHYLAMINE

SYNTHESIS: To a solution of 72.3 g 2,6-dimethoxyphenol in 400 mL MeOH, there was added 53.3 g of a 40% solution of aqueous dimethylamine folowed by 40 g of a 40% aqueous solution of formaldehyde. The dark solution was heated under reflux for 1.5 h on a steambath. The volatiles were then removed under vacuum

yielding a dark oily residue of 2,6-dimethoxy-4-dimethylaminomethylphenol. This residue was dissolved in 400 mL of IPA, to which there was added 50 mL of methyl iodide. The spontaneously exothermic reaction deposited crystals within 3 min, and was allowed to return to room temperature and occasionally stirred over the course of 4 h. The solids were removed by filtration, washed with cold IPA, and allowed to air dry yielding 160 g of the methiodide of 2,6-dimethoxy-4-dimethylamino-methylphenol as a cream-colored crystalline solid.

A suspension of 155 g of the above methiodide of 2,6-dimethoxy-4-dimethylaminophenol in 600 mL H_2O was treated with a solution of 130 g KCN in 300 mL H_2O. The reaction mixture was heated on a steam bath for 6 h during which time there was a complete dissolving, the development of a brownish color with a bright blue film on the surface and the walls of the flask, and the gentle evolution of fine gas bubbles. The hot reaction mixture was poured into 1.2 L H_2O and acidified with concentrated HCl (careful, HCN evolution). The aqueous solution was extracted with 3x150 mL CH_2Cl_2, the extracts pooled, washed with saturated $NaHCO_3$ which removed much of the color. The solvent was removed under vacuum yielding about 70 g of a viscous black oil. This was distilled at 0.4 mm/Hg at 150-160 °C to provide 52.4 g of homosyringonitrile (3,5-dimethoxy-4-hydroxyphenylacetonitrile) as a white oil that spontaneously crystallized to lustrous white crystals that melted at 57-58 °C.



A solution of 5.75 g of homosyringonitrile and 12.1 g ethyl iodide in 50 mL dry acetone was treated with 6.9 g finely powdered anhydrous K_2CO_3 and held at reflux for 18 h. The mixture was diluted with 100 mL Et_2O, filtered, and the filtrate solvent removed under vacuum The residue was recrystallized from Et_2O/hexane to yield 5.7 g 3,5-dimethoxy-4-ethoxyphenylacetonitrile with a mp 57-58 °C. Anal. ($C_{12}H_{15}NO_3$) C,H,N.

A solution of 2.21 g 3,5-dimethoxy-4-ethoxyphenylacetonitrile in 25 mL EtOH containing 2.5 mL concentrated HCl and 400 mg 10% palladium on charcoal, was shaken in a 50 lb/sq.in. atmosphere of hydrogen for 24 h. Celite was added to the reaction suspension and, following filtration, the solvents were removed under vacuum. The residue was recrystallized from IPA/Et_2O to yield 2.14 g 3,5-dimethoxy-4-ethoxyphenethylamine hydrochloride (E) with a mp of 166-167 °C.

Synthesis from syringaldehyde: A well-stirred suspension of 21.9 g syringaldehyde in 45 mL H_2O was heated to reflux in a heating mantle. There was then added a solution of 15 g NaOH in 60 mL H_2O. The heating and stirring was continued until the generated solids redissolved. Over a period of 10 min, there was added 23 g diethyl sulfate, then refluxing was continued for 1 h. Four additional portions each of 5 g diethyl sulfate and of 6 mL 20% NaOH were alternately added to the boiling solution over the course of 2 h. The cooled reaction mixture was extracted with Et_2O, the extracts pooled and dried over anhydrous $MgSO_4$, de-

colorized with Norite, and stripped of solvent. The crude 3,5-dimethoxy-4-ethoxybenzaldehyde weighed 21.8 g and melted at 51-52 °C.

A solution of 14.7 g 3,5-dimethoxy-4-ethoxybenzaldehyde and 7.2 mL nitromethane in 50 mL glacial acetic acid was treated with 4.4 g anhydrous ammonium acetate and held at reflux for 30 min. Cooling the reaction allowed the formation of yellow crystals which were removed by filtration and washed sparingly with cold acetic acid. The dried 3,5-dimethoxy-4-ethoxy-ß-nitrostyrene weighed 11.5 g and melted at 108-109 °C after recrystallization from EtOH Anal. ($C_{12}H_{15}NO_5$) C,H. Alternately, this product may be prepared from 3.9 g. 3,5-dimethoxy-4-ethoxybenzaldehyde in 60 mL nitromethane containing 0.7 g ammonium acetate and heated on a steam bath for 1 h. The solvent was removed under vacuum, and the residue dissolved in a minimum of hot MeOH. Cooling provided, after filtration and air drying, 2.3 g of bright yellow crystals of 3,5-dimethoxy-4-ethoxy-ß-nitrostyrene, with a mp of 105-107 °C.

A solution of 2.25 g LAH in 45 mL anhydrous THF was vigorously stirred and cooled to 0 °C under He. There was added 1.5 mL 100% H_2SO_4 dropwise, followed by 2.3 g 3,5-dimethoxy-4-ethoxy-ß-nitrostyrene in anhydrous THF. After the addition was complete, the mixture was allowed to stir for 30 min, and then brought to room temperature. The unreacted hydride was decomposed with 2.3 mL H_2O in THF, followed by the addition of 9.2 mL of 15% NaOH. The white suspension was filtered, the filter cake was washed with THF, the filtrate and washings combined, and the solvent removed under vacuum. The residue was dissolved in 300 mL dilute H_2SO_4, washed with 2x75 mL CH_2Cl_2, made basic with 25% NaOH, and the product extracted with 3x75 mL CH_2Cl_2. After removal of the solvent, the residue was distilled at 110-120 °C at 0.3 mm/Hg yielding 1.4 g of a colorless oil. A solution of this oil in 20 mL IPA was neutralized with 17 drops of concentrated HCl and diluted with 100 mL anhydrous Et_2O. After a few minutes there was the spontaneous formation of white crystals of 3,5-dimethoxy-4-ethoxyphenethylamine hydrochloride (E) which was recrystallized from 40 mL boiling EtOAc containing 1 mL MeOH. The mp was 165-166 °C.

DOSAGE: 40 - 60 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 40 mg) "This is a powerful and complex intoxicant — I could not have coordinated any rational muscular activity. I could not walk; I could not tie my shoe-laces. There is analgesia and an incoordination that I cannot shake. My menstrual flow started a bit ahead of time, but it was light."

(with 50 mg) "I felt that the body tensions outweighed the psychological and sensory rewards, in that I had a lot of dehydration and my sleep had a nightmare quality. This pretty much offset the few virtues that I felt I had obtained."

(with 60 mg) "There is a quality of rational analysis and insight that is totally impressive. Many subtle factors in my life can be viewed with insight, and usefully dissected. I got into a deep discussion, but I was not argumentative or even defensive and I remained detached and kept a tone of cool impersonality. I had a good appetite. But I also had some tachycardia and muscular tension. There was unquestionable sensory enhancement, but without an intellectual component. Overall it was most pleasant."

EXTENSIONS AND COMMENTARY: In an isolated situation, there is easy fantasy, but little synthesis of external sensory inputs such as music or visual stimulae. A gradual decline brings the subject back to a restful baseline somewhere before the 12th hour. The following day is often seen as one of tiredness and low energy. An anonymous flyer appeared in the California drug community in 1984 stating an effective range to be 50 to 100 milligrams, but it described the drug as the sulfate. The above data all pertain to the hydrochloride salt.

The replacement of that one methyl group with an ethyl group leads to a nice *jeu de mots.* The play on words depends on a remarkable coincidence. The name of the alkaloid mescaline stems from an ancient Nahuatl word for a drink (Mexcalli) which also provided the source of the term Mescal (an Agave of entirely different pharmacology). The prefix for the simplest, the one carbon organic radical, is methyl. This is from the Greek word "methy" and represents wine from wood. Such is, indeed, methyl alcohol, or methanol, or wood alcohol, the simplest one-carbon drink and a rather dangerous one for the human animal. And this is the group that is on the central oxygen of mescaline.

It is customary to refer to homologs (bigger-by-one) of methanol by their classical chemical names, so the natural extension of methyl is ethyl, and that of mescaline would be escaline. One carbon-chain on the 4-position oxygen becoming a two-carbon chain. This is all entymologically appealing, but there is no botanical support for any of it. The ethyl group is much more rare in nature. It is just a happy coincidence that mescaline (the plant), and methyl (the alkyl group involved), and methoxy (the group on the 4-position of the aromatic ring) all happen to start with the letter "M".

Very few of the homomescaline phenethylamines have been synthesized as their three-carbon chain counterparts, the corresponding analogues of amphetamine. And only three of them have been explored in man (four, if you count the amphetamine analogue of mescaline itself, TMA). The obvious names for these compounds have, unfortunately, already been used. It would be logical to use the letter M for a methoxy, and the letter E for ethoxy, etc. and simply read the groups from around the ring. But this is the naming system for the 2,4,5-trisubstituted amphetamines. MEM is, for example, 2,5-dimethoxy-4-ethoxyamphetamine (in sequence, methoxy, ethoxy, methoxy reading around the ring, and a fascinating compound talked about at length in this book), so this term cannot represent 3,5-dimethoxy-4-ethoxyamphetamine.

A truly simple code employs the length of the carbon chain. The

phenethylamine chain is two carbons long, and the amphetamine chain is three carbons long.

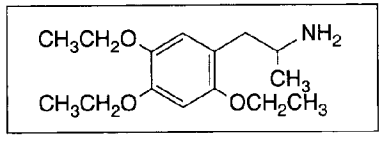
If a drug has been initially developed (and initially named) as an amphetamine derivative (three carbon chain) then the two-carbon chain analogue will use the original name (or a symbolic part of it) with the term 2C ahead of it. The two-carbon analogue of DOB (a three-carbon chain compound) will become 2C-B. DOI becomes 2C-I, DON becomes 2C-N, and DOET becomes 2C-E. Each of these is a substituted amphetamine derivative lacking one carbon atom, thus becoming a phenethylamine derivative. Most of these have 2,4,5-substitution patterns.

And if a drug has been initially developed (and initially named) as a phenethylamine derivative (two carbon chain) then the three-carbon chain analogue will use the original name with the term 3C ahead of it. The three carbon analogue of E (escaline, a two-carbon chain compound) will become 3C-E. P becomes 3C-P and CPM becomes 3C-CPM. Most of these have 3,4,5-substitution patterns.

Thus, "2-C" implies that a known amphetamine drug has been shortened to a phenethylamine, and "3-C" inplies that a known phenethylamine has been lengthened to an amphetamine. A great number of the former have been made and have proven to be most rewarding. Only a few of the latter are known, but most of them will eventually prove to be potent psychedelics.

#73 EEE; 2,4,5-TRIETHOXYAMPHETAMINE

SYNTHESIS: A solution of 13.3 g 3,4-diethoxyphenol (see the recipe for MEE for its preparation) in 20 mL MeOH, and a solution of 4.8 g KOH in 100 mL hot MeOH were combined. There was added 8.2 g ethyl bromide and the mixture was held at reflux on the steam bath for 2 h. The reaction was quenched by the addition of three volumes H_2O, made strongly basic by the addition of 10% NaOH, and extracted with 3x150 mL CH_2Cl_2. The solvent was removed from the pooled extracts under vacuum giving a residue of 9.1 g 1,2,4-triethoxybenzene that solidified to a crystalline mass. The mp was 28.5-29.5 °C, but the infra-red analysis showed the presence of unreacted phenol. The CH_2Cl_2 solution was again washed thoroughly with 10% NaOH and, after removal of the solvent, the solidified residue weighed 6.0 g and appeared free of impurities. The mp of this sample was 33-34 °C.



To a mixture of 10.5 g N-methyl formanilide and 11.9 g $POCl_3$ that had incubated at room temperature for 0.5 h (it had become quite red in color) there was added 6.4 g of the solid ether, 1,2,4-triethoxybenzene. The mixture was heated on the steam bath for 2.5 h, then poured into 500 mL of shaved ice. After a few minutes stirring, crystals appeared. The reaction was allowed to stand for a few h, then

filtered and sucked as dry as possible. The damp 14.4 g of slate-green crude solids were dissolved in 30 mL boiling MeOH, and allowed to cool to room temperature overnight. Filtration of the cream-colored product, and air drying, gave 6.1 g of 2,4,5-triethoxybenzaldehyde with a mp of 94-95 °C. A solution containing 0.5 g of this aldehyde and 0.4 g malononitrile in 7 mL absolute EtOH was treated with three drops of triethylamine. There was an immediate formation of granular yellow crystals of 2,4,5-triethoxybenzalmalononitrile which, on filtering and air drying, weighed 0.4 g and had a mp of 169-170 °C.

A solution of 5.0 g 2,4,5-triethoxybenzaldehyde and 2.6 g nitroethane in 14.8 g glacial acetic acid was treated with 1.6 g anhydrous ammonium acetate and heated on the steam bath for 2 h. The addition of an equal volume of H_2O gave a slightly turbid solution which, upon the administration of a small amount of externally developed seed, smoothly set up as orange crystals as the reaction mix returned to room temperature. The product was removed by filtration, washed with a little 50% acetic acid, and allowed to air dry to constant weight. There was thus obtained 2.5 g of fluffy yellow-orange (almost yellow) crystals of 2-nitro-1-(2,4,5-triethoxyphenyl)propene with a mp of 91-92.5 °C. Anal. ($C_{15}H_{21}NO_5$) C,H.

To a gently refluxing suspension of 1.7 g LAH in 200 mL anhydrous Et_2O under a He atmosphere, there was added 2.5 g 2-nitro-1-(2,4,5-triethoxyphenyl)-propene by allowing the condensing Et_2O to drip into a shunted Soxhlet thimble containing the nitrostyrene, thus effectively adding a warm saturated solution of the nitrostyrene dropwise. Refluxing was maintained for 5 h, and then the reaction mixture was cooled with an external ice bath. The excess hydride was destroyed by the cautious addition of 300 mL 1.5 N H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated, and 50 g of potassium sodium tartrate were dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was above 9, and this was extracted with 3x200 mL CH_2Cl_2. Removal of the solvent under vacuum produced an amber oil that was dissolved in anhydrous Et_2O and saturated with anhydrous HCl gas. After a few min delay, there com-menced the separation of fine white crystals of 2,4,5-triethoxyamphetamine hydro-chloride, (EEE). These weighed, after filtration, Et_2O washing, and air drying to constant weight, 1.75 g and had a mp of 167-168 °C, with prior softening at 162 °C. Anal. ($C_{15}H_{26}ClNO_3$) C,H,N.

DOSAGE: unknown.

DURATION: unknown.

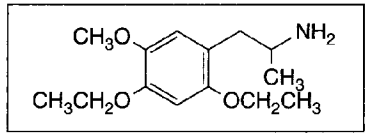
EXTENSIONS AND COMMENTARY: This amphetamine, the final item on the ethoxy homologue of TMA-2 project, has never been tried in man. I do not know how it tastes, but I suspect that it is probably bitter. An interesting sidelight concerning this project, and one which can serve as a measure of the enthusiasm that went into it, is that (except for the 2-ethoxy homologue EMM) all of the possible

ethoxy homologues of TMA-2, including MEM, MME, EEM, EME, MEE and EEE, their precursor nitrostyrenes, the precursor aldehydes (and their malononitrile derivatives), the precursor ethers, and the precursor phenols, for a total of 33 compounds, were all synthesized, purified, and characterized within a period of just over three weeks. Actually it was 23 days, and that was a magically exciting time.

And there were two true treasures that came out of it all. The compound MEM, and the knowledge that the 4-position was where the action is.

#74 EEM; 2,4-DIETHOXY-5-METHOXYAMPHETAMINE

SYNTHESIS: To a solution of 12.3 g 3-ethoxy-4-methoxyphenol (see recipe for MEM for the preparation of this phenol) in 20 mL MeOH, there was added a warm solution of 4.8 g KOH in 100 mL MeOH. There was then added 8.2 g ethyl bromide, and the mixture held at reflux on the steam bath. Within 0.5 h, severe bumping ensued. An additional 3 g ethyl bromide were added, refluxing continued for another 0.5 h, then the reaction mixture was allowed to come to room temperature and to stand overnight. It was poured into 3 volumes H_2O which produced crystals spontaneously. There was added additional base, and the mixture was extracted with 3x150 mL CH_2Cl_2. Removal of the solvent from the pooled extracts under vacuum gave 6.4 g of 2,4-diethoxyanisole as tan crystals with a mp of 48-48.5 °C.



A mixture of 10.9 g N-methylformanilide and 12.3 g $POCl_3$ was allowed to stand at room temperature for 0.5 h producing a deep red claret color. There was then added 6.2 g 2,4-diethoxyanisole and the mixture was heated on the steam bath for 2 h. All was poured into 200 g chipped ice, and stirred mechanically. The dark viscous gummy oil gradually became increasingly granular and finally appeared as jade-green solids. These were removed by filtration and washed with H_2O, giving a wet cake weighing 18 g and having a mp (from a porous plate) of 95.5-96.5 °C. The entire crop was recrystallized from 75 mL boiling MeOH which gave, after filtering, washing lightly with cold MeOH, and air drying, 5.4 g of 2,4-diethoxy-5-methoxybenzaldehyde with a mp of 98-99 °C. A solution of 0.2 g of this aldehyde, and 0.3 g malononitrile in 2.0 mL warm EtOH was treated with a drop of triethylamine. There was an immediate generation of crystals which were removed by filtration, EtOH-washed, and dried to constant weight. The bright yellow needles of 2,4-diethoxy-5-methoxybenzalmalononitrile weighed 0.15 g and had a mp of 172-172.5 °C.

A solution of 5.0 g 2,4-diethoxy-5-methoxybenzaldehyde in 16 g glacial acetic acid was treated with 2.7 g nitroethane followed by 1.7 g anhydrous ammonium acetate. The mixture was heated for 2.5 h on the steam bath, then

removed and diluted with a equal volume of H_2O. With cooling there was the generation of a heavy crop of orange crystals which was removed, washed with 50% acetic acid, and sucked as dry as possible. The product had a mp of 97-104 °C, and there was spectrographic evidence of some unreacted starting aldehyde. A small sample was recrystallized from boiling MeOH, with considerable loss, to give an analytical sample of 1-(2,4-diethoxy-5-methoxyphenyl)-2-nitropropene as orange-yellow crystals with a mp of 112-113 °C. Anal. ($C_{14}H_{19}NO_5$) C,H. The unpurified first crop was employed in the following synthesis of the corresponding amphetamine.

To a gently refluxing suspension of 2.9 g LAH in 400 mL anhydrous Et_2O under a He atmosphere, there was added 4.0 g of impure 1-(2,4-diethoxy-5-methoxyphenyl)-2-nitropropene by allowing the condensing ether to drip into a shunted Soxhlet thimble apparatus containing the nitrostyrene. This effectively added a warm saturated solution of the nitrostyrene dropwise over the course of 1 h. Refluxing was maintained for 5 h and the reaction mixture was cooled with an external ice bath with the stirring continued. The excess hydride was destroyed by the cautious addition of 400 mL of 1.5 N H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated, and 100 g of potassium sodium tartrate was dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was above 9, and this was then extracted with 3x150 mL CH_2Cl_2. Removal of the solvent under vacuum produced 2.7 g of a pale amber oil that was dissolved in 300 mL anhydrous Et_2O and saturated with anhydrous HCl gas. After a few minutes delay, there commenced the separation of fine white crystals of 2,4-diethoxy-5-methoxyamphetamine hydrochloride (EEM). After the crystallization was complete, these were removed by filtration, washed with Et_2O and air dried, providing 2.55 g of a fine white crystalline solid with mp 158-159 °C. Anal. ($C_{14}H_{24}ClNO_3$) C,H,N.

DOSAGE: unknown.

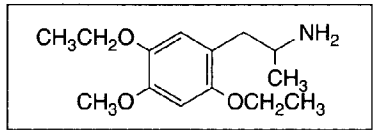
DURATION: unknown.

EXTENSIONS AND COMMENTARY: This particular identity and arrangement of the alkoxy groups on the amphetamine molecule, EEM, is a totally unexplored molecule. It is reasonable to assume that it would be way down in potency, but there is no way of guessing what the nature of its activity might be at the dosage that would be active.

#75 EME; 2,5-DIETHOXY-4-METHOXYAMPHETAMINE

SYNTHESIS: To a solution of 14.0 g 4-ethoxy-3-methoxyphenol (see the recipe for MME for the preparation of this starting material) in an equal volume of EtOH, there was added a solution of 5.3 g KOH in 100 mL hot MeOH. This was followed with 9.1 g ethyl bromide, and the mixture was held at reflux for 2 h. The first deposition of KBr was apparent in 5 min, and there was rather severe bumping by the end of the reaction. The mixture was diluted with 3 volumes H_2O and 1 volume 5% NaOH, and extracted with 2x200 mL Et_2O. The extracts were pooled, and the solvent removed under vacuum, yielding 14.3 g of a pale amber oil that set to crystals of 2,5-diethoxyanisole with a mp of 44-45 °C. The compound had been reported in the literature from the action of diethyl sulfate on methoxyhydroquinone.

To a mixture of 24.1 g N-methylformanilide and 27.3 g $POCl_3$ that had been allowed to stand at room temperature until strongly red-colored (about 0.5 h) there was added 13.8 g solid 2,5-diethoxyanisole and the mixture was heated on the steam bath for 2 h. The black, thick reaction product was poured over chipped ice and, with continuous stirring, the color lightened and there was the formation of a yellowish powder. After a few h standing, this was removed by filtration and sucked as dry as possible. The 32 g of damp product showed the presence of isomeric contaminatiion by GC, and the aqueous mother liquor, upon extraction with CH_2Cl_2 and concentration, showed yet more aldehyde-like impurities. The isolated solids were recrystallized from 125 mL boiling MeOH giving 15.8 g yellowish crystals (wet weight) that still showed detectable impurities by GC. A second recrystallization from 100 mL boiling MeOH gave off-white fluffy crystals of 2,5-diethoxy-4-methoxybenzaldehyde which weighed, after air drying, 8.5 g. The mp was 109-110 °C. The combined mother liquors from the two MeOH crystallizations were stripped of solvent, and the resulting solid mass c 'lized again from MeOH to give a second crop of aldehyde, 5.7 g, with a . 110-111 °C. A solution of 1.0 g of this aldehyde and 0.7 g malononitrile in 40 mL warm absolute EtOH was treated with a few drops of triethylamine. In a minute or so, there was the formation of crystals. These were removed by filtration, washed with EtOH, and air dried, giving 0.6 g of 2,5-diethoxy-4-methoxybenzalmalononitrile as brilliant yellow crystals with a mp of 156.5-158 °C.



A solution of 6.7 g 2,5-diethoxy-4-methoxybenzaldehyde in 21 g glacial acetic acid was treated with 3.1 g nitroethane and 1.93 g anhydrous ammonium acetate, and heated on the steam bath for 2.5 h. The addition of a small amount of H_2O to the hot reaction mixture instituted crystallization of an orange product which, after the mixture had come to room temperature and stood for several h, was removed by filtration, H_2O washed, and air dried. The product, 1-(2,5-diethoxy-4-methoxyphenyl)-2-nitropropene, was dull orange in color, weighed 3.0 g and had a mp of 84-86 °C. An analytical sample from toluene had a mp of 85-86 °C. Anal. ($C_{14}H_{19}NO_5$) C,H.

To a gently refluxing suspension of 2.0 g LAH in 250 mL anhydrous Et_2O under a He atmosphere, there was added 2.8 g 1-(2,5-diethoxy-4-methoxyphenyl)-2-nitropropene by allowing the condensing Et_2O to drip into a shunted Soxhlet thimble containing the nitrostyrene. This effectively added a warm saturated solution of the nitrostyrene dropwise. The addition took 1 h and the refluxing was continued for an additional 6 h. The reaction mixture was brought down to ice-bath temperature, and the excess hydride was destroyed by the cautious addition of 150 mL 1.5 N H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated and 50 g of potassium sodium tartrate were dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was >9, and this was then extracted with 3x150 mL CH_2Cl_2. Removal of the solvent under vacuum produced 2.3 g of a clear white oil that was dissolved in 300 mL anhydrous Et_2O and saturated with anhydrous HCl gas. At first the solution remained completely clear, and finally there was the start of the formation of fine white crystals. When the crystallization was complete, these solids were removed by filtration, Et_2O washed, and air dried. There was thus obtained 2.2 g of 2,5-diethoxy-4-methoxyamphetamine hydrochloride (EME) with a mp of 162-164 °C with prior softening at 154 °C. Anal. ($C_{14}H_{24}ClNO_3$) C,H,N.

DOSAGE: unknown.

DURATION: unknown.

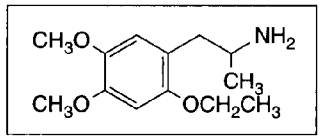
EXTENSIONS AND COMMENTARY: This is another of the collection of all possible ethoxy homologues of TMA-2. The latter and heavier members of this series were synthesized and completed before the directions of biological activity had become evident from the earlier ones. This compound has never been assayed, and it is a reasonable guess that it will have a very low potency, with hints of toxicity at higher dose levels. I suspect that it will never be assayed, certainly not by me.

#76 EMM; 4,5-DIMETHOXY-2-ETHOXYAMPHETAMINE

SYNTHESIS: A solution of 166 g 3,4-dimethoxybenzaldehyde in 600 mL acetic acid was well stirred, and brought up to an internal temperature of exactly 25 °C. There was added, in very small portions, a 40% solution of peracetic acid in acetic acid. The evolved heat was removed with an external ice bath, and the rate of addition was dictated by the requirement that the internal temperature should not exceed 25 °C. A total of 210 g of the 40% peracetic acid was used. The reaction mixture was poured into 3 L H_2O, and the acetic acid neutralized by the addition of solid K_2CO_3. The neutral aqueousphase was extracted with 5x150 mL Et_2O, and the

solvent from the pooled extracts was removed under vacuum. To the red-colored residue there was added 300 mL 10% NaOH, and the mixture was heated for 1 h on the steam bath. This was cooled, washed once with CH_2Cl_2, acidified with HCl, and extracted with 5x150 mL Et_2O. The pooled extracts were washed once with saturated $NaHCO_3$ (which removed most of the color) and the removal of the solvent under vacuum gave 105 g of 3,4-dimethoxyphenol as an amber oil that slowly set up to crystals.

The above crude 3,4-dimethoxyphenol was dissolved in 200 mL EtOH, and treated with a solution of 38.1 g KOH in 300 mL hot EtOH. The clear solution of the potassium salt was a deep red color, and was promptly treated with 94.3 g allyl bromide, at a rate commensurate with the exothermic reaction. The mixture was held at reflux for 2 h. This was then added to 1 L H_2O and extracted with 5x100 mL Et_2O. The extracts were pooled, and removal of the solvent under vacuum gave a residue of 98 g of a black oil. This was distilled at 104-108 °C at 0.7-1.0 mm/Hg to give 59.3 g 1-allyloxy-3,4-dimethoxybenzene as a pale yellow oil with a greenish cast.



A total of 59 g of the neat 1-allyloxy-3,4-dimethoxybenzene was provided with an internal thermometer, and heated with an open flame. The color quickly became purple, then lightened to a red at 70 °C, and finally to a pale pink by 210 °C. At 240 °C an exothermic reaction set in with the temperature going up to almost 290 °C. It was held in the 270-280 °C range for several min, then allowed to return to room temperature. GC analysis showed two peaks, the second and major one being the desired 1,2,4,5-isomer. A small sample was caught by prep-GC, and it successfully seeded the crude Claissen rearrangement product. The isolated 2-allyl-4,5-dimethoxyphenol, pressed on a porous plate, had a mp of 39.5-40.5 °C which was improved to 41.5-42 °C by recrystallization from hexane.

To a solution of 9.7 g 2-allyl-4,5-dimethoxyphenol in a few mL EtOH, there was added a solution of 2.8 g KOH in 25 mL boiling EtOH followed by 5.5 g ethyl bromide. The mixture was held at reflux for 3.5 h and then poured into 200 mL H_2O and extracted with 3x100 mL CH_2Cl_2. Pooling the extracts and removal of the solvent under vacuum gave a residue of 10.4 g of 4,5-dimethoxy-2-ethoxy-1-allylbenzene as a clear, mobile oil. It was substantially a single component by GC and was used in the following isomerization step without further purification.

A solution of 9.4 g 4,5-dimethoxy-2-ethoxy-1-allylbenzene in 10 mL EtOH was treated with 20 g flaked KOH, and heated on the steam bath. The progress of the isomerization was followed by the assay of isolates by GC. After 5 h, the reaction mixture was poured into 250 mL H_2O which immediately generated a pasty solid. This was sucked free of solvent and other liquids on a sintered funnel, giving 5.5 g of trans-4,5-dimethoxy-2-ethoxy-1-propenylbenzene as an amber solid with a mp of 65-67 °C. A small analytical sample from hexane had a mp of 68 °C.

A solution of 5.0 g trans-4,5-dimethoxy-2-ethoxy-1-propenylbenzene in

27 g acetone that contained 2.2 g pyridine was magnetically stirred and cooled to 0 °C. There was then added 4.5 g tetranitromethane and, after 2 minutes stirring at this temperature, the reaction mixture was quenched with a solution of 1.5 g KOH in 26 mL H_2O. The reaction mixture remained a clear deep orange color, and additional H_2O was required to institute crystallization. There was the slow deposition of bright yellow crystals of 1-(4,5-dimethoxy-2-ethoxyphenyl)-2-nitropropene which weighed, after EtOH washing and air drying to constant weight of 4.4 g. The mp was 75-76 °C.

To a gently refluxing suspension of 3.5 g LAH in 250 mL anhydrous Et_2O under a He atmosphere, there was added 3.9 g 1-(4,5-dimethoxy-2-ethoxyphenyl)-2-nitropropene by allowing the condensing Et_2O to drip into a shunted Soxhlet apparatus with the thimble containing the nitrostyrene. This effectively added a warm saturated solution of the nitrostyrene dropwise; the nitrostyrene was very soluble in Et_2O. Refluxing was maintained for 2.5 h and the reaction continued to stir at room temperature for an additional 3.5 h. The excess hydride was destroyed by the cautious addition of 225 mL 1.5 N H_2SO_4. When the aqeous and Et_2O layers were finally clear, they were separated, and 75 g of potassium sodium tartrate was dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was >9, and this was then extracted with 3x100 mL CH_2Cl_2. Evaporation of the solvent under vacuum produced 2.8 g of a clear, almost colorless oil that was dissolved in anhydrous Et_2O and saturated with anhydrous HCl gas. This initially generated a solid that then oiled out. After a few minutes stirring, this began to solidify again and it finally transformed into a loose fine white solid. This was recrystallized by dissolution in 50 mL warm IPA followed by dilution with 300 mL Et_2O. After a few minutes, crystals of 4,5-dimethoxy-2-ethoxyamphetamine hydrochloride (EMM) formed which were removed by filtration, Et_2O washed, and air dried. These weighed 2.7 g and had a mp of 171-172 °C. Anal. ($C_{13}H_{22}ClNO_3$) C,H,N.

DOSAGE: greater than 50 mg.

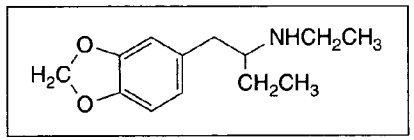
DURATION: unknown.

QUALITATIVE COMMENTS: (with 50 mg) "There were no effects."

EXTENSIONS AND COMMENTARY: This was the first of the ethoxy homologues of TMA-2, and it was immediately (well, within a couple of months) run up from an initial dab to 25 milligrams. This was in early 1963, and the lack of activity of EMM was keenly disappointing. This was a level at which the prototype, TMA-2, was very active, and the conclusion was that maybe any change on the molecule would result in a loss of activity. So this approach was shelved for a while, and all efforts were directed into the relocation, rather than the elongation, of the methoxy groups. A few months later, the ethoxy question was addressed again, and the discovery of MEM rekindled full interest in this ethoxy question.

#77 ETHYL-J; 2-ETHYLAMINO-1-(3,4-METHYLENEDIOXYPHENYL)BUTANE; N-ETHYL-1-(1,3-BENZODIOXOL-5-YL)-2-BUTANAMINE

SYNTHESIS: A stirred solution of 9.0 g 1-(3,4-methylenedioxyphenyl)-2-butanone (see the recipe for J for its preparation) in 150 mL MeOH was treated with 9.0 g ethylamine hydrochloride, 4.0 g anhydrous NaOAc, and 3.0 g sodium cyanoborohydride. The pH was maintained between 6 and 7 by the periodic addition of HCl. After the base formation had stabilized, there was added an additional 9.0 g ethylamine hydrochloride, 9.0 g NaOAc and 2.0 g sodium cyanoborohydride. With continuous stirring, there was HCl added over the course of 1 h until the final pH was approximately 2. The reaction mixture was poured into 700 mL dilute NaOH, and extracted with 3x75 mL CH_2Cl_2. These extracts were pooled, and back-extracted with dilute H_2SO_4. This was washed with 2x50 mL CH_2Cl_2, then made basic with dilute NaOH and extracted with 2x75 mL CH_2Cl_2. Removal of the solvent under vacuum gave a 0.81 g residue which was dissolved in 10 mL IPA. Neutralization with concntrated HCl formed white crystals spontaneously. These were diluted with Et_2O, filtered, Et_2O washed and air dried to provide 0.85 g 2-ethylamino-1-(3,4-methylenedioxyphenyl)butane hydrochloride (ETHYL-J), with mp of 176-177 °C. Anal. ($C_{13}H_{20}ClNO_2$) C,H. The neutral fraction that remained in the organic phase following the dilute sulfuric acid extraction, was recovered by removal of the solvent under vacuum. There was obtained about 5 g of an amber liquid that was largely 2-hydroxy-1-(3,4-methylenedioxyphenyl)butane.



DOSAGE: greater than 90 mg.

DURATION: probably short.

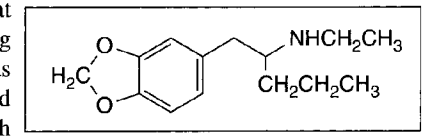
QUALITATIVE COMMENTS: (with 65 mg) "Perhaps aware at 20 minutes. Definitely aware at 45 minutes. Diffusing to nothing at 3-4 hours."

(with 90 mg) "I am somewhere between ± and +. And everything became lost in the evening with a couple of glasses of wine and talk that went on to 3 AM."

EXTENSIONS AND COMMENTARY: And nothing higher has ever been looked at. If the analogy with the amphetamine counterparts (J with MDA, METHYL-J with MDMA, and this, with MDE) were to hold up (a drop of about a third in potency with the lengthening of the chain by a carbon atom), one might guess that this compound would be an interesting intoxicant, but probably not until you got up into the area at or above a 200 milligram dose. And that is a lot of chemical for the body to have to handle. Some day, maybe.

#78 ETHYL-K; 2-ETHYLAMINO-1-(3,4-METHYLENEDIOXYPHENYL)PENTANE; N-ETHYL-1-(1,3-BENZODIOXOL-5-YL)-2-PENTYLAMINE

SYNTHESIS: A solution of 120 mg mercuric chloride in 160 mL H_2O was poured over 4.7 g aluminum foil (Reynolds Wrap, regular weight, cut into 1 inch squares) and allowed to stand until the amalgamation was well underway (about 30 min). The H_2O was then drained and the foil washed with 2x200 mL H_2O with thorough draining. There was then added, in sequence and with good swirling and agitation between each addition, 8.5 g ethylamine hydrochloride dissolved in 7 mL H_2O, 21 mL IPA, 17 mL 25% NaOH, 7.1 g 1-(3,4-methylenedioxyphenyl)-2-pentanone (see the recipe for METHYL-K for its preparation), and finally 40 mL IPA. The reaction mixture was periodically heated on the steam bath to keep the reaction moving and active. After all the metal had been consumed, the mixture was filtered, and the filter cake washed with MeOH. The solvent was removed from the combined filtrate and washings, and the residue suspended in 800 mL dilute HCl. This was washed with 3x100 mL Et_2O, made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. The pooled extracts were stripped of solvent under vacuum yielding a residue of 6.3 g of an amber oil. This was distilled at 115-125 °C at 0.4 mm/Hg to give 5.61 g of an almost white liquid which was dissolved in 28 mL IPA, neutralized with concentrated HCl, and diluted with 100 mL anhydrous Et_2O. The resulting clear solution became cloudy, then set up in a cottage cheese texture, and then all broke up to a beautiful loose solid. This was filtered, Et_2O washed and air dried to give 5.99 g 2-ethylamino-1-(3,4-methylenedioxyphenyl)pentane hydrochloride (ETHYL-K) with a mp of 157-158 °C. Anal. ($C_{14}H_{22}ClNO_2$) C,H.



DOSAGE: (greater than 40 mg).

DURATION: unknown.

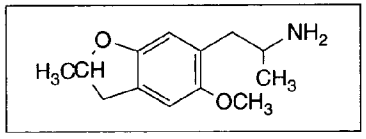
QUALITATIVE COMMENTS: (with 40 mg) "There was a paresthetic twinge in my shoulder area at about an hour — other than that, absolutely nothing."

EXTENSIONS AND COMMENTARY: And that is as high a dose as has apparently ever been tried with ETHYL-K. The compounds with the hexane chain (L-series) rather than the pentane chain of the K-series have been made, but they have been spun into the recipe for METHYL-K.

#79 F-2; 2-M; 6-(2-AMINOPROPYL)-5-METHOXY-2-METHYL-2,3-DIHYDROBENZOFURAN

SYNTHESIS: To a solution of 43.2 g KOH pellets in 250 boiling EtOH there was added 96 g 4-methoxyphenol followed by the slow addition of 131.2 g allyl bromide, and the mixture was held under refluxing conditions for 16 h. After cooling, the reaction was added to 1.6 L H_2O, and made strongly basic with 25% NaOH. This was extracted with 3x100 mL CH_2Cl_2, the extracts pooled, washed once with dilute NaOH and then once with dilute HCl. Removal of the solvent under vacuum gave 93.8 g of 4-allyloxyanisole as a pale amber oil, which was used in the following reaction without further purification.

A round-bottomed flask containing 93 g crude 4-allyloxyanisole was equipped with an immersed thermometer and heated with an external flame until an exothermic reaction set in at 230 °C. The temperature rose to 270 °C and it was maintained there with the flame for five minutes. After cooling to room temperature, the reaction mix was poured into 2 L H_2O and made strongly basic with the addition of 25% NaOH. This dark aqueous phase was washed with 2x200 mL CH_2Cl_2, and then acidified with HCl. This was then extracted with 2x200 mL CH_2Cl_2, and the pooled extracts washed first with saturated $NaHCO_3$ and then with H_2O. Removal of the solvent under vacuum gave 65.6 g of 2-allyl-4-methoxyphenol as a clear, amber oil. To a solution of 1.66 g of this crude phenol in 5 mL hexane with just enough CH_2Cl_2 added to effect a clear solution, there was added 1.3 g phenyl isocyanate followed with three drops of triethylamine. An exothermic reaction ensued which spontaneously deposited white crystals. These was removed and hexane washed to give 2-allyl-4-methoxyphenyl N-phenyl carbamate, with a mp of 88-89 °C. The acetate ester, from the phenol and acetic anhydride in pyridine, did not crystallize.



To a solution of 37.7 g 2-allyl-4-methoxyphenol in 125 mL glacial acetic acid there was added 19 g zinc chloride followed with 63 mL concentrated HCl. The mixture was held at reflux temperature for 40 min, then cooled to room temperature, diluted with 300 mL H_2O, and extracted with 2x200 mL CH_2Cl_2. The pooled extracts were washed repeatedly with 8% NaOH until the washings remained basic. Removal of the solvent under vacuum gave a clear pale yellow oil that was distilled at the water pump. A fraction boiling at 150-165 °C was 5-methoxy-2-methyl-2,3-dihydrobenzofuran which weighed 25 g and which was a highly refractive colorless oil. The infra-red spectrum indicated that some small amount of hydroxy group was present, but the NMR spectrum was in complete accord with the benzofuran structure. A higher cut in this distillation gave 4.5 g of a phenolic product tentatively assigned the structure of 4-methoxy-2-propenylphenol. The target dihydrobenzofuran has also been synthesized from the open-ring o-allyl phenol in acetic acid solution with the addition of a catalytic amount of concentrated H_2SO_4.

To a half-hour pre-incubated mixture of 69 g $POCl_3$ and 60 g N-methylformanilide there was added 29.0 g 5-methoxy-2-methyl-2,3-dihydrobenzofuran and the mixture was heated on the steam bath for 2 h. The reaction mixture was poured into 1 L H_2O, and allowed to stir overnight. The brown gummy solids were removed by filtration, and air dried as completely as possible. These weighed 32 g and were shown by GC on OV-17 to consist of two benzaldehyde isomers in a ratio of 7:2. This was triturated under 18 mL MeOH, and the undissolved solids removed by filtration and washed with 6 mL additional MeOH. The mother liquor and washings were saved. The 17.8 g of dull yellow solids that were obtained were repeatedly extracted with 75 mL portions of boiling hexane (4 extracts were required) and each extract, on cooling, deposited yellow crystals of the major aldehyde. The dried crystals of 6-formyl-5-methoxy-2-methyl-2,3-dihydrobenzofuran were combined (9.5 g) and had a mp of 80-82 °C. The methanol washes saved from above were stripped of solvent, and the sticky, orange solids that remained were enriched in the minor aldehyde isomer (3:2 ratio). Several injections of this crude material into a preparative GC OV-17 column gave sufficient quantities of the "wrong" isomer for NMR characterization. The 2-methyl group was intact (eliminating the possibility of a dihydrobenzopyran isomer) and the ring meta-proton splitting required that the formyl group be in the benzofuran 7-position. This crystalline solid was, therefore, 7-formyl-5-methoxy-2-methyl-2,3-dihydrobenzofuran.

A solution of 9 g of 6-formyl-5-methoxy-2-methyl-2,3-dihydrobenzofuran in 35 mL glacial acetic acid was treated with 6 mL of nitroethane followed with 3.1 g anhydrous ammonium acetate. This mixture was heated on the steam bath for 4 h, diluted with half its volume with warm H_2O, and seeded with a bit of product that had been obtained separately. The slightly turbid solution slowly crystallized as it cooled, and was finally held at 0 °C for several h. The deep orange product was removed by filtration, washed with 50% acetic acid, and air dried to constant weight. There was thus obtained 7.0 g 5-methoxy-2-methyl-6-(2-nitro-1-propenyl)-2,3-dihydrobenzofuran with a mp of 89-90 °C from MeOH.

A suspension of 5.0 g LAH in 500 mL of well stirred anhydrous Et_2O at a gentle reflux, was treated with a warm, saturated solution of 7.0 g 5-methoxy-2-methyl-6-(2-nitro-1-propenyl)-2,3-dihydrobenzofuran in Et_2O added dropwise. The mixture was kept at reflux temperature for 36 h, allowed to stand 2 days, and then the excess hydride destroyed by the cautious addition of 500 mL 6% H_2SO_4. The phases were separated, and the aqueous phase washed with 2x200 mL CH_2Cl_2. A total of 125 g potassium sodium tartrate was added to the aqueous phase, and sufficient 25% NaOH added to bring the pH to about 10. This phase was extracted with 3x150 mL CH_2Cl_2, and the pooled extracts were stripped of solvent under vacuum. The residual oil (4.8 g, amber in color) was dissolved in 300 mL anhydrous Et_2O which, upon saturation with anhydrous HCl gas gave a clear solution that suddenly deposited white crystals. The hydrochloride salt of 6-(2-aminopropyl)-5-methoxy-2-methyl-2,3-dihydrobenzofuran weighed 2.3 g and was not satisfactory

as a solid derivative, but it appears that the oxalate salt is both nonhygroscopic and quite stable. It (F-2) had a mp of 216-218 °C and it displayed a textbook NMR.

DOSAGE: greater than 15 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: This material, which is certainly a mixture of two diastereoisomeric pairs of racemates since there are two chiral centers present, showed no effects at levels of up to 15 milligrams orally. Doses of 100 mg/Kg were without effects in mice following i.p. injections, although half again this amount proved to be lethal. In rats trained to discriminate LSD from saline, F-2 proved to be about 40 times less potent than the reference compound DOM, requiring some 5 mg/Kg for positive responses. But the human trials were only up to about 0.2 mg/Kg.

This was the prototype compound that was originally put together to justify giving a paper at a marijuana conference in Sweden, in 1968. Although I had never done much with marijuana or with its principal ingredients, I thought maybe I could bend the topic a bit to embrace some potentially active phenethylamines. There is a story of an international conference held in Geneva a few years earlier to discuss the worrisome decrease in the elephant population. A German zoologist invested a full eight-hour day in a summary of his 21 volume treatise on the anatomy and the physiology of the elephant. A French sociologist presented a lively slide show on the mating rituals and rutting behavior of the elephant. And a rabbi from Tel Aviv entitled his talk: "Elephants and the Jewish Problem." My Swedish talk should have been named "Marijuana and the Psychedelic Amphetamines." The memorable story of meeting the chief of the Swedish equivalent of the Bureau of Narcotics, and ending up playing Mozart sonatas in the attic of his home, has been spun out elsewhere in the book.

The original concept was a grand plan to imitate two of the three rings of tetrahydrocannabinol. There is an aromatic ring (with an alkyl group and two oxygens on it) and it is fused to a pyran ring with a couple of methyl groups on it. So, if one were to tie the methyl group at the 4-position of DOM around with a short carbon chain into the oxygen atom at the five position, one could squint and say that the resulting amphetamine was kinda something like an analogue of THC. Thus, the resulting six-membered ring (a pyran) or five-membered ring (a furan) could be peppered with methyl groups at different locations (and up to two per location). If the ring was a five-membered structure, then the parent system would be a benzofuran, and the location of methyl groups on the ring would be indicated by the appropriate numbers following the letter "F" which would stand for "furan". And if it were to be a six-membered ring, the resulting benzopyran would be indicated with a "P" for pyran, and again the methyl group or groups would be indicated by the substitution position. This code would cover all polymethylated homologues

with codes that would look like F-22 and P-2234. If any of them showed up with fascinating activities, I would extend methyls to ethyls, and work out some whole new naming code at some future time. An early system, naming this compound 2-M for a methyl group on the 2-position of the furan ring, was abandoned when it became apparent that the pyran world would screw everything up.

The isolation of characterizable quantities of 7-formyl-5-methoxy-2-methyl-2,3-dihydrobenzofuran from the benzaldehyde recipe above gave a fleeting fantasy of a whole new direction that this little project might go. If this unexpected benzaldehyde were to be converted to the corresponding amphetamine, one would have 7-(2-aminopropyl)-5-methoxy-2-methyl-2,3-dihydrobenzofuran. Suddenly here would be a 2,3,5-trisubstituted thing with a ring at the 2,3-position, similar to the still unmade MMDA-4. The temptation to be diverted in this way lasted, fortunately, only a few minutes, and the project was shelved. Someday, when there are buckets of spare time or hosts of eager graduate students, some fascinating chemistry might lie this way, and maybe some fascinating pharmacology, even.

The plain furan analogue, without any methyl groups on it, has been made. Five-methoxybenzofuran formed the 6-formyl derivative (the aldehyde) with a mp of 79-80 °C and from it the nitrostyrene (orange needles, mp 89-91 °C) and the final amphetamine (white solids, as the methane sulfonate, mp 141-144 °C) were prepared in a manner similar to the preparation of F-2 above. In the rat studies, it was three times more potent than F-2, but still some 15 times less potent than DOM. And in initial human trials (of up to 30 milligrams) there were again no effects noted. Naming of this material is easy chemically (6-(2-aminopropyl)-5-methoxy-2,3-dihydrobenzofuran) but tricky as to code. If the numbers that follow the "F" give the location of the methyl groups, then this material, without any such groups, can have no numbers following, and should properly be simply "F." OK, it is "F." The preparation or the attempted preparations of other homologues such as F-23 and F-233 are outlined under the recipe for F-22.

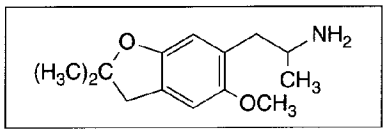
#80 F-22; 6-(2-AMINOPROPYL)-2,2-DIMETHYL-5-METHOXY-2,3-DIHYDROBENZOFURAN

SYNTHESIS: To a solution of 43.2 g flaked KOH in 250 mL hot EtOH there was added 96 g 4-methoxyphenol followed by 90 g 2-methylallyl chloride over the course of 2 h. The mixture was held at reflux for 24 h, then added to 1.6 L H_2O. There was sufficient 25% NaOH added to make the phase strongly basic, and this was then extracted with 3x200 mL CH_2Cl_2. The pooled extracts were washed with H_2O, and the solvent removed under vacuum. The residue, 125 g of a pale amber oil, was crude 4-(2-methylallyloxy)anisole and was used without further purification in the following reaction.

In a round-bottomed flask containing an internal thermometer, there was

placed 125 g of unpurified 4-(2-methylallyloxy)anisole, and this was heated with an open flame. At an internal temperature of 190 °C an exothermic reaction set in, raising the temperature to 250 °C, where it was held for an additional 2 min. After the reaction mixture had cooled to room temperature, it was poured into 500 mL H_2O, made strongly basic with 25% NaOH, and extracted repeatedly with 100 mL portions of CH_2Cl_2 until the extracts were essentially colorless. These extracts were pooled and the solvent removed to provide 80.0 g of a deeply colored oil that proved to be largely the appropriately substituted dihydrobenzofuran. The aqueous residue from above was acidified with concentrated HCl, and again extracted with CH_2Cl_2. Removal of the solvent gave 17.7 g of 4-methoxy-2-(2-methylallyl)phenol as an amber oil which eventually set down as white crystals with a mp of 52.5-54 °C.

A solution of 17 g of 4-methoxy-2-(2-methylallyl)phenol in 56 g acetic acid was treated with 8.4 g zinc chloride followed with 28 mL concentrated HCl. This mixture was heated at reflux temperature with a mantle for 1 h. After cooling, this was poured into H_2O and extracted with 2x150 mL CH_2Cl_2. The pooled extracts were washed with several portions of 8% NaOH, until the extracts were colorless. The organic fraction was then washed with H_2O, and the solvent removed to yield 5.8 g of 2,2-dimethyl-5-methoxy-2,3-dihydrobenzofuran as a pale amber oil with a pungent smell. This was purified by distillation, giving a fraction of an off-white oil with a bp of 136-138 °C at 33 mm/Hg.



To a mixture of 8.0 g N-methylformanilide and 9.2 g $POCl_3$ which had been allowed to stand for 0.5 h, there was added 4.0 g 2,2-dimethyl-5-methoxy-2,3-dihydrobenzofuran, and the mixture held at the steam bath temperature for 2.5 h. This was then poured into 200 mL H_2O which produced a black oily phase that gave no hint of crystallization. This mixture was extracted with 3x150 mL CH_2Cl_2 and the solvent was removed from the pooled extracts under vacuum. The residual oil (which was shown by GC to contain approximately equal quantities of two isomeric benzaldehydes A and B) was extracted with three 75 mL portions of boiling hexane, each of which on cooling deposited a reddish oil that partially crystallized. A fourth hexane extract gave nothing more. The solvent was decanted from these three extracts, and the semi-solid residues were ground under 3.0 mL MeOH giving 1.4 g of pale yellow crystals of 2,2-dimethyl-6-formyl-5-methoxy-2,3-dihydrobenzofuran, isomer "B". After recrystallization from MeOH, the color was almost white, and the mp was 79.5-80.5 °C. The combined mother liquors were enriched in isomer "A" which proved, following preparative GC separation and NMR analysis, to be the 7-formyl isomer. The 80 g of impure dihydrobenzofuran isolated from the Claisen rearrangement above was distilled and a fraction (43.8 g) that boiled from 138-153 °C at 30 mm/Hg was processed as described here to the aldehyde mixture. Following similar hexane extractions, a yield of 4.0 g of a 95% pure isomer "B" was finally obtained. The remaining components of this fraction were not determined, but it is possible that there were some that contained the six-membered benzopyran ring system.

To a solution of 5.2 g of 2,2-dimethyl-6-formyl-5-methoxy-2,3-dihydrobenzofuran in 20 mL glacial acetic acid there was added 3 mL nitroethane followed by 1.6 g anhydrous ammonium acetate. This mixture was heated for 4 h on the steam bath, and then a small amount of H_2O was added to the hot solution. This instigated the formation of a copious deposition of brick-red crystals which were, after cooling, removed by filtration, and recrystallized from 50 mL boiling MeOH. After air drying there was thus obtained 2.7 g of day-glo yum-yum orange crystals of 2,2-dimethyl-5-methoxy-6-(2-nitro-1-propenyl)-2,3-dihydrobenzofuran. An additional 0.6 g of product was obtained by working the mother liquors.

A suspension of 2.5 g LAH in 300 mL refluxing anhydrous Et_2O was treated with a solution of 3.1 g 2,2-dimethyl-5-methoxy-6-(2-nitro-1-propenyl)-2,3-dihydrobenzofuran in Et_2O. The mixture was held at reflux temperature for 18 h. After cooling, the excess hydride was destroyed by the cautious addition of 400 mL H_2O which contained 15 g H_2SO_4. The aqueous phase was separated, washed once with Et_2O, and then once with CH_2Cl_2. There was then added 60 g potassium sodium tartrate, and the pH was brought to above 10 by the addition of 25% NaOH. This was extracted with 3x250 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. There remained 2.8 g of an amber oil with an ammoniacal smell. This was dissolved in 200 mL anhydrous Et_2O, and saturated with anhydrous HCl gas. There was the immediate formation of an oil, from which the supernatent Et_2O was decanted. The residual oil was resuspended in a second 200 mL anhydrous Et_2O, again decanted, and finally a third 200 mL Et_2O effected the dissolving of the remaining oil to give a clear solution. All three solutions became gelatinous over the following few h, and each deposited a crop of white crystals over the following few days. From the first there was obtained 1.4 g of product with a mp of 153-154 °C; from the second, 0.2 g with a mp of 153-154 °C; and from the third, 1.2 g with a mp of 155-156 °C. These crops were combined, and recrystallized from 10 mL of boiling CH_3CN to give 1.7 g 6-(2-aminopropyl)-2,2-dimethyl-5-methoxy-2,3-dihydrobenzofuran hydrochloride (F-22) as a white crystalline solid which had a mp of 154-155 °C. This material, even when dry, showed a tendency to discolor with time.

DOSAGE: greater than 15 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: And here is yet another dihydrobenzofuran which is not of a very high potency if, indeed, it is active at all. This particular dihydrobenzofuran analogue, F-22, had sort of tickled my fancy as being an especially good candidate for activity. It had a certain swing to it. F-22, like LSD-25. And here it was finished, just five days before I had to deliver a paper concerning

the syntheses (and activities!) of all these dihydrobenzofurans to the marijuana congress. Could this possibly be another LSD? I was sufficiently convinced that the possibility was real, that I actually started the screening process at a most unusually low level of 10 micrograms. Two days later, I upped this to a dose of 25 micrograms (no activity again) and three days after that, at 1 AM on the polar flight to Copenhagen, I swallowed the "monstrous" dose of 50 micrograms. Shoot the works. If I were to blossom all over the tourist section of the SAS plane, well, it would be quite a paper to give. If not, I could always say something like, "The active level has not yet been found." No activity. Another Walter Mitty fantasy down the tubes.

And, as it turned out, the entire project pretty much ran out of steam. A number of clever analogs had been started, and would have been pursued if there had been any activity promised of any kind with any of these dihydrobenzofurans. The "other" benzaldehyde described above, could have been run in a manner parallel to that proposed for the counterpart with F-2, to make the eventual amphetamine, 7-(2-aminopropyl)-2,2-dimethyl-5-methoxy-2,3-dihydrobenzofuran. Great strides had been made towards F-233 (I have discussed the naming system under F-2, with the F standing for the furan of benzofuran and the 2 and 3 and 3 being the positions of the methyl groups on it). The reaction of 4-methoxyphenol with 1-chloro-3-methyl-2-butene gave the ether which underwent the thermal Claisen rearrangement to 2-(1,1-dimethylallyl)-4-methoxyphenol with a bp of 148-157 °C at 30 mm/Hg. This was cyclized to the intermediate cycle 2,3,3-trimethyl-2,3-dihydrobenzofuran which, after distillation, was shown to be only 80% pure by GC analysis. This was, nonetheless, (and with the hope that is in the very fiber of a young innocent chemist), pushed on to the benzaldehyde stage (and there were a not-too-surprising four benzaldehydes to be found in the oil that was produced, which refused to crystallize). And then (when sheer desperation replaced hope) these were condensed with nitroethane to form an even worse mixture. Maybe something might crystallize from it? Nothing ever did. Junk. Everything was simply put on the shelf where it still rests today, and F-233, 6-(2-aminopropyl)-5-methoxy-2,3,3-trimethyl-2,3-dihydrobenzofuran, remains the stuff of speculation.

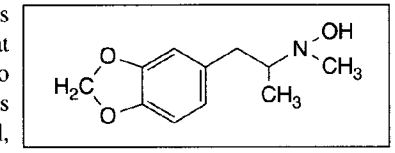
And a start towards F-23, 6-(2-aminopropyl)-2,3-dimethyl-5-methoxy-2,3-dihydrobenzofuran, got just as far as the starting ether, when it occurred to me that the final product would have an unprecedented three chiral centers, and so a total of four racemic pairs of diastereoisomers. And then I discovered that the starting allyl halide, crotyl chloride, was only 80% pure, with the remaining 20% being 3-chloro-1-butene. This would have eventually produced a 2-ethyl-analogue, 6-(2-aminopropyl)-2-ethyl-5-methoxy-2,3-dihydrobenzofuran, with its two chiral centers and two more pairs of stereoisomers (not to speak of the need to devise an entirely new coding system). Unless something were to fall into my lap as a crystalline intermediate, the final mess could have had at least six discreet compounds in it, not even considering optical isomers. And I haven't even begun to think of making the six-membered dihydrobenzopyrans which were the THC analogues that

presented the rationale that started the whole project in the first place. A recent issue of the Journal of Medicinal Chemistry has just presented an article describing the reaction of 6-methoxytetrahydrobenzopyran with dichloromethyl methyl ether, and approximately equal amounts of all three of the possible isomers were obtained. That would have been the first step towards making the prototypic compound 7-(2-aminopropyl) 6-methoxy-1,2,3,4-tetrahydrobenzopyran. Just as the benzofurans were all named as F-compounds, this, as a benzopyran, would have been a P compound, but P also is used for proscaline, and there would have been some repair-work needed for these codes.

Time to abandon ship. The fact that I had just synthesized and discovered the strange activity of ARIADNE at about this time, made the ship abandonment quite a bit easier to accept.

#81 FLEA; N-HYDROXY-N-METHYL-3,4-METHYLENEDIOXYAMPHETAMINE

SYNTHESIS: (from 3,4-methylenedioxyphenylacetone) A solution of 2.1 g N-methylhydroxylamine hydrochloride and 4.4 g 3,4-methylenedioxyphenylacetone in 5.5 mL MeOH was added to a suspension of 4.5 g $NaHCO_3$ in 30 mL boiling MeOH. There was added about 5 mL H_2O (which gave a clear solution) followed by another 50 mL H_2O which produced a pale yellow color. To this solution of the unisolated nitrone there was added 1.7 g sodium cyanoborohydride, which generated a goodly amount of foaming. There was HCl added as needed to maintain the pH at about neutrality. The reaction appeared to have stopped after a day or two, so all was poured into 500 mL H_2O, acidified with HCl, and washed with 2x75 mL CH_2Cl_2. The addition of base brought the pH >9, and this was then extracted with 3x75 mL CH_2Cl_2. Removal of the solvent from the pooled extracts gave a residue of 1.65 g of crude N-hydroxy-N-methyl-3,4-methylenedioxyamphetamine. Efforts to obtain solid seed samples of the salts with hydrochloric acid, perchloric acid, sulfuric acid, phosphoric acid, and with a number of organic acids, all failed. The salt formation from this free-base will be discussed below.



(from MDOH) A solution of 0.75 g crystalline free-base MDOH in a few mL MeOH was treated with a solution of 0.4 g sodium cyanoborohydride in 10 mL MeOH, and there was then added 2 mL of 35% formaldehyde. The stirred reaction mixture was kept at a neutral pH with the occasional addition of HCl. After several days (when additional acid was no longer required) the excess solvent was removed under vacuum, and the residue poured into dilute H_2SO_4. This was washed with 2x75 mL CH_2Cl_2 and then, following the addition of base, this was extracted with

3x75 mL CH_2Cl_2. Removal of the solvent from the pooled extracts gave a viscous oil residue of 0.53 g. The free-base product from these preparations was distilled at 110-120 °C at 0.2 mm/Hg to give the N-hydroxy-N-methyl product as a white oil. An alternate methylation procedure used a solution of MDOH in a 4:1 MeOH/acetic acid solution containing formaldehyde which was reduced with sodium borohydride at dry ice temperatures. Its work-up is identical to that involving sodium cyanoborohydride.

The distilled product was dissolved in an equal volume of MeOH, and treated with a half-equivalent of oxalic acid dihydrate, dissolved in 10 volumes of MeOH. This combination gave the slow deposition of crystals of the full oxalate salt (one acid, two bases) as a white crystalline product. The mp of the crude salt was in the 130-150 °C range, and after recrystallization from CH_3CN, N-hydroxy-N-methyl-3,4-methylenedioxyamphetamine oxalate (FLEA) had a mp of 146-147 °C.

DOSAGE: 100 - 160 mg.

DURATION: 4 - 8 h.

QUALITATIVE COMMENTS: (with 90 mg) "The material tastes terrible, like grapefruit juice that has stayed in the can too long. There was no nausea, no feeling of difficulty in swallowing at any time during the day. I felt a dry mouth and was thirsty — sipped water throughout the day. At the beginning of the experiment, there was a glimmer of the MDMA warmth, but later I felt separated and a bit isolated. I was just floating around, seeing the beauty of colors and objects in the house and outdoors and listening first to this conversation, then to that one. All senses seemed enhanced. I found the material pleasant. I was happy with the amount I took but would not be afraid to take more or to take a supplement. I found it similar to, but not the same as, MDMA."

(with 110 mg) "We found this very similar to MDMA, but perhaps slightly slower. I plateau'd at 2:30 hours and had a very gradual descent. My friend had a marvelous and private 'cone of silence' that was to him unique to MDMA or to 2C-T-8. Teeth problems were minor, and the descent from the top of the experience showed less interactive, and more contemplative action, than with MDMA. Very similar to MDMA, but with its own character."

(with 110 mg) "The onset was at about a half-hour. The come-on was more gradual and much easier than with MDMA, and it seemed to be more head than body oriented. I had about two hours of very complex and personal self-evaluation, and I am not at peace in putting all of it down here in writing. Overall I like it, and I would be interested to see if there's a difference in conjunction with MDMA. Thanks very much."

(with 110 mg + 35 mg) "I saw my onset at 20 minutes, and it was subtle, and very pleasant, and had a mild amphetamine-like elevation for me (body lightness, cognitive functions seemed clear and clean, heightened visual awareness and with some enhancement of color). It seemed as if I were on the fringe of LSD-like visual changes, but that never materialized. The affect was very good, communicative, friendly, accepting, but without the profound emotional bonding of MDMA. The following day felt very much like a post-LSD day; we felt great. The body was light, energy good, emotions high, several insights throughout the day, interactions clear and open — a magnificent gift of a day. I started a menstrual period the day of the experience and it lasted 6 to 7 days; all of this was a couple of weeks early. I have a very favorable impression of FLEA although the body penalty seems high."

EXTENSIONS AND COMMENTARY: Most people who were involved with the evaluation of FLEA quite logically compared it with MDMA, as it was presented as being a very close analogue which might share some of the latter's properties. And to a large measure, the comparison was favorable. The dosages are almost identical, the chronological course of action is almost identical, and there are distinct similarities in the effects that are produced. If there is a consensus of similarities and differences it would be that it is not quite as enabling in allowing a closeness to be established with others. And perhaps there is more of a move towards introspection. And perhaps a slightly increased degree of discoordination in the thought processes. But also, part of this same consensus was that, were MDMA unknown, this material would have played its role completely.

And from the scientific point of view, it lends more weight to a hypothesis that just might be a tremendous research tool in pharmacology. I first observed the intimate connection between an amine and a hydroxylamine with the discovery that N-hydroxy-MDA (MDOH) was equipotent and of virtually identical activity to the non-hydroxylated counterpart (MDA). And I have speculated in the recipe for MDOH about the possible biological interconversions of these kinds of compounds. And here, the simple addition of a hydroxyl group to the amine nitrogen atom of MDMA produces a new drug that is in most of its properties identical to MDMA. The concept has been extended to 2C-T-2, 2C-T-7, and 2C-T-17, where each of these three active compounds was structurally modified in exactly this way, by the addition of a hydroxyl group to the amine nitrogen atom. The results, HOT-2, HOT-7 and HOT-17 were themselves all active, and compared very closely with their non-hydroxylated prototypes.

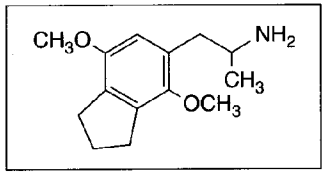
Just how general might this concept be, that an N-hydroxyl analog of an active amine shall be of similar action and duration as the parent drug? What if it really were a generality! What havoc it would wreak in the pharmaceutical industry! If I could patent the concept, then I would be able to make parallel best sellers to all of the primary and secondary amines out there in the industry. Perhaps 90% of all the commercially available drugs that are concerned with the human mental state are amines. And a goodly number of these are primary or secondary amines. And each and every one of these could be converted to its N-hydroxyl analogue,

effectively by-passing the patent protection that the originating corporation so carefully crafted. An example, just for fun. A run-away best seller right now is an antidepressant called fluoxetine, with the trade name Prozac. I will make a small wager that if I were to synthesize and taste N-hydroxy-N-methyl-3-phenyl-3-((α,α,α–trifluoro-p-tolyl)oxy)propylamine, I would find it to be an active antidepressant. Remember, Mr. Eli Lilly and Company; you read about it first, right here!

Of course, I was asked, why call it FLEA? The origin was in a classic bit of poetry. A commonly used code name for MDMA was ADAM, and I had tried making several modest modifications of the MDMA structure in the search for another compound that would maintain its particular music without the annoying tooth-grinding and occasional nystagmus, or eye-wiggle, that some users have mentioned. One of these was the 6-methyl homologue which was, with some perverse logic, called MADAM. And, following this pattern, the 6-fluoroanalogue was to be FLADAM. So, with the N-hydroxy analogue, what about HADAM? Which brought to mind the classic description of Adam's earliest complaint, an infestation of fleas. The poem was short and direct. "Adam had 'em." So, in place of HAD 'EM, the term FLEA jumped into being.

#82 G-3; 2,5-DIMETHOXY-3,4-(TRIMETHYLENE)AMPHETAMINE; 5-(2-AMINOPROPYL)-4,7-DIMETHOXYINDANE

SYNTHESIS: A solution of 3.7 g of 2,5-dimethoxy-3,4-(trimethylene)benzaldehyde (see preparation under 2C-G-3) in 15 mL nitroethane was treated with 0.7 g anhydrous ammonium acetate and heated on the steam bath for 2.5 h. The excess solvent was removed under vacuum leaving some 5 mL of a deep orange-red oil which on cooling, spontaneously crystallized. This was finely ground under 10 mL MeOH, filtered, washed sparingly with MeOH, and air dried to give 3.6 g of orange crystals with a strong smell of old acetamide. The mp was 92-93 °C. All was recrystallized from 30 mL boiling MeOH to give, after filtering and drying, 2.9 g of 1-(2,5-dimethoxy-3,4-(trimethylene)-phenyl)-2-nitropropene as yellow crystals with a mp of 93-94 °C. Anal. ($C_{14}H_{17}NO_4$) C,H,N.



Fifty milliliters of 1 M LAH in THF was placed in an inert atmosphere, well stirred, and cooled to 0 °C with an external ice-bath. There was added, dropwise, 1.35 mL of 100% H_2SO_4 at a rate slow enough to minimize charring. There was then added, dropwise, 2.8 g 1-(2,5-dimethoxy-3,4-(trimethylene)phenyl)-2-nitropropene in 15 mL THF. At the end of the addition, the stirring was continued for an additional 0.5 h, and then the reaction mixture was held at reflux on the steam bath for another 0.5 h. After cooling again to ice-bath temperature, the excess hydride was destroyed with the addition of 11 mL IPA, followed by 5.5 mL 5% NaOH which converted the inorganic mass through a cottage cheese stage into a loose, filterable texture. The solids were removed by filtration, washed with additional THF, and the combined filtrates and washes stripped of solvent under vacuum. There was obtained 2.51 g of a white oil that was distilled at 115-135 °C at 0.2 mm/Hg to give 1.83 g of a clear colorless oil. This was dissolved in 8 mL IPA, neutralized with 28 drops of concentrated HCl, and diluted with 140 mL anhydrous Et_2O. In about 0.5 h there started a slow snowfall of fine fluffy white crystals which was allowed to continue until no additional crystals appeared. After filtering, Et_2O washing and air drying, there was obtained 1.81 g of 2,5-dimethoxy-3,4-(trimethylene)amphetamine hydrochloride (G-3) with a mp of 157-159 °C. Anal. ($C_{14}H_{22}ClNO_2$) C,H.

DOSAGE: 12 - 18 mg.

DURATION: 8 - 12 h.

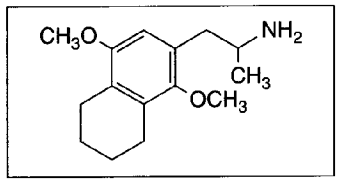
QUALITATIVE COMMENTS: (with 12 mg) "There was a warmth, a mellowness, as things developed. No body disturbance at all, but then there were no visuals either which, for me on this particular occasion, was disappointing. The day was consumed in reading, and I identified completely with the character of my fictional hero. It was a different form of fantasy. I think I prefer music as a structural basis for fantasy."

(with 18 mg) "I am at a plus three, but I am not at all sure of why it is a plus three. With my eyes closed, there are puffy clouds, but no drama at all. Music was not exciting. There could well have been easy eroticism, but there was no push in that direction. No great amount of appetite. Not much of anything, and still a plus three. Simply lying still and surveying the body rather than the visual scene gave some suggestions of neurological sensitivity, but with getting up and moving about and doing things, all was fine. The next morning I was perhaps moving a bit more slowly than usual. I am not sure that there would be reward in going higher."

EXTENSIONS AND COMMENTARY: In a comparison between the 2-carbon compound (2C-G-3) and the 3-carbon compound (G-3) the vote goes towards the phenethylamine (the 2-carbon compound). With the first member of this series (2C-G versus GANESHA) this was a stand-off, both as to quantitative effects (potency) and qualitative effects (nature of activity). Here, with the somewhat bulkier group located at the definitive 3,4-positions, the nod is to the shorter chain, for the first time ever. The potency differences are small, and maybe the amphetamine is still a bit more potent. But there are hints of discomfort with this latter compound that seem to be absent with the phenethylamine. The more highly substituted compounds (q.v.) more clearly define these differences.

#83 G-4; 2,5-DIMETHOXY-3,4-(TETRAMETHYLENE)-AMPHETAMINE; 6-(2-AMINOPROPYL)-5,8-DIMETHOXY-TETRALIN

SYNTHESIS: A solution of 1,4-dimethoxy-5,6,7,8-tetrahydro-ß-naphthaldehyde (see preparation under 2C-G-4) in 20 mL nitroethane was treated with 0.13 g anhydrous ammonium acetate and heated on the steam bath overnight. The volatiles were removed under vacuum and the residue, on cooling, spontaneously crystallized. This crude rust-colored product (1.98 g) was recrystallized from 15 mL boiling MeOH yielding, after filtering and air drying to constant weight, 1.33 g of 1-(2,5-dimethoxy-3,4-(tetramethylene)phenyl)-2-nitropropene as dull gold-colored crystals. The mp was 94-94.5 °C. Anal. ($C_{15}H_{19}NO_4$) C,H.



DOSAGE: unknown.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: The discussion that appeared in the commentary section under 2C-G-4 applies here as well. The major struggles were in the preparation of the aldehyde itself. And although the final product has not yet been made, this last synthetic step should be, as Bobby Fischer once said in his analysis of a master's chess game following a blunder by his opponent, simply a matter of technique.

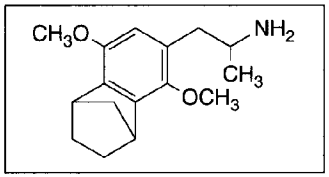
As with the phenethylamine counterpart, G-4 has a structure that lies intermediate between G-3 and G-5, both potent compounds. It is axiomatic that it too will be a potent thing, and all that now needs be done is to complete its synthesis and taste it.

#84 G-5; 3,6-DIMETHOXY-4-(2-AMINOPROPYL)BENZONORBORNANE

SYNTHESIS: A solution of 3.70 g 3,6-dimethoxy-4-formylbenzonorbornane (see under 2C-G-5 for its preparation) in 20 g nitroethane was treated with 0.88 g anhydrous ammonium acetate and held at steam bath temperature overnight. The excess solvent and reagent was removed under vacuum to yield a residual yellow oil. This was allowed to stand at ambient temperature for a period of time (about 3 years) by which time there was a spontaneous crystallization. The dull yellow crystals were removed by filtration and, after air drying, weighed 4.28 g. A small

sample was recrystallized repeatedly from MeOH to provide a pale yellow analytical sample of 3,6-dimethoxy-4-(2-nitropropenyl)benzonorbornane with a mp of 90-91 °C. Anal. ($C_{15}H_{19}NO_4$) C,H.

A solution of LAH (50 mL of 1 M solution in THF) was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.32 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 4.1 g 3,6-dimethoxy-4-(2-nitropropenyl)benzonorbornane in 20 mL anhydrous THF over the course of 10 min. The reaction mixture was stirred and brought to room temperature over the course of 1 h. This was then brought to a gentle reflux on the steam bath for 0.5 h, and then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 10 mL IPA followed by 5 mL 5% NaOH and sufficient H_2O to give a white granular character to the oxides. The reaction mixture was filtered, and the filter cake washed with THF. The filtrate was stripped of solvent under vacuum providing a pale amber oil that was distilled at 125-140 °C at 0.2 mm/Hg to give 2.5 g of an almost white oil. This was dissolved in 10 mL IPA, neutralized with 25 drops of concentrated HCl, and then diluted with 140 mL anhydrous Et_2O. There appeared, after about two minutes, white crystals of 3,6-dimethoxy-4-(2-aminopropyl)benzonorbornane hydrochloride (G-5) which, after filtration and air drying, weighed 2.47 g.



DOSAGE: 14 - 20 mg.

DURATION: 16 - 30 h.

QUALITATIVE COMMENTS: (with 15 mg) "As part of the audience at the San Francisco conference, Angels, Aliens and Archtypes, I could simply listen and observe without having to participate. Each speaker stood in a cone of light that was beautifully bright and colorful, casting everything else on the stage into obscurity. Maybe angels really are illuminated from above, and the aliens lurk out of sight until it is their turn. Where does one look for the archetypes? A half of a cream cheese sandwich was all I could eat, and even at dinner that evening I was not hungry. Sleep that evening was difficult."

(with 20 mg) "Very slow to come on, but then it was up there all of a sudden. There is an unexpected absence of visual activity despite being at a full +++. The mental activity is excellent, with easy writing and a positive flow of ideas. But an absence of the bells and whistles that are expected with a psychedelic in full bloom. There is a real drop by the 16th hour and the next day was free of effect except for occasional cat-naps."

(with 20 mg) "The transition period, which usually lasts for most compounds for the first hour or two, with this seems to be much longer. This

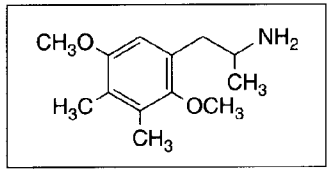
presages a long-acting material, as usually the slow-in slow-out rule applies. But there are exceptions. There is an indifference towards the erotic, but no separation at all from personal interactions and emotions. I believe in integration, not separation of all parts of ourselves, distrusting any drug states (particularly those that have the reputation of being strongly 'cosmic)' which divorce the consciousness from the body. And with this material there is no separation from feelings, only from my particular color language."

EXTENSIONS AND COMMENTARY: This is as potent as any of the three-carbon Ganesha compounds, but it somehow lacks a little something that would have made it a completely favorite winner. Perhaps it is the generally commented upon absence of visual and related sensory entertainment. There seems to be no bodily threat to discourage further exploration, but there simply was not the drive to explore it much. The comments concerning the enlargement of the ring system (mentioned under 2C-G-5) are equally valid here. The "shrubbery" that is the hallmark of the Ganesha family is, with G-5, about as bulky as has ever been put onto a centrally active molecule. The norbornane group has a one carbon bridge and a two carbon bridge sticking out of it at odd angles. The replacement of the one-carbon bridge with a second two-carbon bridge would make the compound G-6. It would be makeable, but is there really a driving reason to do so? There is a simplification intrinsic in this, in that G-5 actually has two centers of asymmetry (the α-carbon atom on the amphetamine chain, and the norbornyl area itself) and so it is really a mixture of two racemic diastereoisomers. G-6 would still be a racemate, but it would be only a single compound, as are all the other substituted amphetamine derivatives.

Someday I may try making G-6, but it's not a high priority right now.

#85 GANESHA; G; 2,5-DIMETHOXY-3,4-DIMETHYLAMPHETAMINE

SYNTHESIS: A solution of 15.4 g 2,5-dimethoxy-3,4-dimethylbenzaldehyde (see under 2C-G for the preparation) in 50 mL nitroethane was treated with 3 g anhydrous ammonium acetate and heated on the steam bath for 12 h. The excess nitroethane was removed under vacuum, and the residual oil was diluted with a equal volume of MeOH. There was the slow generation of deep red cottage-cheese-like crystals which were removed by filtration and air-dried to constant weight (9.3 g) with a mp 71-74 °C. Recrystallization from MeOH (10 ml/g) gave an analytical sample of 1-(2,5-dimethoxy-3,4-dimethylphenyl)-2-nitropropene with a mp of 82 °C sharp. Anal. ($C_{13}H_{17}NO_4$) C,H,N.



The NMR spectra (in $CDCl_3$) and CI mass spectrograph (MH+ = 252) were proper.

To a suspension of 3.3 g LAH in 200 mL refluxing THF, well stirred and maintained under an inert atmosphere, there was added 4.2 g 1-(2,5-dimethoxy-3,4-dimethylphenyl)-2-nitropropene in 25 mL THF. The mixture was held at reflux for 48 h. After cooling, 3.3 mL H_2O was added cautiously to decompose the excess hydride, followed by 3.3 mL 15% NaOH and finally another 10 mL H_2O. The inorganic solids were removed by filtration, and washed with additional THF. The combined filtrate and washes were stripped of solvent under vacuum, and the residue (4.7 g of a deep amber oil) dissolved in dilute HCl. This was washed with CH_2Cl_2 (3x75 mL), then made basic with 5% NaOH and extracted with CH_2Cl_2. Removal of the solvent under vacuum yielded an amber oil that was distilled (105-115 °C at 0.4 mm/Hg) to give 1.2 g of a white oil. This was dissolved in 8 mL IPA, neutralized with 15 drops of concentrated HCl, and diluted with 250 mL anhydrous Et_2O. After a period of time, there was a spontaneous appearance of white crystals which were removed by filtration, Et_2O washed, and air dried. Thus was obtained 1.0 g of 2,5-dimethoxy-3,4-dimethylamphetamine hydrochloride (GANESHA) with a mp of 168-169 °C. This was not improved by recrystallization from either EtOAc or nitroethane. Anal. ($C_{13}H_{22}ClNO_2$) N.

DOSAGE: 20 - 32 mg.

DURATION: 18 - 24 h.

QUALITATIVE COMMENTS: (with 24 mg) "There was a slow buildup to a ++ or more over the course of about three hours. Extremely tranquil, and no hint of any body toxicity whatsoever. More than tranquil, I was completely at peace, in a beautiful, benign, and placid place. There was something residual that extended into the sleep period, and was possibly still there in the morning. Probably I was simply tired from an inadequate sleep."

(with 32 mg) "A rapid and full development. Lying down with music, the eyes-closed visuals were quite something. There was sudden awareness of a potential toe cramp which I possibly exaggerated, but it kept spinning itself into my awareness, and somehow locked in with my visual imagery. It was not easy to keep the visual/somatic/ cognitive worlds in their proper places. The almost-cramp went away and I forgot about it. There was a back spasm somewhere in this drama, and it really didn't matter either. This dosage may be a bit much for good housekeeping, though! Towards the end of the experiment, I looked at a collection of photos from a recent trip to Europe, and the visual enhancement was wonderful. A rolling +++."

EXTENSIONS AND COMMENTARY: This compound was the seventh of the ten possible Classic Ladies. I have mentioned the concept already under the discussions on ARIADNE. This is the teutonic replacement of each of the distinguishable hydrogen atoms of DOM with a methyl group. The findings with GANESHA were

a total surprise. The extension of a hydrogen in the 3-position of DOM with a methyl group should have a minor influence on its steric association with whatever receptor site might be involved. A much greater impact might come not from the size of the group but from its location. This, coupled with a full order of magnitude of *decrease* in potency, seemed to call for an involvement of that particular position as being one that is affected by metabolism. And since the activity is decreased, the obvious role is in the blocking of the metabolic promotion of DOM-like things to active intermediates.

The remarkable point being emphasized here is that the placement of a dull methyl group at a dull position of the DOM molecule actually inactivated (for all intents and purposes) the activity of DOM. It is not the presence of the methyl that has decimated the potency, but the removal of the hydrogen atom.

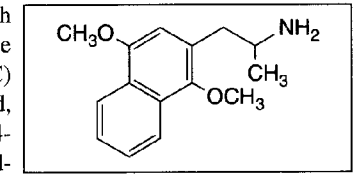
How can such a hypothesis be explored? A historic premise of the medicinal chemist is that if a structure gives an unusual response in a receptor, vary it slightly and see how the response varies. This is exactly the principle that led to the ten Classic Ladies, and with this particular Lady (who actually turned out to be a gentleman), the same concept should hold. There are two involved methyl groups in GANESHA, one at the 3-position and one at the 4-position. Why not homologate each to an ethyl group, and as a wrap up make both of them into ethyl groups. Look at the differences along two lines of variation; the effects of the homologation of the 3- and 4-positions, coupled with the effects of the homologation intrinsic in the comparison of the two-carbon chain of the phenethylamine with the three-carbon chain of the amphetamine.

There are thus six compounds involved in such a study. And they have been named (as have all the other GANESHA analogues) in accordance with the collective carbon inventory in and about these two ring positions. The first two compounds are related to DOET and to 2C-E. Maintain the methyl group at the 3-position but homologate the 4-position to an ethyl. The ring pattern would become 2,5-dimethoxy-4-ethyl-3-methyl, and the phenethylamine and amphetamine would be called 2C-G-12 and G-12 respectively (a one carbon thing, the methyl, at position-3 and a two carbon thing, an ethyl, at position-4). Reversal of these groups, the 3-ethyl homologues of 2C-D and DOM would thus become 2C-G-21 and G-21. And, finally, the diethyl homologues would be 2C-G-22 and G-22. In each of these cases, the paired numbers give the lengths of the chains at the two positions, the 3- and the 4-positions that are part of the GANESHA concept. And this code is easily expandable to longer things such as 2C-G-31 and 2C-G-41, which would be the 3-propyl-4-methyl, and the 3-butyl-4-methyl homologues, resp.

Unfortunately, these six initially proposed compounds have so far resisted all logical approaches to synthesis, and are at present still unknown. What has been successfully achieved, the building up of a big bulky hydrocarbon glob at these positions, has rather unexpectedly led to a remarkable enhancement of potency. As with all true exploration into areas of the unknown, the deeper you get, the less you understand.

#86 G-N; 1,4-DIMETHOXYNAPHTHYL-2-ISOPROPYLAMINE

SYNTHESIS: To a solution of 3.9 g 1,4-dimethoxy-2-naphthaldehyde (see under 2C-G-N for the preparation) in 13.5 mL nitroethane there was added 0.7 g anhydrous ammonium acetate, and the mixture heated on the steam bath for 5 h. The deep orange reaction mixture was stripped of excess solvent under vacuum. The residue was a red oil that, upon dilution with two volumes MeOH, immediately set to orange crystals. This crude product (mp 115-118 °C) was recrystallized from 70 mL EtOH to yield, after filtering and air drying, 3.3 g of 1-(1,4-dimethoxy-2-naphthyl)-2-nitropropene as gold-orange crystals, with a mp of 121-123 °C. Recrystallization from MeOH gave a gold-colored product with a mp of 119-120 °C. Anal. ($C_{15}H_{15}NO_4$) C,H,N.



A solution of LAH (50 mL of 1 M solution in THF) was cooled, under He, to 0 °C with an external ice-bath. With good stirring there was added 1.32 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 3.12 g 1-(1,4-dimethoxy-2-naphthyl)-2-nitropropene in 40 mL anhydrous THF. After stirring for 1 h, the temperature was brought up to a gentle reflux on the steam bath for 0.5 h, and then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 16 mL IPA followed by 6 mL 5% NaOH to give a white, filterable, granular character to the oxides, and to assure that the reaction mixture was basic. The reaction mixture was filtered, and the filter cake washed with additional THF. The combined filtrate and washes were stripped of solvent under vacuum providing 3.17 g of a deep amber oil. Without any further purification, this was distilled at 140-160 °C at 0.3 mm/Hg to give 1.25 g of a pale yellow oil. This was dissolved in 8 mL IPA, neutralized with 20 drops of concentrated HCl, and diluted with 60 mL anhydrous Et_2O which was the point at which the solution became slightly turbid. After a few min, fine white crystals began to form, and these were eventually removed, washed with Et_2O, and air dried to provide 1.28 g 1,4-dimethoxynaphthyl-2-isopropylamine hydrochloride (G-N) as the monohydrate salt. The mp was 205-206 °C. Even after 24 h drying at 100 °C under vacuum, the hydrate salt remained intact. Anal. ($C_{15}H_{20}ClNO_2 \cdot H_2O$) C,H.

DOSAGE: unknown.

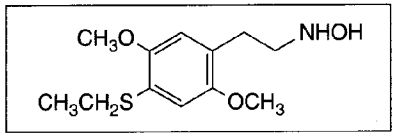
DURATION: unknown,

EXTENTIONS AND COMMENTARY: The evaluation of this compound is not yet complete. An initial trial at the 2 milligram level showed neither central action, nor toxicity. It could be guessed from the activity of the two-carbon counterpart, that an active level will be found in the tens of milligrams area. But, as of the moment, this level is not known to anyone, anywhere, because no one has yet

defined it. And when the potency is finally found out, the nature of the activity will also have been found out, all the result of a magical interaction of a virgin compound with a virgin psyche. At the immediate moment, the nature of G-N is not only unknown, it has not yet even been sculpted. There can be no more exciting area of research than this, anywhere in the sentient world.

#87 HOT-2; 2,5-DIMETHOXY-4-ETHYLTHIO-N-HYDROXYPHENETHYLAMINE

SYNTHESIS: A solution of 5.50 g 2,5-dimethoxy-4-ethylthio-ß-nitrostyrene (see under 2C-T-2 for its preparation) was made in 80 mL boiling anhydrous THF. On cooling, there was some separation of a fine crystalline phase, which was kept dispersed by continuous stirring. Under an inert atmosphere there was added 3.5 mL of a 10 M borane dimethylsulfide complex, followed by 0.5 g sodium borohydride as a solid. There was a slight exothermic response, and the color slowly faded. Stirring was continued for a week. There was then added 40 mL H_2O and 20 mL concentrated HCl, and the reaction mixture heated on the steam bath for 15 minutes, with the THF at reflux. After cooling again to room temperature, all was poured into 1 L H_2O and washed with 3x75 mL CH_2Cl_2, which removed all of the color but little of the product. The aqueous phase was made basic with 25% NaOH, and extracted with 3x75 mL CH_2Cl_2. The extracts were pooled and the solvent removed under vacuum to give a residue of 3.88 g of an amber oil. This was dissolved in 30 mL IPA, acidified with concentrated HCL to a bright red on universal pH paper, and then diluted with 200 mL anhydrous Et_2O. After a short period of time, crystals started to form. These were removed by filtration, washed with Et_2O, and air dried to constant weight. Thus was obtained 2.86 g 2,5-dimethoxy-4-ethylthio-N-hydroxyphenethylamine hydrochloride (HOT-2) as off-white crystals, with a melting point of 122 °C with decomposition. Anal. ($C_{12}H_{20}ClNO_3S$) H; C: calcd, 49.05; found, 50.15, 49.90.



DOSAGE: 10 - 18 mg.

DURATION: 6 - 10 h.

QUALITATIVE COMMENTS: (with 12 mg) "Tastes OK. Some activity noticed in 30 minutes. Very smooth rise with no body load for next two hours. At that time I noted some visuals. Very pleasant. The bright spots in the painting over the fireplace seemed to be moving backwards (as if the clouds were moving in the painting). Upon concentrating on any item, there was perceptual movement with a little flowing aspect. The visuals were never all that strong, but could not be turned off during the peak. At hour three there was still some shimmering, and it was hard to focus when reading. Additionally, there was difficulty concentrating (some mental confusion). The material seemed to allow erotic actions; there was no problem about obtaining an erection. I ate very well, some crazy dips, as well as a fabulous cake. A very gentle down trend and I became close to baseline by 6 or 7 PM. I had no trouble driving. The dosage was good for me. I did not want more or less."

(with 12 mg) "Comes on smoothly, nicely. In 40 minutes I feel nice euphoria, feel home again. Then I begin to get uncomfortable feelings. Gets more and more uncomfortable, feel I am sitting on a big problem. Blood pressure, pulse, go up considerably. Have hard time communicating, lie down for a while, get insight that most important thing for me to do is learn to listen, pay attention to what is going on. I do this the rest of the day, at first with considerable difficulty, then easier and easier. Discomfort stays with me for several hours, and although I get more comfortable towards the end of the day, I am never animated or euphoric. I feel very humbled, that I have a great deal to work out in my life. The next day I find myself very strong and empowered. I see that all I have to do is let things be as they are! This feels marvelous, and a whole new way to be — much more relaxed, accepting, being in the moment. No more axes to grind. I can be free."

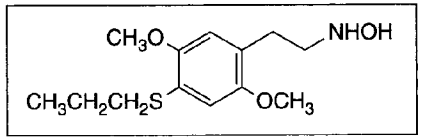
(with 18 mg) "I found myself with complete energy. I was completely centered with an absolute minimum of the dark edges that so often appear as components of these experiences. The ease of talking was remarkable. There was some blood-pressure run-up in the early part of the day, but that quickly returned to normal. I would repeat without hesitation."

EXTENSIONS AND COMMENTARY: Again, a case of where the potency range of the "hot," or hydroxylated compound (HOT-2, 10 to 18 milligrams) is very similar to that of the non-hydroxylated prototype (2C-T-2, 12-25 milligrams). It seems to be a well tolerated, and generally pleasant material, with a mixture of sensory as well as insightful aspects. Something for everyone.

#88 HOT-7; 2,5-DIMETHOXY-N-HYDROXY-4-(n)-PROPYLTHIOPHENETHYLAMINE

SYNTHESIS: A well-stirred solution of 1.77 g 2,5-dimethoxy-ß-nitro-4-(n-propylthio)styrene (see under 2C-T-7 for its preparation) in 20 mL anhydrous THF was placed in an He atmosphere and treated with 1.5 mL of 10 M borane-dimethyl sulfide complex. This was followed by the addition of 0.2 g sodium borohydride, and the stirring was continued at room temperature for a week. The volatiles were removed under vacuum, and the residue was treated with 20 mL dilute HCl and

heated on the steam bath for 30 min. The cooled yellow solution set up as solids. The addition of H_2O was followed by sufficient K_2CO_3 to make the aqueous phase basic. All efforts to work with an acidified aqueous phase resulted in terrible emulsions. The basic phase was extracted with 3x75 mL CH_2Cl_2, and the pooled extracts washed with H_2O, then stripped of solvent under vacuum. The residual yellow oil was dissolved in 20 mL IPA, neutralized with 15 drops of concentrated HCl, and then diluted with 50 mL anhydrous Et_2O. After a few minutes stirring, a white crystalline solid separated. This was removed by filtration, washed with Et_2O, and air dried to constant weight to provide 0.83 g of 2,5-dimethoxy-N-hydroxy-4-(n)-propylthiophenethylamine hydrochloride (HOT-7).



DOSAGE: 15 - 25 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 15 mg) "I am lightheaded, and maybe a little tipsy. I am well centered, but I don't want to go outside and meet people. Shades of alcohol woozy. The effects were going already by the fifth hour and were gone by the seventh hour. I would call it smoothly stoning."

(with 22 mg) "The transition into the effects was a bit difficult, with a faint awareness in the tummy. But by the second hour it was quite psychedelic, and the body was not thought of again, except in terms of sexual fooling around. Very rich in eyes-closed imagery, and very good for interpretive and conceptual thinking. But the eyes-open visuals were not as much as they might have been. At the seventh hour, drifted into an easy sleep."

(with 22 mg) "The experience was very positive, but at each turn there seemed to be a bit of sadness. Was it a complete plus three experience? Not quite. But it didn't miss by much. The erotic explorations somehow just failed to knit by the thinnest of margins. It was a truly almost-magnificent experience."

EXTENSIONS AND COMMENTARY: There is a working hypothesis that has been growing in substance over the last few years in this strange and marvelous area of psychedelic drugs. It all was an outgrowth of the rather remarkable coincidence that I had mentioned in the discussion that followed MDOH. There, an assay of what was thought to be MDOH gave a measure of activity that was substantially identical to MDA, and it was later found out that the material had decomposed to form MDA. So, MDA was in essence rediscovered. But when the true, valid, and undecomposed sample of MDOH was actually in hand, and assayed in its own rights, it was found to have a potency that really was the same as MDA. So, the working hypothesis goes something like this:

AN N-HYDROXY AMINE HAS APPROXIMATELY THE SAME POTENCY AND THE SAME ACTION AS ITS N-HYDROGEN COUNTERPART.

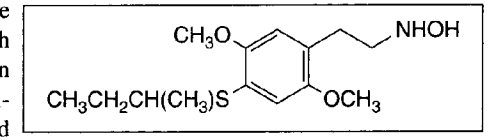
Maybe the N-hydroxy compound reduces to the N-H material in the body, and the latter is the intrinsically active agent. Maybe the N-H material oxidizes to the N-hydroxy material in the body, and the latter is the intrinsically active agent. Either direction is reasonable, and there is precedent for each. The equivalence of MDA and MDOH was the first suggestion of this. And I have made a number of NH vs. NOH challenges of this hypothesis. The interesting 2C-T-X series has provided a number of amines that are amenable to N-hydroxylation, and this is the first of them. And, after all, if you put a hydroxy (HO) group on a thio material (T), you have a HOT compound.

So, as far as nomenclature is concerned, the family of N-hydroxy analogues of N-H amines is known as the HOT family.

How does HOT-7 compare with 2C-T-7? They are almost identical. The same range of dose (centering on 20 milligrams) and if anything, perhaps slightly less long lived. Lets try some other N-hydroxys!

#89 HOT-17; 2,5-DIMETHOXY-4-(s)-BUTYLTHIO-N-HYDROXYPHENETHYLAMINE

SYNTHESIS: To a well-stirred solution of 6.08 g 2,5-dimethoxy-4-(s)-butylthio-ß-nitrostyrene (see under 2C-T-17 for its preparation) in 80 mL anhydrous THF under a He atmosphere, there was added 3.5 mL 10 M borane dimethylsulfide complex, followed by 0.5 g of sodium borohydride. As the stirring continued, the slightly exothermic reaction slowly faded from bright yellow to pale yellow, and eventually (after three days stirring) it was substantially colorless. There was then added 80 mL of 3 N HCl and the mixture heated on the steam bath for 1 h, and then allowed to return to room temperature. An additional 600 mL H_2O was added (there was a combination of crystals and globby chunks in the aqueous phase) and this was then extracted with 3x75 mL CH_2Cl_2. The color went completely into the organic phase. This was washed with 2x50 mL aqueous K_2CO_3, yielding a rusty-red colored CH_2Cl_2 solution, which on removal of the solvent, yielded 4.5 g of a red oil. A side effort to make the sulfate salt at this stage with H_2O and a little H_2SO_4, indeed gave solids, but all of the color remained in the sulfate salt. The red oil was dissolved in 45 mL IPA and neutralized with concentrated HCl to bright red, not yellow, on universal pH paper. The addition of 350 mL anhydrous Et_2O instituted the slow precipitation of white crystals. After filtering and air drying, there was



obtained 1.32 g 2,5-dimethoxy-4-(s)-butylthio-N-hydroxyphenethylamine hydrochloride (HOT-17). The aqueous phase from above was just neutralized with 25% NaOH (cloudy, slightly pink color) and then made basic with K_2CO_3 (the color becomes green). This was extracted with 3x75 mL CH_2Cl_2, the extracts pooled, and the solvent removed to yield 0.5 g of a white oil. This was dissolved in 5 mL IPA, neutralized with concentrated HCl, and diluted with a equal volume of Et_2O. An additional 0.36 g of product was thus obtained.

DOSAGE: 70 - 120 mg.

DURATION : 12 - 18 h.

QUALITATIVE COMMENTS: (with 70 mg) "There was a light feeling, a little off-the-ground feeling, which made walking about a most pleasant experience. No distortion of the senses. And there was no sense of the beginning of a drop of any kind until about the eighth hour. Sleeping was a bit tricky but it worked out OK (at the twelfth hour of the experience). A completely valid ++."

(with 120 mg) "HOT-17 has an unbelievably GRIM taste — not bitter, but simply evil. There is a steady and inexorable climb for three hours to a sound and rolling plus three. There was absolutely no body difficulty, but there was still something going on upstairs well into the next day. Writing was surprisingly easy; I was completely content with the day, and would be interested in exploring it under a variety of circumstances."

(with 120 mg) "This is my first time with this material. It is 4:45 PM. Small nudge at 30 minutes, but not too real. At one hour, threshold, quite real. 6:15 to a +1. By 7:25, +3 about. 7:45, no doubt +3. Possibly still climbing; I hope so. No body discomfort at all, no apparent body push. This aspect of it is similar to the easy body of the HOT-2. However, it's at times like these that I reflect on just exactly how hard-headed we two are. I mean, +3 is no longer the out-of-body, nearly loss of center state it used to be, four years ago. The question intrudes: would a novice experience this as a very scary, ego-disintegrating kind of experiment, or not? Silly question which answers itself. Yes, of course. At 3 hours, aware of some mild time-distortion. More a tendency to not think in terms of clock-time, than actual distortion. The mind lazy when attempting to keep track of clock time. Feel it would be quite easy and pleasant to continue writing. The energy could very well go in that direction. However, the idea of the erotic is also quite agreeable. This is, so far, a good-humored Buddha area of the self."

EXTENSIONS AND COMMENTARY: Two virtues sought by some users of psychedelic drugs are high intensity and brief action. They want a quicky. Something that is really effective for a short period of time, then lets you quickly return to baseline, and presumably back to the real world out there.

Intensity is often (but not always) regulated by dose. The pharmacological

property of dose-dependency applies to many of these drugs, in that the more you take, the more you get. If you want more intensity, take a second pill. And often, you get a longer duration as an added property. But it is instructive to inquire into the rationale that promotes brevity as a virtue. I believe that it says something concerning the reasons for using a psychedelic drug. A trade off between learning and entertainment. Or between the achieving of something and the appearance of achieving something. Or, in the concepts of the classics, between substance and image.

In a word, many people truly believe that they cannot afford the time or energy required for a deep search into themselves. One has to make a living, one has to maintain a social life, one has a multitude of obligations that truly consume the oh-so-few hours in the day. I simply cannot afford to take a day off just to indulge myself in such-and-such (choose one: digging to the bottom of a complex concept, giving my energies to those whom I can help, to search out my inner strengths and weaknesses) so instead I shall simply do such-and-such (choose one: read the book review, go to church on Sunday morning, use a short-acting psychedelic). The world is too much with us. This may be a bit harsh, but there is some merit to it.

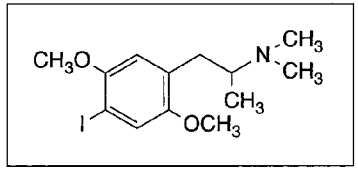
HOT-17 is by no means a particularly potent compound. The hundred milligram area actually has been the kiss of death to several materials, as it is often at these levels that some physical concerns become evident. And it certainly is not a short lived compound. But, as has been so often the case, the long lived materials have proven to be the most memorable, in that once the entertainment aspect of the experience is past you, there is time for dipping deeply into the rich areas of the thought process, and the working through of ideas and concepts that are easily available. And when this access is coupled to the capability of talking and writing, then a rewarding experience is often the result.

As with the parent compound, 2C-T-17 itself, the presence of an asymmetric carbon atom out there on the (s)-butyl side chain will allow the separation of HOT-17 into two components which will be different and distinct in their actions. The activity of the racemic mixture often is an amalgamation of both sets of properties, and the separate assay of each component can often result in a fascinating and unexpected fractionation of these properties.

#90 IDNNA; 2,5-DIMETHOXY-N,N-DIMETHYL-4-IODOAMPHETAMINE

SYNTHESIS: To a stirred solution of 0.4 g 2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) in 12 mL MeOH containing 4 mL of a 40% formaldehyde solution there was added 1 g sodium cyanoborohydride. The pH was kept at about 6 by the occasional addition of HCl. When the pH was stable (about 48 h) the reaction mixture was poured into 250 mL H_2O and made strongly basic by the

addition of aqueous NaOH. This was extracted with 3x75 mL CH_2Cl_2, the extracts pooled, and extracted with 2x75 mL dilute H_2SO_4, and the pooled acidic extracts again made basic and again extracted with CH_2Cl_2. The solvent was removed under vacuum to give 0.38 g of a colorless oil. This was dissolved in 2 mL IPA and treated with a solution of 0.13 g oxalic acid dihydrate in 1.5 mL warm IPA, and then anhydrous Et_2O was added dropwise until a turbidity persisted. Slowly a granular white solid appeared, which was filtered off, Et_2O washed, and air dried to give 0.38 g of 2,5-dimethoxy-N,N-dimethyl-4-iodoamphetamine oxalate (IDNNA) with a mp of 145-146 °C. Anal. ($C_{15}H_{22}INO_6$) C,H. The hydrochloride salt of this base proved to be hygroscopic.



DOSAGE: greater than 2.6 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: This base, if it were given a code name based upon its substituents arranged in their proper alphabetical order, would have to be called something like DNDIA, which is quite unpronounceable. But by a rearrangement of these terms, one can achieve IDNNA (Iodo-Dimethoxy-N,N-dimethyl-Amphetamine) which has a nice lilt to it.

One of the major goals of research in nuclear medicine is a drug that can be used to demonstrate the brain blood flow pattern. To do this job, a drug should demonstrate four properties. First, it must carry a radioactive isotope that is a positron emitter (best, a fluorine or an iodine atom, for use with the positron camera) that can be put onto the molecule quickly, synthetically, and which will stay on the molecule, metabolically. Second, as to brain entry, the drug should be rapidly and extensively taken up by brain tissue, without being selectively absorbed or concentrated at any specific sites. In other words, it should go where the blood goes. Thirdly, the absorption should be strong enough that it will stay in the brain, and not be washed out quickly. This allows time to both locate and count the radioactivity that was carried in there. And lastly, the drug must be without pharmacological action.

IDNNA looked like a promising candidate when tried with a radioactive iodine label, and there was quite a flurry of interest in using it both as an experimental drug, and as a prototype material for the synthesis of structural variants. It went in quickly, extensively and quite diffusely, and it stayed in for a long time.

But was it pharmacologically active? Here one finds a tricky road to walk. The animal toxicity and behavioral properties can be determined in a straightforward manner. Inject increasing amounts into an experimental animal and observe him closely. IDNNA was quite inert. But, it is a very close analogue to the extremely

potent psychedelic DOI, and it is widely admitted that animal assays are of no use in trying to determine this specific pharmacological property. So, a quiet human assay was called for. Since it did indeed go into the brain of experimental animals, it could quite likely go into the brain of man. In fact, that would be a needed property if the drug were to ever become useful as a diagnostic tool.

It was assayed up to levels where DOI would have been active, and no activity was found. So one could state that it had none of the psychedelic properties of DOI at levels where DOI would be active (this, at 2.6 milligrams orally). But you don't assay much higher, because sooner or later, something might indeed show up. So it can be honestly said, IDNNA is less active than DOI itself, in man. Let's wave our hands a bit, and make our statement with aggressive confidence. IDNNA has shown no activity in the human CNS at any level that has been evaluated. This sounds pretty good. Just don't go too far up there, and don't look too carefully. This is not as unscrupulous as it might sound since, in practical terms, the extremely high specific activities of the radioactive ^{122}I that would be used, would dictate that only an extremely small amount of the drug would be required. One would be dealing, not with milligram quantities, but with microgram quantities, or less.

Some fifteen close analogues of IDNNA were prepared, to see if any had a better balance of biological properties. A valuable intermediate was an iodinated ketone that could be used either to synthesize IDNNA itself or, if it were to be made radio-labelled, it would allow the preparation of any desired radioactive analogue in a single synthetic step. The iodination of p-dimethoxybenzene with iodine monochloride in acetic acid gave 2,5-diiodo-1,4-dimethoxybenzene as white crystals from acetonitrile, with a mp of 167-168 °C. Anal. ($C_8H_8I_2O_2$) C,H. Treatment of this with an equivalent of butyllithium in ether, followed with N-methyl formanilide, gave 2,5-dimethoxy-4-iodobenzaldehyde as pale yellow crystals from ethanol, with a mp of 136-137 °C. Anal. ($C_9H_9IO_3$) C,H. This, in solution in nitroethane with a small amount of anhydrous ammonium acetate, gave the nitrostyrene 1-(2,5-dimethoxy-4-iodophenyl)-2-nitropropene as gold-colored crystals from methanol, mp 119-120 °C. Anal. ($C_{11}H_{12}INO_4$) C,H. This was smoothly reduced with elemental iron in acetic acid to give 2,5-dimethoxy-4-iodophenylacetone as white crystals from methylcyclopentane. These melted at 62-63 °C and were both spectroscopically and analytically correct. Anal. ($C_{11}H_{13}IO_3$) C,H.

This intermediate, when reductively aminated with dimethylamine, gives IDNNA identical in all respects to the product from the dimethylation of DOI above. But it has also been reacted with ^{131}I NaI in acetic acid at 140 °C for 10 min, giving the radioactive compound by exchange, and this was reductively aminated with over a dozen amines to give radioactive products for animal assay. There was produced in this way, 2,5-dimethoxy-4-iodo-N-alkyl-amphetamine where the alkyl group was methyl, isopropyl, cyclopropylmethyl, hexyl, dodecyl, benzyl, cyanomethyl, and 3-(dimethylaminopropyl). Several dialkyl homologue were made, with the alkyl groups being dimethyl (IDNNA itself), diethyl, isopropyl-methyl, and benzyl-methyl. These specific homologues and analogues are tallied

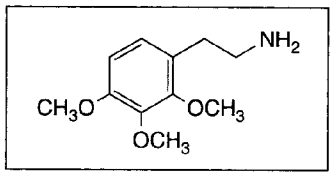
in the index, but a number of other things, such as hydrazine or hydroxylamine derivatives, were either too impure or made in amounts too small to be valid, and they are ignored.

The diethyl compound without the iodine is 2,5-dimethoxy-N,N-diethylamphetamine, which was prepared by the reductive alkylation of DMA with acetaldehyde and sodium cyanoborohydride. This product, DEDMA, was a clear white oil, bp 82-92 °C at 0.15 mm/Hg which did not form a crystalline hydrochloride. An interesting measure of just how different these N,N-dialkylated homologues can be from the psychedelic primary amines, pharmacologically, can be seen in the published report that the beta-hydroxy derivative of DEDMA is an antitussive, with a potency the same as codeine.

None of these many iodinated IDNNA analogues showed themselves to be superior to IDNNA itself, in the rat model, and none of them have been tasted for their psychedelic potential in man.

#91 IM; ISOMESCALINE; 2,3,4-TRIMETHOXY-PHENETHYLAMINE

SYNTHESIS: A solution of 8.0 g 2,3,4-trimethoxybenzaldehyde in 125 mL nitromethane containing 1.4 g anhydrous ammonium acetate was held at reflux for 1.5 h. The conversion of the aldehyde to the nitrostyrene was optimum at this time, with a minimum development of a slow-moving spot as seen by thin layer chromatography on silica gel plates using $CHCl_3$ as a developing solvent; the Rf of the aldehyde was 0.31 and the Rf of the nitrostyrene was 0.61. The excess nitromethane was removed under vacuum, and the residue was dissolved in 20 mL hot MeOH. On cooling, the yellow crystals that formed were removed by filtration, washed with cold MeOH and air dried yielding 4.7 g yellow crystals of 2,3,4-trimethoxy-ß-nitrostyrene, with a mp of 73-74 °C. From the mother liquors, a second crop of 1.2 g was obtained.



A solution of 4.0 g LAH in 80 mL THF under He was cooled to 0 °C and vigorously stirred. There was added, dropwise, 2.7 mL of 100% H_2SO_4, followed by a solution of 4.7 g 2,3,4-trimethoxy-ß-nitrostyrene in 40 mL anhydrous THF. The mixture was stirred at 0 °C for 1 h, at room temperature for 1 h, and then brought briefly to a reflux on the steam bath. After cooling again, the excess hydride was destroyed with 4.7 mL H_2O in THF, followed by the addition of 18.8 mL 15% NaOH which was sufficient to convert the solids to a white and granular form. These were removed by filtration, the filter cake washed with THF, the mother liquor and filtrates combined, and the solvent removed under vacuum. The residue was added to dilute H_2SO_4, and washed with 2x75 mL CH_2Cl_2. The aqueous phase was made basic with 25% NaOH, and extracted with 2x50 mL CH_2Cl_2. The solvent was removed from these pooled extracts and the amber-colored residue distilled at 95-100 °C at 0.3 mm/Hg to provide 2.8 g of 2,3,4-trimethoxyphenethylamine as a white oil. This was dissolved in 20 mL IPA, neutralized with about 1 mL concentrated HCl, and diluted with 60 mL anhydrous Et_2O. After filtering, Et_2O-washing, and air drying, there was obtained 3.2 g of 2,3,4-trimethoxyphenethylamine hydrochloride (IM) as a white crystalline product.

DOSAGE: greater than 400 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 300 mg) "No effects whatsoever."
(with 400 mg) "Maybe a slight tingle at the hour-and-a-half point. Maybe not. Certainly nothing an hour later. Put this down as being without action."

EXTENSIONS AND COMMENTARY: Some fifty years ago this material was given the name "reciprocal mescaline" in that it was believed to exacerbate the clinical symptoms in schizophrenic patients. In the original report, one finds: "Thus we have discovered an extremely remarkable dependency of the intoxicating action upon the position of the three methoxy groups. Mescaline, the 3,4,5-trimethoxy-ß-phenethylamine, produces in the normal subject a much stronger over-all intoxication than in the schizophrenic patient, whereas 2,3,4-trimethoxy-ß-phenethylamine has quite the opposite effect. It has little action in healthy individuals, being almost without intoxicating properties, but it is very potent in the schizophrenic. The metabolic conversion products of the "reciprocal" mescaline will be further studied as soon as the study of the metabolism of the proper mescaline is complete."

This is a pretty rich offering, and one that the present medical community has no qualms about discarding. At the bookkeeping level, the promised further studies have never appeared, so all may be forgotten as far as potential new discoveries might be concerned.

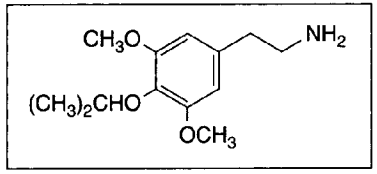
One recent related study has been reported, tying together isomescaline and schizophrenia. Through the use of radioactive labelling, the extent of demethylation (the metabolic removal of the methyl groups from the methoxyls) was determined in both schizophrenic patients and normal subjects. When there was a loading of the person with methionine (an amino acid that is the principal source of the body's methyl groups), the schizophrenics appeared to show a lesser amount of demethylation.

But might either of these two observations lead to a diagnostic test for schizophrenia? At the present time, the conventional thinking is that this probably cannot be. The illness has such social and genetic contributions, that no simple measure of a response to an almost-psychedelic, or minor shift of some urinary metabolite pattern could possibly be believed. No independent confirmation of

these properties has been reported. But maybe these findings are valid. A major problem in following these leads does not involve any complex research protocols. What must be addressed are the present regulatory restrictions and the Federal law structure. And these are formidable obstacles.

#92 IP; ISOPROSCALINE; 3,5-DIMETHOXY-4-(i)-PROPOXY-PHENETHYLAMINE

SYNTHESIS: A solution of 5.8 g of homosyringonitrile (see under ESCALINE for its preparation) and 13.6 g isopropyl iodide in 50 mL dry acetone was treated with 6.9 g finely powdered anhydrous K_2CO_3 and held at reflux on the steam bath. After 6 h another 5 mL of isopropyl iodide was added, and refluxing continued for an additional 12 h. The mixture was filtered and the solids washed with acetone. The mother liquor and washes were stripped of solvent under vacuum, The residue was taken up in dilute HCl, and extracted with 3x100 mL CH_2Cl_2. The pooled extracts (they were quite deeply yellow colored) were washed with 2x75 mL 5% NaOH, and finally once with dilute HCl. Removal of the solvent under vacuum yielded 9.8 g of an amber oil, which on distillation at 125-135 °C at 0.3 mm/Hg provided 6.0 g of 3,5-dimethoxy-4-(i)-propoxyphenylacetonitrile as a pale yellow oil. A pure reference sample is a white solid with a mp of 33-34 °C. Anal. ($C_{13}H_{17}NO_3$) C,H,N.



A solution of AH was prepared by the cautious addition of 0.84 mL of 100% H_2SO_4 to 32 mL of 1.0 M LAH in THF, which was being vigorously stirred under He at ice-bath temperature. A solution of 5.93 g of 3,5-dimethoxy-4-(i)-propoxyphenylacetonitrile in 10 mL anhydrous THF was added dropwise. Stirring was continued for 30 min, then the reaction mixture was brought up to reflux on the steam bath for another 30 min. After cooling again to room temperature, 5 mL IPA was added to destroy the excess hydride, followed by about 10 mL of 15% NaOH, sufficient to make the aluminum salts loose, white, and filterable. The reaction mixture was filtered, the filter cake washed with IPA, the mother liquor and washes combined, and the solvent removed under vacuum. The residue (7.0 g of an amber oil) was dissolved in dilute H_2SO_4 and washed with 3x75 mL CH_2Cl_2. The aqueous phase was made basic with aqueous NaOH, and the product extracted with 3x75 mL CH_2Cl_2. The extracts were evaporated to a residue under vacuum, and this was distilled at 125-140 °C at 0.3 mm/Hg yielding 3.7 g of a colorless oil. This was dissolved in 15 mL IPA, neutralized with 50 drops of concentrated HCl which allowed the deposition of a white crystalline product. Dilution with anhydrous Et_2O and filtration gave 3.7 g. of 3,5-dimethoxy-4-(i)-propoxyphenethylamine hydrochloride (IP) with a mp of 163-164 °C. Anal. ($C_{13}H_{22}ClNO_3$) C,H,N. The catalytic

hydrogenation process for reducing the nitrile that gives rise to escaline, also works with this material.

DOSAGE: 40 - 80 mg.

DURATION: 10 - 16 h.

QUALITATIVE COMMENTS: (with 75 mg) "Starts slowly. I develop some queasiness, turning into nausea. Feels good to lie down and let go, but the uneasiness remains. Just beginning to break through in 2 hours. But the occasional sense of relief, the breaking into the open, were transient as new sources of discomfort were always being dredged up. Then for some reason I chose to dance. Letting go to dancing, a marvelous ecstatic experience, flowing with and being the energy, body feeling completely free. Noticing how this letting go got one completely out of the feeling of unease, as though attention simply needs to be put elsewhere. Comedown was very slow, gentle, euphoric; a very signicant experience. Sleep that night was impossible, but felt good to simply release to the feelings. Keeping mind still, no thinking, just allowing feelings to go where they wished, became more and more ecstatic. Tremendous feeling of confidence in life and the life process. Complete sense of resolution."

(with 80 mg) "It took about two hours for the body to settle down. Emotions were true and well felt, a fact that is an all-important thing to me as it probably is to everyone else I know in this kind of exploration. Any sense that there is a dulling of the feeling and emotional area of the self is a negative, to be watched and noted as are other things such as disturbed sleep, unpleasant dreams, or irritability or depression the next day. I was interacting with others with a great deal of intensity. People found themselves wandering inside and out, listening to music, stirring soup, eating a bit and enjoying eating, talking, laughing a great deal, and being silent in great contentment. It's not a very silent material, though. Talking is too enjoyable. There was a slight descent noted at 6-7 hours, but very gentle and smooth. Slow and pleasant descent until about 12th hour, when sleep was attempted. Next day, everyone slightly irritable but good mood anyway. The next night I slept deeply and well, and awoke whole and in excellent mood."

EXTENSIONS AND COMMENTARY: These two excerpts give the color and complexity of IP. It has proven to be a completely fascinating phenethylamine. And, as with all the phenethylamines, there is an amphetamine that corresponds to it. This would be 3,5-dimethoxy-4-isopropoxyamphetamine, or 3C-IP. The preparation of it would require access through the O-isopropoxylation product with syringaldehyde, followed by nitrostyrene formation with nitroethane, followed by reduction probably with lithium aluminum hydride. It has not been synthesized, as far as I know, and so it has probably not been evaluated in man. What would be the active level? It would probably be more potent than IP, but I would guess not by

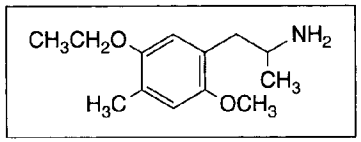
much. Maybe in the 30 milligram area.

A moment's aside for a couple of the words that are so much a part of the chemist's jargon. Room temperature, as used above, means the natural temperature that something comes to if it is put on the table and is neither heated nor cooled. The phrase, I discovered during my year at Gif, is completely un-understandable in French. A room has no temperature. Only things in rooms have temperatures. Their expression is more exact. The object achieves, in the French terminology, a *temperature normale d'interieur*, or about 15 to 16 °C. But in common laboratory parlance it has become the *temperature d'ambiance*.

And one finds the prefix "iso" used everywhere. Considerable care should be taken in the two different uses of the prefix "iso" in the nomenclature with the mescaline analogues. In general, the term "iso" means the other one of two possibilities. If you are allowed to paint a house only with green paint or red paint, and green is the color you actually use, then red could be called iso-green. With isoproscaline (here) there is a rearranging of the propyl group on the 4-oxygen of mescaline. It has been replaced with its branched analogue, the other of two possibilities, the isopropyl group. Everything is still with the 3,4,5-orientation on the benzene ring. However, with IM (isomescaline) there is a rearrangement of substitution pattern on the benzene ring, with the repositioning of the trimethoxyl substitution pattern from the 3,4,5- arrangement to the 2,3,4- arrangement. It has been the side-chain that has taken the other of two possible positions. The term "iso" must always be interpreted in precise context.

#93 IRIS; 5-ETHOXY-2-METHOXY-4-METHYLAMPHETAMINE

SYNTHESIS: To a solution of 9.5 g flaked KOH (10% excess) in 500 mL 95% EtOH there was added 20.4 g 4-methoxy-2-methylphenol (see under 2C-D for its preparation). This was followed with 23.5 g ethyl iodide, and the mixture was held at reflux overnight. The solvent was removed under vacuum and the residue suspended in 250 mL H_2O. This was made strongly basic with NaOH and extracted with 3x50 mL CH_2Cl_2. Removal of the solvent gave 15.75 g of 2-ethoxy-5-methoxytoluene as an amber oil, which was used in the following step without further purification. Acidification of the aqueous phase followed by CH_2Cl_2 extraction gave, after removal of the solvent, crude recovered starting phenol as a dark brown crystalline solid. The reasonably pure phenol was best isolated by sequential extractions with portions of 80 °C H_2O which, on cooling, deposited the phenol as white crystals.



A mixture of 38 mL $POCl_3$ and 43 mL N-methylformanilide was allowed to incubate for 1 h and then there was added to it 15.7 g 2-ethoxy-5-methoxytoluene.

This was heated in the steam bath for 2 h, then poured into 1 L H_2O and allowed to stir overnight. The solids that formed were removed by filtration and H_2O washed, giving 20.7 g of a crude, amber product. This was extracted with 2x150 mL boiling hexane which gave crystals on cooling. These were filtered and hexane washed, giving 12.85 g of 5-ethoxy-2-methoxy-4-methylbenzaldehyde as pale cream-colored solids with a mp of 75-76 °C. Recrystallization of an analytical sample from EtOH two times gave a product with a white color, and a mp of 81-82 °C.

To a solution of 11.35 g 5-ethoxy-2-methoxy-4-methylbenzaldehyde in 48 mL glacial acetic acid containing 4 g anhydrous ammonium acetate there was added 10 mL nitroethane, and the mixture heated on the steam bath for 2 h. Standing at room temperature overnight allowed a heavy crop of brilliant crystals to deposit. These were removed by filtration, washed cautiously with acetic acid, and air dried to give 8.6 g 1-(5-ethoxy-2-methoxy-4-methylphenyl)-2-nitropropene with a mp of 118-120 °C. Recrystallization of all from 200 mL boiling MeOH gave 8.3 g of lustrous crystals with a mp of 121-122 °C.

To a gently refluxing suspension of 6.4 g LAH in 500 mL anhydrous Et_2O under a He atmosphere, there was added 8.1 g 1-(5-ethoxy-2-methoxy-4-methylphenyl)-2-nitropropene by allowing the condensing ether to drip into a shunted Soxhlet thimble containing the nitrostyrene. This effectively added a warm saturated solution of the nitrostyrene dropwise. Refluxing was maintained overnight, and the cooled reaction flask stirred for several additional days. The excess hydride was destroyed by the cautious addition of 400 mL H_2O containing 40 g H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated, and 160 g of potassium sodium tartrate was dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was >9, and this was then extracted with 3x50 mL CH_2Cl_2. Evaporation of the solvent under vacuum produced an oil that was dissolved in anhydrous Et_2O and saturated with anhydrous HCl gas. There appeared 5-ethoxy-2-methoxy-4-methylamphetamine hydrochloride (IRIS) as fine white crystals. These weighed, after filtration, Et_2O washing, and air drying to constant weight, 5.3 g and had a mp of 192-193 °C. Recrystallization of an analytical sample from boiling CH_3CN gave lustrous crystals with a mp of 196-197 °C with decomposition.

DOSAGE: greater than 9 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 7.5 mg) "At about three hours I felt that I was at threshold, but an hour later there was nothing."

(with 9 mg) "Maybe a little light headed? Maybe not. Little effect if any."

EXTENSIONS AND COMMENTARY: This is one of the ten Classic Ladies, the ten possible homologues of DOM, which I had discussed under ARIADNE (the first

of the Ladies). The active level is unknown, but it is higher than 9 milligrams (the highest dose tried) and since DOM itself would have been smashingly active at this level, it is obvious that IRIS is a homologue with decreased potency.

This lack of activity brings up a fascinating point. I have referred to a drug's action on the mind, quite frequently in these notes, with the phrase "reasonably complex." By that, I do not mean that a drug's action simply shows many facets, and if these were to be tallied, the drug-mind interaction would become clear. There is quite a bit of importance intrinsically implied by the term, complex. Simple things, as we have come to appreciate and depend upon them in our day-to-day living, can have simple explanations. By this, I mean explanations that are both completely satisfactory and satisfactorily complete. Answers that have all the earmarks of being correct. What is the sum of two plus three, you ask? Let's try five. And for most of our needs, five is both factual and complete.

But some years ago, a mathematician named Gödel devised a proof for a theorem that anything that is reasonably complex cannot enjoy this luxury (I believe he used the word "interesting" rather than reasonably complex). If your collection of information is factual, it cannot be entirely complete. And if it is complete, it cannot be entirely factual. In short, we will never know, we cannot ever know, every fact that constitutes an explanation of something. A complete book of knowledge must contain errors, and an error-free book of knowledge must be incomplete.

There is a small warning light deep inside me that starts flashing any time I hear someone begin to advance an explanation of some reasonably complex phenomenon with an air of confidence that implies, "Here is how it works." What the speaker usually has is an intense familiarity with one particular discipline or specialty and the phenomenon is viewed through those eyes, often with the assurance that looking at it that way, intently enough and long enough, will reveal the complete explanation. And be attentive to the phrase, "We are not yet completely sure of exactly how it works." What is really meant is, "We haven't the slightest idea of how it really works."

I must admit to some guilt in this matter, certainly as much as the next person. I am a chemist and I suspect that the way that the psychedelic drugs do their thing can eventually be understood through a comparison of the structures of the molecules that are active and those that are inactive. I put those that have methoxyl groups in pigeon hole #1, and those that are bicyclic into pigeon hole #2. And then, if pigeon hole #2 becomes more and more cluttered, I will subdivide the contents into pigeon hole $\#2_A$ for bicyclics with heteroatoms and pigeon hole $\#2_B$ for bicyclics without heteroatoms. The more information I can accumulate, the more pigeon holes I need.

But in the adjoining lab, there is a molecular biologist who feels that the eventual explanation for the action of the psychedelic drug will come from the analysis and understanding of the intimate geometry of the places in the brain where they act. These classification pigeon holes are called receptor sites. But they, too, can become more and more subdivided as they become cluttered. One reads of a

new sub-sub type quite regularly in the literature. The favorite neurotransmitter of the moment, as far as the current thinking of how these marvelous drugs work, is serotonin, or 5-HT (for 5-hydroxytryptamine). There are 5-HT_1 and 5-HT_{2A} and 5-HT_{2B} and (for all I know right now) 5-HT_{2C} and 5-HT_{2D} receptors, and I don't really think that either he or I have come much closer to understanding the mechanism of action.

And, since the mind is a reasonably complex system, Gödel has already informed us both that neither of us will be completely successful. Sometimes I feel that the pigeon hole approach to the classification of knowledge might actually limit our views of the problem. A Harvard Professor of Medicine recently noted: "We must recognize for what it is, man's predilection for dividing things into tidy categories, irrespective of whether clarity is gained or lost thereby."

No. No one will ever have it all together. It is like sitting down in front of a jigsaw with a zillion zillion pieces spread all over the kitchen table. With diligent searching you will occasionally find a piece that matches another, but it rarely provides any insight into the final picture. That will remain a mystery, unless you had the chance to see the cover of the box in some other incarnation. But Oh my, what fun it is, whenever you do happen to find a new piece that fits!

This harangue is really a lengthy prelude to the story of putting an ethoxy group in place of a methoxy on the 2,5-dimethoxy skeleton of these psychedelic families. The making of IRIS was the first move in this direction, done back in 1976. One can have a pigeon hole that is named "Ethoxy In Place of Methoxy" and toss in there the names of perhaps twenty pairs of compounds, which differ from one another by just this feature. Yet when they are looked at from the potency point of view, there are some which show a decrease in potency (which is the case with IRIS and most of the Tweetios) and there are some which seem to maintain their potency (such as the TMA-2/MEM pair) and there are some where there is a distinct potency increase (the mescaline/escaline pair, for example).

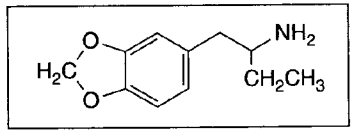
What does one do to clarify the contents of this particular pigeon hole? The current fad would be to subdivide it into three subdivisions, maybe something like "Ethoxy in Place of Methoxy if 2- or 5-located" and "Ethoxy in Place of Methoxy if 4-located and other things 2,5" and "Ethoxy in Place of Methoxy if 4-located, and other things 3,5." The end point that soon becomes apparent, down the line, will be to have as many pigeon holes as compounds! And at the moment, this particular piece of the jigsaw puzzle doesn't seem to fit anywhere at all.

Perhaps both my neighboring molecular biologist and I are asking the wrong questions. I am looking at the molecules and asking, "What are they?" And he is following them and asking, "Where do they go?" And neither of us is fully attentive to the question, "What do they do?" It is so easy to replace the word "mind," in our inquiries, with the word "brain."

Yup. The operation of the mind can certainly be classified as a "reasonably complex" phenomenon. I prefer Gödel's term. The mind is without question an "interesting" phenomenon.

#94 J; BDB; 2-AMINO-1-(3,4-METHYLENEDIOXYPHENYL)-BUTANE; 1-(1,3-BENZODIOXOL-5-YL)-2-BUTANAMINE

SYNTHESIS: The Grignard reagent of propyl bromide was made by the dropwise addition of 52 g 1-bromopropane to a stirred suspension of 14 g magnesium turnings in 50 mL anhydrous Et_2O. After the addition, stirring was continued for 10 min, and then a solution of 50 g piperonal in 200 mL anhydrous Et_2O was added over the course of 30 min. The reaction mixture was heated at reflux for 8 h, then cooled with an external ice bath. It was quenched with the addition of a solution of 75 mL cold, saturated aqueous ammonium chloride. The formed solids were removed by filtration, and the two-phase filtrate separated. The organic phase was washed with 3x200 mL dilute HCl, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum. The crude 62.2 g of 1-(3,4-methylenedioxyphenyl)-2-butanol, which contained a small amount of the olefin that formed by dehydration, was distilled at 98 °C at 0.07 mm/Hg to give an analytical sample, but the crude isolate served well in the next reaction. Anal. ($C_{11}H_{14}O_3$) C,H.



A mixture of 65 g crude 1-(3,4-methylenedioxyphenyl)-2-butanol and 1 g finely powdered potassium bisulfate was heated with a soft flame until the internal temperature reached 170 °C and H_2O was no longer evolved. The entire reaction mixture was then distilled at 100-110 °C at 0.8 mm/Hg to give 55 g of 1-(3,4-methylenedioxyphenyl)-1-butene as a colorless oil. Anal. ($C_{11}H_{12}O_2$) C,H.

To 240 mL of stirred and cooled formic acid there was added 30 mL H_2O followed, slowly, by 45 mL of 35% hydrogen peroxide. There was then added a solution of 48 g 1-(3,4-methylenedioxyphenyl)-1-butene in 240 mL acetone at a rate that maintained the internal temperature at less than 40 °C. After the addition, the reaction mixture was allowed to stand and stir for several additional days. The excess volatiles were removed under vacuum with the temperature never allowed to exceed 40 °C. The residue was dissolved in 90 mL MeOH and diluted with 450 mL 15% H_2SO_4. This mixture was heated on the steam bath for 2.5 h, cooled, and then extracted with 3x100 mL Et_2O. The extracts were pooled, washed with 2x200 mL H_2O, 2x200 mL 5% NaOH, 2x200 mL brine, and then dried over anhydrous $MgSO_4$. After removal of the solvent under vacuum, the residue was distilled at 105-135 °C at 0.3 mm/Hg to give 28.2 g 1-(3,4-methylenedioxyphenyl)-2-butanone as an amber oil. Redistillation gave a colorless oil, with a bp of 98 °C at 0.11 mm/Hg. Anal. ($C_{11}H_{12}O_3$) C,H. This intermediate ketone could be prepared by the Wittig reaction between piperonal and the derivative of triphenylphosphonium propyl bromide and dibutyldisulfide, followed by hydrolysis in a HCl/acetic acid mixture, but the yields were no better, Efforts to prepare this ketone by the iron and acid reduction of the appropriate nitrostyrene (1-(3,4-methylenedioxyphenyl)-2-nitro-1-butene, mp 64-65 °C) were thwarted by the consistently unsatisfactory yield of the precursor from the reaction between piperonal and 1-nitropropane.

A stirred solution of 20 g anhydrous ammonium acetate and 4.6 g 1-(3,4-methylenedioxyphenyl)-2-butanone in 50 mL MeOH was treated with 1.57 g sodium cyanoborohydride. Droplets of HCl were added as needed to maintain the pH at approximately 6. The reaction mixture was made basic with the addition of 250 mL dilute NaOH and extracted with 3x100 mL CH_2Cl_2. The pooled organic extracts were extracted with 2x100 mL dilute H_2SO_4, the pooled aqueous extracts made basic again, and extracted again with 2x100 mL CH_2Cl_2. Removal of the solvent gave a residue which was distilled to give 2.6 g of a colorless oil which was dissolved in 15 mL IPA, neutralized with concentrated HCl, and diluted with an equal volume of anhydrous Et_2O. Crystals of 2-amino-1-(3,4-methylenedioxyphenyl)butane hydrochloride (J) separated slowly. After filtering, Et_2O washing, and air drying there was obtained 2.8 g of white crystals that melted at 159-161 °C. Anal. ($C_{11}H_{16}ClNO_2$) C,H,N.

DOSAGE: 150 - 230 mg.

DURATION: 4 - 8 h.

QUALITATIVE COMMENTS: (with 175 mg) "The first stirrings were evident in a half hour, pleasant feelings, and without any untoward body effects. Within another half hour I was at a plus 2 and there it leveled off. I would be reluctant to drive a car, but I could were it necessary. There were no visual distortions, no giddiness, no introspective urges, and no rise to a psychedelic intoxication of any significance. After about an hour and a half at this level, I gradually dropped back over another two hours. Afterwards I was quite fatigued and languorous."

(with 200 mg and a 75 mg supplement) "A very strong climb, and a very good, interior feeling. It has some of the MDMA properties, but it is difficult to concentrate on any one point. There is a tendency to slide off. Excellent emotional affect; music is fine but not gripping. Someone had used the phrase, mental nystagmus, and there is something valid there. The supplement was taken at the 2 hour point when I was already aware of some dropping, and its action was noticed in about a half hour."

(with 230 mg) "Physically, there was a bit of dry mouth but no teeth clenching, some nystagmus, maybe the slightest bit of dizziness, very anorexic, and it is not a decongestant. Mentally, it is extremely benign and pleasant, funny and good-humored. No visuals. Peaceful. Easy silences, easy talking. More stoning than MDMA."

EXTENSIONS AND COMMENTARY: In general, all subjects who have explored J have accepted it and commented favorably. Perhaps those who have used supplements (in an imitation of the common MDMA procedure) achieved an additional period of effect, but also tended to drop to baseline afterwards more rapidly. The physical side effects, such as teeth clench and nystagmus, were

infrequent. The consensus is that J is a bit more "stoning" than MDMA, more like MDA, but with a chronology that is very much the same.

Two nomenclature problems have to be faced in the naming of these compounds. One deals with the Chemical Abstracts terminology as contrasted with the logical and intuitive terminology. The other invokes the concept of the Muni-Metro, delightfully simple, but neither Chemical Abstracts-approved nor intuitive in form. The first problem is addressed here; the second is discussed where it better belongs, under the N-methyl homologue of J (see under METHYL-J).

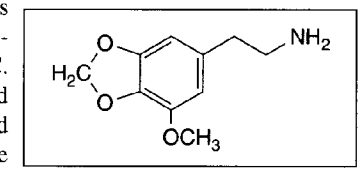
In short, the two-ring system of J, or of any of the MDA-MDMA family of drugs, can be named as one ring being attached to the other, or by a single term that encompasses both. The first procedure, an old friend with chemists and the one that had been used for years in the abstracting services, calls the combination methylenedioxybenzene and, as a prefix, it becomes methylenedioxyphenyl-something. The benzene or the phenyl-something is the foundation of the name, and there happens to be a methylenedioxy-ring attached to it. On this basis, this compound J should be named as if it had no methylenedioxy ring anywhere, and then simply attach the new ring as an afterthought. So, the one-ring parent of J is 1-phenyl-2-aminobutane, and J is 1-(3,4-methylenedioxyphenyl)-2-aminobutane (or, to be a purist, the amino should alphabetically come first, to give 2-amino-1-(3,4-methylenedioxyphenyl)butane). The synthesis of the chemical intermediates given above uses this old-fashioned nomenclature.

But the name currently in vogue for this two-ring system is 1,3-benzodioxole. As a prefix it becomes 1,3-benzodioxol-5-yl-something, and so J would be called 1-(1,3-benzodioxol-5-yl)-2-aminobutane. This is the source of the code name BDB. And the N-methyl homologue, the alpha-ethyl analogue of MDMA, is named MBDB, or METHYL-J, and is with its own separate entry in this footnote.

There is a psychological nuance to this new nomenclature. The virtues and potential medical value of MDMA lie in its most remarkable property of facilitating communication and introspective states without an overlay of psychedelic action. This property has prompted the coining of a new pharmacological class name, Entactogen, which comes from the Greek roots for "touching within." But MDMA has been badly smeared in both the public and the scientific view, by its wide popular misuse, its precipitous placement into a Schedule I category of the Federal Drug Law, and a flood of negative neurotoxicological findings in animal studies. There are some properties of both this compound and its methyl-homologue that suggest this "entactogen" world, so why not avoid the "MD" prefix that, in many eyes, is pejorative? Stick with the totally obscure chemical names, and call them BDB and MBDB. Or, even more simply, J and METHYL-J.

#95 LOPHOPHINE; 3-METHOXY-4,5-METHYLENEDIOXY-PHENETHYLAMINE

SYNTHESIS: A solution of 50 g myristicinaldehyde (3-methoxy-4,5-methylenedioxybenzaldehyde, see under MMDA for its preparation) in 200 mL acetic acid was treated with 33 mL nitromethane and 17.4 g anhydrous ammonium acetate and held on the steam bath for 5 h. The reaction mixture was diluted with a little H_2O and cooled in an external ice-acetone bath. A heavy crop of yellow crystals formed, which were removed by filtration, washed with cold acetic acid, and dried to constant weight. There was thus obtained 19.3 g 3-methoxy-4,5-methylenedioxy-ß-nitrostyrene with a mp of 210-212 °C. The mother liquors were diluted with H_2O, and extracted with 3x100 mL CH_2Cl_2. The pooled extracts were washed with 5% NaOH, and the solvent removed under vacuum yielding 34 g of a dark residue that was largely unreacted aldehyde. This residue was reprocessed in acetic acid with nitromethane and ammonium acetate, as described above, and provided an additional 8.1 g of the nitrostyrene with the same mp.



A suspension of 25 g LAH in 1.5 L anhydrous Et_2O in an inert atmosphere was stirred magnetically, and brought up to a gentle reflux. Through a Soxhlet condenser modified to allow Et_2O to return continuously to the reaction mixture, there was added 27.0 g of 3-methoxy-4,5-methylenedioxy-ß-nitrostyrene. The addition require many h, and when it was completed, the reaction was held at reflux for an additional 9 days. After cooling the reaction mixture in an external ice bath, the excess hydride was destroyed by the cautious addition of dilute H_2SO_4. The final amount used was 1800 mL H_2O containing 133 g H_2SO_4. The phases were separated, and the aqueous phase was washed with 2x100 mL Et_2O. To it was then added 625 g potassium sodium tartrate, and sufficient base to bring the pH to >9. This was extracted with 3x250 mL CH_2Cl_2, and the pooled extracts stripped of solvent under vacuum. The residue was dissolved in anhydrous Et_2O and saturated with anhydrous HCl gas, giving a heavy crystallization of salts. These were removed by filtration, Et_2O washed, and air dried, to give 17.7 g 3-methoxy-4,5-methylenedioxyphenethylamine (LOPHOPHINE) as an off-white solid with a mp of 160-161 °C. This was dissolved in CH_3CN containing 5% EtOH, decolorized with activated charcoal, filtered, and the removed charcoal washed with boiling CH_3CN. Slow cooling of the solution provided 11.7 g of a white product which melted at 164-164.5 °C.

DOSAGE: greater than 200 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 150 mg) "Between two and five hours, very peaceful and euphoric mood elevation, similar to mescaline, but without any visual distortion. Mild enhancement of color perception, possibly a function of mood elevation. There was no nausea, no eyes-closed vision. Slept easily that evening."

(with 250 mg) "Possibly something of a threshold effect from 2:30 to 4:30 of the experiment. Intangible, and certainly there is nothing an hour later."

EXTENSIONS AND COMMENTARY: It looks as if this compound is not active. There is an excellent argument as to why it really should be, and the fact that it is not active is completely unexpected. Let me try to explain.

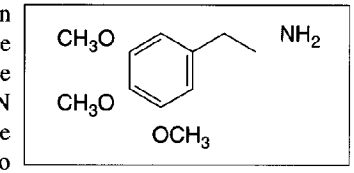
Quite simply, mescaline is a major component and a centrally active alkaloid of the Peyote plant. It is a phenethylamine, which can undergo a cyclization within the plant to produce a pile of derivatives (tetrahydroisoquinolines) such as anhalonine and O-methylanhalonidine that are marvelously complex alkaloids, all natural components of this magical cactus. But there is another pile of derivatives (tetrahydroisoquinolines) such as anhalonine, and lophophorine, and peyophorine which are the logical cyclization products of another phenethylamine which does not exist in the cactus. It should be there, but it is not. If it were there it would be the natural precursor to a host of bicyclic alkaloids, but it is absent. This is 3-methoxy-4,5-methylenedioxyphenethylamine. I feel that some day it will be discovered as a plant component, and when it is it can be given a name that reflects the generic binomial of the plant. And since the plant has been known as *Lophophora williamsii*, why not give a name to this compound (which should be in the plant), one derived from the Latin name, but one that has never before been used? What about LOPHOPHINE? And so, I have named it, but I have not found it, nor has anyone else. Yet.

It is inevitable that this simple and most appealing precursor will be found to be present in the cactus, at some future time when we will have tools of sufficient sensitivity to detect it. And certainly, it would be reasonable to expect it to be an active psychedelic, and to be as interesting in man as its close cousin, mescaline. But, at the present time, LOPHOPHINE is not known to be present in the plant, and it is not known to be active in man. I am confident that both statuses will change in the future.

#96 M; MESCALINE; 3,4,5-TRIMETHOXYPHENETHYLAMINE

SYNTHESIS: A solution of 20 g 3,4,5-trimethoxybenzaldehyde, 40 mL nitromethane, and 20 mL cyclohexylamine in 200 mL of acetic acid was heated on the steam bath for 1 h. The reaction mixture was then diluted slowly and with good stirring, with 400 mL H_2O, which allowed the formation of a heavy yellow crystalline mass. This was removed by filtration, washed with H_2O, and sucked as dry as possible. Recrystallization from boiling MeOH (15 mL/g) yielded, after filtration and air drying, ß-nitro-3,4,5-trimethoxystyrene as bright yellow crystals weighing 18.5 g. An alternate synthesis was effective, using an excess of nitromethane as solvent as well as reagent, if the amount of ammonium acetate catalysis was kept small. A solution of 20 g 3,4,5-trimethoxybenzaldehyde in 40 mL nitromethane containing 1 g anhydrous ammonium acetate was heated on the steam bath for 4 h. The solvent was stripped under vacuum and the residual yellow oil was dissolved in two volumes of hot MeOH, decanted from some insolubles, and allowed to cool. The crystals formed are removed by filtration, washed with MeOH and air dried yielding 14.2 g. of bright yellow crystals of ß-nitro-3,4,5-trimethoxystyrene. The use of these proportions but with 3.5 g ammonium acetate gave extensive side-reaction products even when worked up after only 1.5 h heating. The yield of nitrostyrene was, in this latter case, unsatisfactory.

To a gently refluxing suspension of 2 g LAH in 200 mL Et_2O, there was added 2.4 g ß-nitro-3,4,5-trimethoxystyrene as a saturated Et_2O solution by use of a Soxhlet extraction condenser modified to allow the continuous return of condensed solvent through the thimble. After the addition was complete, the refluxing conditions were maintained for another 48 h. After cooling the reaction mixture, a total of 150 mL of 1.5 N H_2SO_4 was cautiously added, destroying the excess hydride and untimately providing two clear phases. These were separated, and the aqueous phase was washed once with 50 mL Et_2O. There was then added 50 g potassium sodium tartrate, followed by sufficient NaOH to bring the pH >9. This was then extracted with 3x75 mL CH_2Cl_2, and the solvent from the pooled extracts was removed under vacuum. The residue was distilled at 120-130 °C at 0.3 mm/Hg giving a white oil that was dissolved in 10 mL IPA and neutralized with concentrated HCl. The white crystals that formed were diluted with 25 mL Et_2O, removed by filtration, and air dried to provide 2.1 g 3,4,5-trimethoxyphenethylamine hydrochloride (M) as glistening white crystals. The sulfate salt formed spectacular crystals from water, but had a broad and uncharacteristic mp. An alternate synthesis can employ 3,4,5-trimethoxyphenylacetonitrile, as described under ß-D.



DOSAGE: 200-400 mg (as the sulfate salt), 178-356 mg (as the hydrochloride salt).

DURATION: 10-12 h

QUALITATIVE COMMENTS: (with 300 mg) "I would have liked to, and was expecting to, have an exciting visual day, but I seemed to be unable to escape self-analysis. At the peak of the experience I was quite intoxicated and hyper with energy, so that it was not hard to move around. I was quite restless. But I spent most of the day in considerable agony, attempting to break through without success. I

if measured as the sulfate, although the actual form used was usually the hydrochloride salt. The conversion factor is given under "dosage" above.

Mescaline has always been the central standard against which all other compounds are viewed. Even the United States Chemical Warfare group, in their human studies of a number of substituted phenethylamines, used mescaline as the reference material for both quantitative and qualitative comparisons. The Edgewood Arsenal code number for it was EA-1306. All psychedelics are given properties that are something like "twice the potency of mescaline" or "twice as long-lived as mescaline." This simple drug is truly the central prototype against which everything else is measured. The earliest studies with the "psychotomimetic amphetamines" had quantitative psychological numbers attached that read as "mescaline units." Mescaline was cast in concrete as being active at the 3.75 mg/kg level. That means for a 80 kilogram person (a 170 pound person) a dose of 300 milligrams. If a new compound proved to be active at 30 milligrams, there was a M.U. level of 10 put into the published literature. The behavioral biologists were happy, because now they had numbers to represent psychological properties. But in truth, none of this represented the magic of this material, the nature of the experience itself. That is why, in this Book II, there is only one line given to "dosage," but a full page given to "qualitative comments."

Four simple N-modified mescaline analogues are of interest in that they are natural and have been explored in man.

The N-acetyl analogue has been found in the peyote plant, and it is also a major metabolite of mescaline in man. It is made by the gentle reaction of mescaline with acetic anhydride (a bit too much heat, and the product N-acetyl mescaline will cyclize to a dihydroisoquinoline, itself a fine white crystalline solid, mp 160-161 °C) and can be recrystallized from boiling toluene. A number of human trials with this amide at levels in the 300 to 750 milligrams range have shown it to be with very little activity. At the highest levels there have been suggestions of drowsiness. Certainly there were none of the classic mescaline psychedelic effects.

If free base mescaline is brought into reaction with ethyl formate (to produce the amide, N-formylmescaline) and subsequently reduced (with lithium aluminum hydride) it is converted to the N-methyl homologue. This base has also been found as a trace component in the Peyote cactus. And the effects of N-methylation of other psychedelic drugs have been commented upon elsewhere in these recipes, all with consistently negative results (with the noteworthy exception of the conversion of MDA to MDMA). Here, too, there is no obvious activity in man, although the levels assayed were only up to 25 milligrams.

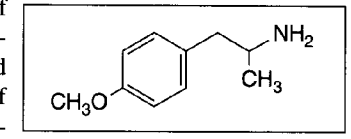
N,N-Dimethylmescaline has been given the trivial name of Trichocerine as it has been found as a natural product in several cacti of the *Trichocereus* Genus but, interestingly, never in any Peyote variant. It also has proven inactive in man in dosages in excess of 500 milligrams, administered parenterally. This observation, the absence of activity of a simple tertiary amine, has been exploited in the development of several iodinated radiopharmaceuticals that are mentioned elsewhere in this book.

The fourth modification is the compound with the nitrogen atom oxidatively removed from the scene. This is the mescaline metabolite, 3,4,5-trimethoxyphenylacetic acid, or TMPEA. Human dosages up to 750 milligrams orally failed to produce either physiological or psychological changes.

One additional manipulation with some of these structures has been made and should be mentioned. These are the analogues with an oxygen atom inserted between the aromatic ring and the aliphatic chain. They are, in essence, aminoethyl phenyl ethers. The first is related to mescaline itself, 2-(3,4,5-trimethoxyphenoxy)ethylamine. Human trials were conducted over the dose range of 10 to 300 milligrams and there were no effects observed. The second is related to trichocerine, N,N-dimethyl-2-(3,4,5-trimethoxyphenoxy)ethylamine. It was inactive in man over the range of 10 to 400 milligrams. Mescaline, at a dose of 420 milligrams, served as the control in these studies.

#97 4-MA; PMA; 4-METHOXYAMPHETAMINE

SYNTHESIS: A solution of 27.2 g anisaldehyde and 18.0 g nitroethane in 300 mL benzene was treated with 2.0 mL cyclohexane and refluxed using a Dean Stark trap until H_2O ceased to accumulate. A total of 3.8 mL was generated over about 5 days. After the removal of the solvent under vacuum, the viscous red oily residue was cooled and it spontaneously crystallized. This was ground under an equal volume of MeOH, producing lemon-yellow crystals of 1-(4-methoxyphenyl)-2-nitropropene. The final yield was 27.4 g of product with a mp of 45-46 °C. Recrystallization from 4 volumes MeOH did not improve the mp. An excellent alternate synthesis with a comparable yield involved letting a solution of equimolar amounts of the aldehyde and nitroethane and a tenth mole of n-amylamine stand in the dark at room temperature for a couple of weeks. The product spontaneously crystallized, and could be recrystallized from MeOH. The more conventional synthesis involving acetic acid as a solvent and ammonium acetate as a catalyst, produced a poor yield of the nitrostyrene and it was difficult to separate from the white diacetate of the starting anisaldehyde, mp 59-60 °C.



A suspension of 32 g LAH in 1 L anhydrous Et_2O was well stirred and 32.6 g 1-(4-methoxyphenyl)-2-nitropropene in Et_2O was added at a rate that maintained a reflux. After the addition was complete, reflux was continued for 48 h. The reaction mixture was cooled, and the excess hydride was destroyed by the cautious addition of dilute H_2SO_4. The Et_2O was separated, and extracted with additional aqueous H_2SO_4. A solution of 700 g potassium sodium tartrate in 600 mL H_2O was added, and the pH brought to >9 with 25% NaOH. This aqueous phase was extracted

with 3x200 mL CH_2Cl_2 which provided, after removal of the solvent, 32.5 g of a clear amber oil. This was dissolved in 100 mL IPA, neutralized with concentrated HCl, and then diluted with 300 mL anhydrous Et_2O. There was obtained white crystals of 4-methoxyamphetamine hydrochloride (4-MA) that weighed, after filtering, Et_2O washing and air drying, 22.2 g and had a mp of 208-209 °C. The amphetamine metabolite, 4-hydroxyamphetamine hydrochloride (4-HA), was prepared by heating 5.0 g 4-MA in 20 mL concentrated HCl at 15 lbs/in. After recrystallization from aqueous EtOH, the product weighed 3.8 g and had a mp of 171-172 °C.

DOSAGE: 50 - 80 mg.

DURATION: short.

QUALITATIVE COMMENTS: (with 60 mg) "At just over an hour, there was a sudden blood pressure rise, with the systolic going up 55 mm. This was maintained for another hour. I found the effects reminiscent of DET, distinct after-images, and some parasthesia. I was without any residue by early evening (after 5 hours)."

(with 70 mg) "It hit quite suddenly. I had a feeling of druggedness, almost an alcohol-like intoxication, and I never was really high in the psychedelic sense."

EXTENSIONS AND COMMENTARY: This is another of the essential amphetamines, because of the appearance of the 4-methoxy group in two most important essential oils. These are the allylbenzene (estragole or esdragol) and the propenyl isomer (anethole). Their natural sources have been discussed under TMA.

Two comments are warranted concerning 4-MA, one of scientific interest, and the other about a social tragedy.

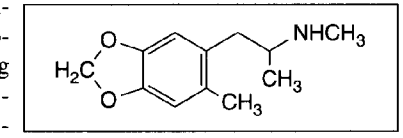
A major metabolites of amphetamine is 4-hydroxyamphetamine, from oxidation at the 4-position. It has been long known that with chronic amphetamine usage there is the generation of tolerance, which encourages ever-increasing doses to be used. When the daily load gets up around one or two hundred milligrams, the subject can become quite psychotic. The question was asked: might the chronic amphetamine user be methylating his endogenously produced 4-hydroxyamphetamine to produce 4-methoxyamphetamine (4-MA), and maybe this is the agent that promotes the psychosis? To address this question, several studies were done with normal subjects, about 20 years ago, to see if 4-MA might produce a psychotic state (it didn't at the highest levels tried, 75 milligrams) and to see if it was excreted to some extent unchanged in the urines of these normal subjects (it was seen even at the lowest dosage tried, 10 milligrams). It produced excitation and other central effects, it produced adrenergic pressor effects, and it consistently produced measurable quantities of 4-MA in the urine, but it produced no amphetamine-like crazies. And since the administration of up to 600 milligrams of amphetamine produced no detectable 4-MA in the urine, this theory of psychotomimesis is not valid.

On the tragic side, a few years later, 4-MA became widely distributed in both the US (as the sulfate salt) and in Canada (as the hydrochloride), perhaps inspired by some studies in rats that had reported that it was second only to LSD in potency as a hallucinogen. The several deaths that occurred probably followed overdose, and it was clear that 4-MA was involved as it had been isolated from both urine and tissue during post mortems. It had been sold under the names of Chicken Power and Chicken Yellow, and was promoted as being MDA. I could find no record of a typical street dosage, but comments collected in association with the deaths implied that the ingested quantites were in the hundreds of milligrams. Rrecently, the ethoxy homologue, 4-EA, appeared on the streets of Canada. The dosage, again, was not reported. It was promptly illegalized there.

The two positional analogues of 4-MA are known; vis., 2-MA and 3-MA. Their synthesis is straightforward, in imitation of that for 4-MA above. The meta-compound, 3-MA, has been metabolically explored in man, but no central effects were noted at a 50 milligram dose (2x25 milligrams, separated by three hours). There appears to be no report of any human trial of 2-MA. The N-methyl homologue of 2-MA is a commercial adrenergic bronchodilator called Methoxyphenamine, or Orthoxine. It has been used in the prevention of acute asthma attacks in doses of up to 200 milligrams, with only slight central stimulation. The N-methyl homologues of 3-MA and 4-MA are known, and the latter compound is the stuff of a separate entry in this book.

#98 MADAM-6; 2,N-DIMETHYL-4,5-METHYLENEDIOXYAMPHETAMINE

SYNTHESIS: A mixture of 102 g $POCl_3$ and 115 g N-methylformanilide was allowed to stand for 0.5 h at room temperature during which time it turned a deep claret color. To this there was added 45 g 3,4-methylenedioxytoluene and the mixture was held on the steam bath for 3 h. It was then added to 3 L H_2O. Stirring was continued until the oil which had separated had become quite firm. This was removed by filtration to give a greenish, somewhat gummy, crystalline solid, which was finely ground under 40 mL MeOH and again filtered giving, when air dried, 25 g of an almost white solid. Recrystallization of a small sample from methylcyclopentane gave ivory-colored glistening crystals of 2-methyl-4,5-methylenedioxybenzaldehyde with a mp of 88.5-89.5 °C. In the infra-red, the carbonyl was identical to that of the starting piperonal (1690 cm^{-1}) but the fingerprint was different and unique, with bands at 868, 929, 1040 and 1052 cm^{-1}.



A solution of 23 g 2-methyl-4,5-methylenedioxybenzaldehyde in 150 mL nitroethane was treated with 2.0 g anhydrous ammonium acetate and heated on the

steam bath for 9 h. The excess solvent was removed under vacuum to give a dark yellow oil which was dissolved in 40 mL hot MeOH and allowed to crystallize. The solids were removed by filtration, washed modestly with MeOH and air dried, to give 21.2 g of 1-(2-methyl-4,5-methylenedioxyphenyl)-2-nitropropene as beautiful yellow crystals with a mp of 116-118 °C. Recrystallization of an analytical sample from MeOH gave lustrous bright yellow crystals with a mp of 120-121 °C. Anal. ($C_{11}H_{11}NO_4$) C,H,N.

A suspension of 54 g electrolytic elemental iron in 240 g glacial acetic acid was warmed on the steam bath, with frequent stirring. When the reaction between them started, there was added, a portion at a time, a solution of 18.2 g 1-(2-methyl-4,5-methylenedioxyphenyl)-2-nitropropene in 125 mL warm acetic acid. The orange color of the nitrostyrene solution became quite reddish, white solids of iron acetate appeared, and a dark tomato-colored crust formed which was continuously broken back into the reaction mixture. Heating was continued for 1.5 h, and then all was poured into 2 L H_2O. All the insolubles were removed by filtration, and these were washed well with CH_2Cl_2. The filtrate and washes were combined, the phases separated, and the aqueous phase extracted with 2x100 mL additional CH_2Cl_2. The combined organics were washed with 5% NaOH, and the solvent removed under vacuum. The residue weighed 15.9 g, and was distilled at 90-110 °C at 0.4 mm/Hg to give 13.9 g of 2-methyl-4,5-methylenedioxyphenylacetone that spontaneously crystallized. A small sample from methylcyclopentane had a mp of 52-53 °C, another from hexane a mp of 53-54 °C, and another from MeOH a mp of 54-55 °C. Anal. ($C_{11}H_{12}O_3$) H; C calcd, 68.73; found 67.87, 67.84.

To a stirred solution of 30 g methylamine hydrochloride in 200 mL warm MeOH there was added 13.5 g 2-methyl-4,5-methylenedioxyphenylacetone followed, after returning to room temperature, by 7 g sodium cyanoborohydride. There was added HCl as needed to maintain the pH at approximately orange on external damp universal pH paper. After a few days, the reaction ceased generating base, and all was poured into 2 L dilute H_2SO_4 (caution, HCN evolved). This was washed with 3x75 mL CH_2Cl_2, made basic with 25% NaOH, and the resulting mixture extracted with 3x100 CH_2Cl_2. The pooled extracts were stripped of solvent under vacuum and the residue, 15 g of a pale amber oil, was distilled at 95-110 °C at 0.4 mm/Hg. There was obtained 12.3 g of a white oil that was dissolved in 60 mL IPA, neutralized with approximately 5.5 mL concentrated HCl, and crystals of the salt formed spontaneously. These were loosened with the addition of another 10 mL IPA, and then all was diluted by the addition of an equal volume of anhydrous Et_2O. The white crystals were separated by filtration, Et_2O washed, and air dried to give 14.1 g of 2,N-dimethyl-4,5-methylenedioxyamphetamine hydrochloride (MADAM-6) as a brilliant white powder with a mp of 206-207 °C. Anal. ($C_{12}H_{18}ClNO_2$) C,H.

DOSAGE: greater than 280 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 180 mg) "There is a hint of good things there, but nothing more than a hint. At four hours, there is no longer even a hint."

(with 280 mg) "I took 150 milligrams, waited an hour for results, which was niente, nada, nothing. Took supplements of 65 milligrams twice, an hour apart. No effect. Yes, we giveth up."

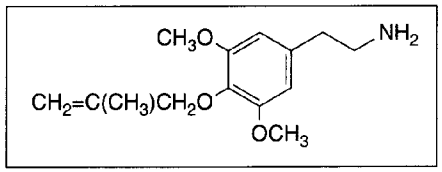
EXTENSIONS AND COMMENTARY: The structure of MADAM-6 was designed to be that of MDMA, with a methyl group attached at what should be a reasonably indifferent position. In fact, that is the genesis of the name. MDMA has been called ADAM, and with a methyl group in the 6-position, MADAM-6 is quite understandable. And the other ortho-position is, using this nomenclature, the 2-position, and with a methyl group there, one would have MADAM-2. I should make a small apology for the choice of numbers. MDMA is a 3,4-methylenedioxy compound, and the least ambiguous numbering scheme would be to lock the methylenedioxy group inescapably at the 3,4-place, letting the other ring position numbers fall where they may. The rules of chemistry ask that if something is really a 3,4,6-orientation it should be renumbered as a 2,4,5-orientation. Let's quietly ignore that request here.

How fascinating it is, that a small methyl group, something that is little more than one more minor bump on the surface of a molecule that is lumpy and bumpy anyway, can so effectively change the action of a compound. A big activity change from a small structure change usually implies that the bump is at a vital point, such as a target of metabolism or a point of critical fit in some receptor site. And since 6-MADAM can be looked upon as 6-bump-MDMA, and since it is at least 3x less potent than MDMA, the implication is that the action of MDMA requires some unbumpiness at this position for its particular action. There are suggestions that the body may want to put a hydroxyl group right there (a 6-hydroxy-dopamine act), and it couldn't if there was a methyl group right there. The isopropylamine side chain may want a certain degree of swing-around freedom, and this would be restricted by a methyl bump right next to it. And there are all kinds of other speculations possible as to why that position should be open.

Anyway, MADAM-6 is not active. And the equally intriguing positional isomer, the easily made MADAM-2, will certainly contribute to these speculations. A quiz for the reader! Will 2,N-dimethyl-3,4-methylenedioxyamphetamine (MADAM-2) be: (1) Of much reduced activity, akin to MADAM-6, or (2) Of potency and action similar to that of MDMA, or (3) Something unexpected and unanticipated? I know only one way of finding out. Make the Schiffs' base between piperonal and cyclohexylamine, treat this with butyl lithium in hexane with some TMEDA present, add some N-methylformanilide, convert the formed benzaldehyde to a nitrostyrene with nitroethane, reduce this with elemental iron to the phenylacetone, reduce this in the presence of methylamine with sodium cyanoborohydride, then taste the result.

#99 MAL; METHALLYLESCALINE; 3,5-DIMETHOXY-4-METHALLYLOXYPHENETHYLAMINE)

SYNTHESIS: To a solution of 5.8 g of homosyringonitrile (see under ESCALINE for its preparation) in 50 mL of acetone containing 100 mg of decyltriethylammonium iodide there was added 7.8 mL methallyl chloride followed by 6.9 g of finely powdered anhydrous K_2CO_3. The suspension was kept at reflux by a heating mantle, with effective stirring. After 6 h an additional 4.0 mL of methallyl chloride was added, and the refluxing was continued for an additional 36 h. The solvent and excess methallyl chloride was removed under vacuum and the residue was added to 400 mL H_2O. This solution was extracted with 3x75 mL CH_2Cl_2. The extracts were pooled, washed with 2x50 mL 5% NaOH, and the solvent removed to provide a dark brown oil. This was distilled at 120-130 °C at 0.4 mm/Hg to provide 6.1 g of 3,5-dimethoxy-4-methyallyloxyphenylacetonitrile as a lemon-colored viscous oil. Anal. ($C_{14}H_{17}NO_3$) C,H.



A suspension of 4.2 g LAH in 160 mL anhydrous THF under He was stirred, cooled to 0 °C, and treated with 2.95 ml of 100% H_2SO_4 added dropwise. This was followed by the addition of 6.0 g of 3,5-dimethoxy-4-methallyloxyphenylacetonitrile dissolved in 10 mL anhydrous THF, at a slow rate with vigorous stirring. The reaction mixture was held at reflux on the steam bath for 0.5 h, brought back to room temperature, and the excess hydride destroyed with IPA. Sufficient 15% NaOH was added to convert the formed solids to a loose, granular texture, and the entire mixture filtered and washed with THF. The filtrate and washings were pooled, the solvent removed under vacuum, and the residue added to 500 mL dilute HCl. This solution was washed with 2x50 mL CH_2Cl_2, made basic with aqueous NaOH, and extracted with 3x75 mL CH_2Cl_2. The extracts were pooled, the solvent removed under vacuum, and the residual pale amber oil distilled at 120-130 °C at 0.3 mm/Hg to provide 1.5 g of a white oil. This was dissolved in 8.0 mL of IPA and neutralized with 25 drops of concentrated HCl. The addition of 40 ml of anhydrous Et_2O with stirring produced, after a few moments delay, a spontaneous crystallization of 3,5-dimethoxy-4-methallyloxyphenethylamine hydrochloride (MAL) as fine white needles. After standing overnight these were removed by filtration, washed with an IPA/Et_2O mixture, then with Et_2O, and allowed to air dry to constant weight. The product weighed 1.1 g, and had a mp of 153-154 °C. Anal. ($C_{14}H_{22}ClNO_3$) C,H.

DOSAGE: 40 - 65 mg.

DURATION: 12 - 16 h.

QUALITATIVE COMMENTS: (with 45 mg) "Too much overload. I am surrounded with unreality. I do not choose to repeat the experiment."

(with 45 mg) "I am basically favorably impressed. I believe the initial discomfort would be alleviated by taking two 30 milligram doses separated by an hour."

(with 45 mg) "Much too much too much. There are shades of what might become amnesia. I am losing immediate contact. I will not repeat."

(with 50 mg) "A good level. I found myself totally caught up in the visual theater. Although I had trouble sleeping, I would willingly repeat the experiment at the same level."

(with 60 mg) "Extremely restless. Am very impressed with all the activity. But if I repeated it would be at a lower dose."

(with 60 mg) "Friendly territory. There is much kaleidoscopic 'neon' colors. Eyes closed very active. Eyes open there is considerable visual distortions seen in melted wax. Faces are distorted (friendly) but the sinister is not far away."

(with 65 mg) "Completely involved — good psychedelic state — visual entertainment with alternation (i.e., depth and movement) at the retinal level — detail in watercolors. Later in the experience (the 8 hour point) easy childhood memory recall."

(with 65 mg) "Beautiful. To a +2 by the 1st hr and continued climbing. Intense +3 within 2 hrs. Quite strong body. Diuretic. Fantasy, imagery, erotic. Way up, good connections between parts of self. Slight slowing of pulse in 7th to 8th hour. Excellent solid sleep with strong, clear, balancing dreams. But not until after 12 hrs."

EXTENSIONS AND COMMENTARY: This testimony can be accurately described as a mixed bag!

This base, MAL, lies as a hybrid of two other compounds, AL and CPM. It is an olefin (as is AL) which means that it has a place of unsaturation in its structure. And it is an isostere of CPM which means that the carbon atoms are all in the same location, but just the connecting electrons (called the chemical bonds) are in different places. Actually there is yet a third compound in this same picture, called PROPYNYL. And yet, although all of them have extremely close structural similarities, there are such great differences in action that one does not dare to generalize. CPM leads largely to fantasy, MAL largely to visual imagery, AL is twice as potent as either of these but it doesn't show either effect, and PROPYNYL is almost without any action at all.

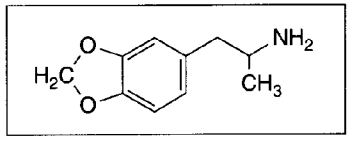
Speaking of generalization, I am glad that there are always exceptions. Some years ago, I had a most difficult experience with a strain of marijuana that was known by the name of DRED. The only word that I can use to describe my response to it is to say that I felt I had been poisoned. From this I warned myself to beware (and to believe in) whatever common name a drug might have been given. Fortunately, MAL did not live up to its name (at least for me), although some of the experimental subjects might disagree!

One additional compound was suggested by these parallels. Each of these three drugs can be viewed as having a negative something hanging out a-ways from the molecular center. With AL and MAL, this is the olefin double bond. With CPM this is a very strained three-member ring. What about an oxygen? The reaction between homosyringonitrile and methoxyethyl chloride produced the precursor to such a product (3,5-dimethoxy-4-(2-methoxyethoxy)-phenethylamine) but the yield was so bad that the project was abandoned. This same grouping has successfully been put into the 4-position of the sulfur-containing analog, and the result (2C-T-13) has proved to be quite a potent and interesting material. Maybe someday hang a sulfur atom out there at the end of that chain.

The name methallylescaline actually is completely unsound. There is no union of a methallyl with an escaline. What is really there is not an escaline at all, but rather a mescaline with a 2-propene attached to the methyl of the methoxy on the 4-position. There is no way of naming the thing in that manner, so the only logical solution is to take off the methyl entirely, and then put the methallyl on in its place. The name of this would then be 4-methylallyldesmethylmescaline. That would have received the abbreviation MAD which would have been even more difficult to deal with. MAL is preferable.

#100 MDA; 3,4-METHYLENEDIOXYAMPHETAMINE

SYNTHESIS: (from piperonal) To a solution of 15.0 g piperonal in 80 mL glacial acetic acid there was added 15 mL nitroethane followed by 10 g cyclohexylamine. The mixture was held at steam-bath temperature for 6 h, diluted with 10 mL H_2O, seeded with a crystal of product, and cooled overnight at 10 °C. The bright yellow crystals were removed by filtration, and air dried to yield 10.7 g of 1-(3,4-methylenedioxyphenyl)-2-nitropropene with a mp of 93-94 °C. This was raised to 97-98 °C by recrystallization from acetic acid. The more conventional efforts of nitrostyrene synthesis using an excess of nitroethane as a solvent and anhydrous ammonium acetate as the base, gives impure product in very poor yields. The nitrostyrene has been successfully made from the components in cold MeOH, with aqueous NaOH as the base.



A suspension of 20 g LAH in 250 mL anhydrous THF was placed under an inert atmosphere and stirred magnetically. There was added, dropwise, 18 g of 1-(3,4-methylenedioxyphenyl)-2-nitropropene in solution in THF and the reaction mixture was maintained at reflux for 36 h. After being brought back to room temperature, the excess hydride was destroyed with 15 mL IPA, followed by 15 mL of 15% NaOH. An additional 50 mL H_2O was added to complete the conversion of the aluminum salts to a loose, white, easily filtered solid. This was removed by filtration, and the filter cake washed with additional THF. The combined filtrate and washes were stripped of solvent under vacuum, and the residue dissolved in dilute H_2SO_4. Washing with 3x75 mL CH_2Cl_2 removed much of the color, and the aqueous phase was made basic and reextracted with 3x100 mL CH_2Cl_2. Removal of the solvent yielded 13.0 g of a yellow-colored oil that was distilled. The fraction boiling at 80-90 °C at 0.2 mm weighed 10.2 g and was water-white. It was dissolved in 60 mL of IPA, neutralization with concentrated HCl, and diluted with 120 mL of anhydrous Et_2O which produced a lasting turbidity. Crystals formed spontaneously which were removed by filtration, washed with Et_2O, and air dried to provide 10.4 g of 3,4-methylenedioxyamphetamine hydrochloride (MDA) with a mp of 187-188 °C.

(from 3,4-methylenedioxyphenylacetone) To a solution of 32.5 g anhydrous ammonium acetate in 120 mL MeOH, there was added 7.12 g 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 2.0 g sodium cyanoborohydride. The resulting yellow solution was vigorously stirred, and concentrated HCl was added periodically to keep the pH of the reaction mixture between 6 and 7 as determined by external damp universal pH paper. After several days, undissolved solids remained in the reaction mixture and no more acid was required. The reaction mixture was added to 600 mL of dilute HCl, and this was washed with 3x100 mL CH_2Cl_2. The combined washes were back-extracted with a small amount of dilute HCl, the aqueous phases combined, and made basic with 25% NaOH. This was then extracted with 3x100 mL CH_2Cl_2, these extracts combined, and the solvent removed under vacuum to provide 3.8 g of a red-colored residue. This was distilled at 80-90 °C at 0.2 mm/Hg to provide 2.2 g of an absolutely water-white oil. There was no obvious formation of a carbonate salt when exposed to air. This was dissolved in 15 mL IPA, neutralized with 25 drops of concentrated HCl, and diluted with 30 mL anhydrous Et_2O. Slowly there was the deposition of white crystals of 3,4-methylenedioxyamphetamine hydrochloride (MDA) which weighed 2.2 g and had a mp of 187-188 °C. The preparation of the formamide (a precursor to MDMA) and the acetamide (a precursor to MDE) are described under those entries.

DOSAGE: 80 - 160 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 100 mg) "The coming on was gradual and pleasant, taking from an hour to an hour and one half to do so. The trip was euphoric and intense despite my having been naturally depleted from a working day and having started so late. One thing that impressed itself upon me was the feeling I got of seeing the play of events, of what I thought to be the significance of certain people coming into my life, and why my 'dance', like everyone else's, is unique. I saw that every encounter or event is a potential for growth, and an opportunity for me to

realize my completeness at where I am, here and now, not at some future where I must lug the pieces of the past for a final assemblage 'there.' I was reminded of living the moment to its fullest and I felt that seeing this was indicative that I was on the right track."

(with 128 mg) "Forty-five minutes after the second dosage, when I was seated in a room by myself, not smoking, and where there was no possible source of smoke rings, an abundance of curling gray smoke rings was readily observed in the environment whenever a relaxed approach to subjective observation was used. Visually these had complete reality and it seemed quite unneccessary to test their properties because it was surely known and fully appreciated that the source of the visual phenomena could not be external to the body. When I concentrated my attention on the details of the curling gray forms by trying to note how they would be affected by passing a finger through their apparent field, they melted away. Then, when I relaxed again, the smoke rings were there. I was as certain that they were really there as I am now sure that my head is on top of my body."

(with 140 mg) "I vomited quite abruptly, and then everything was OK. I had been drinking probably excessively the last two days, and maybe the body needed to unpoison itself. The tactile sense is beautiful, but there seems to be some numbness as well, and I feel that nothing erotic would be do-able. Intimacy, yes, but no performance I'm pretty sure. I saw the experience start drifting away only four hours into it, and I was sad to see it go. It was an all around delightful day."

(with 200 mg, 2x100 mg spaced 1 h) "The first portion was apparent at one-half hour. There was microscopic nausea shortly after the second portion was taken, and in an hour there was a complete +++ developed. The relaxation was extreme. And there seemed to be time distortion, in that time seemed to pass slowly. There was a occasional LSD-like moment of profoundness, but by and large it was a simple intoxication with most things seeming quite hilarious. The intoxication was also quite extreme. Some food was tried later in the experiment, and it tasted good, but there was absolutely no appetite. None at all."

(with 60 mg of the "R" isomer) "There was a light and not too gentle development of a somewhat brittle wound-up state, a + or even a ++. Chills, and I had to get under an electric blanket to be comfortable. The effects smoothed out at the fourth hour, when things started to return to baseline. Not too entertaining."

(with 100 mg of the "R" isomer) "Rapid development from the 40 minute point to an hour and a quarter; largely a pleasant intoxication, but there is something serious there too. No great insights, and not too much interference with the day's goings-on. Completely clear at the 8 hour point."

(with 120 mg of the "R" isomer) "This is a stoning intoxicant. I would not choose to drive, because of possible judgement problems, but my handwriting seems to be clear and normal. The mental excitement dropped rapidly but I was aware of physical residues for several additional hours."

(with 80 mg of the "S" isomer) "A very thin, light threshold, which is quite delightful. I am quite willing to push this a bit higher."

(with 120 mg of the "S" isomer) "Perhaps to a one +. Very light, and very much like MDMA, but perhaps shorter lived. I am pretty much baseline in three hours."

(with 160 mg of the "S" isomer) "The development is very rapid, and there is both muscular tremor and some nausea. The physicals are quite bothersome. With eyes closed, there are no effects noticeable, but with eyes open, things are quite bright and sparkling. The muscular spasms persist, and there is considerable teeth clenching. I feel that the mental is not worth the physical."

EXTENSIONS AND COMMENTARY: There are about twenty different synthetic routes in the literature for the preparation of MDA. Many start with piperonal, and employ it to make methylenedioxyphenylacetone or a methylenedioxydihydrocinnamic acid amide instead of the nitrostyrene. The phenylacetone can be reduced in several ways other than the cyanoborohydride method mentioned here, and the amide can be rearranged directly to MDA. And there are additional methods for the reduction of the nitrostyrene that use no lithium aluminum hydride. Also there are procedures that have safrole or isosafrole as starting points. There is even one in the underground literature that starts with sassafras root bark. In fact, it is because safrole is one of the ten essential oils that MDA can humorously be referred to as one of the Ten Essential Amphetamines. See the comments under TMA.

There is a broad and checkered history concerning the use and abuse of MDA, and it is not the case that all the use was medical and all the abuse was social. One of the compulsive drives of both the military and the intelligence groups, just after World War II, was to discover and develop chemical agents which might serve as "truth serums" or as incapacitating agents. These government agencies considered the area of the psychedelics to be a fertile field for searching. The giving of relatively unexplored drugs in a cavalier manner to knowing and unknowing subjects was commonplace. There was one case in 1953, involving MDA and a psychiatric patient named Howard Blauer that proved fatal. The army had contracted with several physicians at the New York State Psychiatric Institute to explore new chemicals from the Edgewood Arsenal and one of these, with a chemical warfare code number of EA-1298, was MDA. The last and lethal injection into Blauer was an intravenous dose of 500 milligrams.

There have been a number of medical explorations. Under the code SKF-5 (and trade name of Amphedoxamine) it was explored as an anorexic agent. It has been found promising in the treatment of psychoneurotic depression. There are several medical reports, and one book (Claudio Naranjo's *The Healing Journey*), that describe its values in psychotherapy.

MDA was also one of the major drugs that was being popularly used in the late 1960's when the psychedelic concept exploded on the public scene. MDA was called the "hug-drug" and was said to stand for Mellow Drug of America. There was no difficulty in obtaining unending quantities of it, as it was available as a research chemical from several scientific supply houses (as were mescaline and LSD) and

was sold inexpensively under its chemical name.

A few experimental trials with the pure optical isomers show a consistency with all the other psychedelic compounds that have been studied in their separated forms, the higher potency with the "R" isomer. The less potent "S" isomer seemed to be more peaceful and MDMA-like at lower doses, but there were worrisome toxic signs at higher levels.

The structure of MDA can be viewed as an aromatic ring (the 3,4-methylenedioxyphenyl ring) with a three carbon chain sticking out from it. The amine group is on the second of the three carbon atoms. The isomers, with the amine function moved to the first of these carbons atoms (a benzylamine) and with the amine function moved to the third (furthest out atom) of these carbon atoms (a (n)-propylamine), are known and both have been assayed.

The benzylamine counterpart (as if one were to move the amine function from the beta-carbon to the alpha-carbon of the three carbon chain of the amphetamine molecule) is alpha-ethyl-3,4-methylenedioxybenzylamine or 1-amino-1-(3,4-methylenedioxyphenyl)propane, ALPHA. The hydrochloride salt has a mp of 199-201 °C. At low threshold levels (10 milligram area) there were eyes-closed "dreams" with some body tingling. The compound was not anorexic at any dose (up to 140 milligrams) and was reported to produce a pleasant, positive feeling. It is very short-lived (about 3 hours). The N-methyl homologue is alpha-ethyl-N-methyl-3,4-methylenedioxybenzylamine or 1-methylamino-1-(3,4-methylenedioxyphenyl)propane, M-ALPHA. It is similar in action, but is perhaps twice as potent (a plus one or plus two dose is 60 milligrams) and of twice the duration.

The (n)-propylamine counterpart (as if one were to move the amine function the other direction, from the beta-carbon to the gamma-carbon of the three carbon chain of the amphetamine molecule) is gamma-3,4-methylenedioxyphenylpropylamine or 1-amino-3-(3,4-methylenedioxyphenyl)propane, GAMMA. The hydrochloride salt has a mp of 204-205 °C. At oral levels of 200 milligrams there was some physical ill-at-ease, possible time distortion, and a feeling of being keenly aware of one's surroundings. The duration of effects was 4 hrs.

The phenethylamine that corresponds to MDA (removing the alpha-methyl group) is 3,4-methylenedioxyphenethylamine, or homopiperonylamine, or MDPEA, or simply H in the vocabulary of the Muni-Metro world. This compound is an entry in its own rights. The adding of another carbon atom to the alpha-methyl group of MDA gives compound J, and leads to the rest of the Muni-Metro series (K, L etc). All of this is explained under METHYL-J. The bending of this alpha-methyl group back to the aromatic ring gives an aminoindane, and with J one gets an aminotetralin. Both compounds react in animal discrimination studies identically to MDMA, and they appear to be free of neurochemical toxicity.

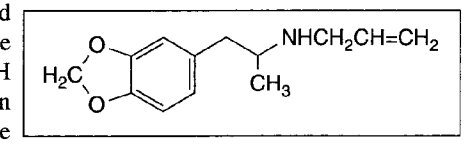
The two possible homologues, with either one or two methyl groups on the methylene carbon of the methylenedioxy group of MDA, are also known. The ethylidene compound (the acetaldehyde addition to the catechol group) has been encoded as EDA, and the acetone (isopropylidine addition to the catechol group) is

called IDA. In animal discrimination studies, and in *in vitro* neurotransmitter studies, they both seem to be of decreased potency. EDA is down two to three-fold from MDA, and IDA is down by a factor of two to three-fold again. Human trials of up to 150 milligrams of the hydrochloride salt of EDA produced at best a threshold light-headedness. IDA remains untested as of the present time. The homologue of MDA (actually of MDMA) with the added carbon atom in, rather than on, the methylenedioxy ring, is a separate entry; see MDMC.

A final isomer to be mentioned is a positional isomer. The 3,4-methylenedioxy group could be at the 2,3-position of the amphetamine skeleton, giving 2,3-methylenedioxyamphetamine, or ORTHO-MDA. It appears to be a stimulant rather than another MDA. At 50 milligrams, one person was awake and alert all night, but reported no MDA-like effects.

#101 MDAL; N-ALLYL-MDA; 3,4-METHYLENEDIOXY-N-ALLYLAMPHETAMINE

SYNTHESIS: A total of about 20 mL allylamine was introduced under the surface of 20 mL concentrated HCl, and the mixture stripped of volatiles under vacuum The resulting 24 g of wet material did not yield any crystals with either acetone or Et_2O. This was dissolved in 75 mL MeOH, treated with 4.45 g 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation), and finally with 1.1 g sodium cyanoborohydride. Concentrated HCl was added as needed over the course of 5 days to keep the pH constant at about 6. The reaction mixture was then added to a large amount of H_2O, acidified with HCl, and extracted with 3x100 mL CH_2Cl_2. The aqueous phase was made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. Evaporation of the solvent from these extracts yielded 3.6 g of an amber oil which, on distillation at 90-95 °C at 0.2 mm/Hg, yielded 2.6 g of an off-white oil. This was dissolved in 10 mL IPA, neutralized with about 25 drops of concentrated HCl, and the resulting clear but viscous solution was diluted with Et_2O until crystals formed. These were removed by filtration, washed with IPA/Et_2O (1:1), then with Et_2O, and air dried to constant weight. There was thus obtained 2.5 g of 3,4-methylenedioxy-N-allylamphetamine hydrochloride (MDAL) with a mp of 174-176 °C and a proton NMR spectrum that showed that the allyl group was intact. Anal. ($C_{13}H_{18}ClNO_2$) N.



DOSAGE: greater than 180 mg.

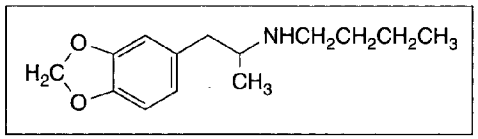
DURATION: unknown.

EXTENSIONS AND COMMENTARY: Here is another inactive probe, like MDPR, that could possibly serve as a primer to LSD. The three carbon chain on the nitrogen seen with MDPR is almost identical to the three carbon chain on the nitrogen atom of MDAL. And yet, where an "inactive" level of 180 milligrams of MDPR is a rather fantastic enhancer of LSD action, the same weight of this compound not only does not enhance, but actually seems to somewhat antagonize the action of LSD. All this difference from just a couple of hydrogen atoms. Identical carbon atoms, identical oxygen atoms, and an identical nitrogen atom. And all in identical places. Simply $C_{13}H_{18}ClNO_2$ rather than $C_{13}H_{20}ClNO_2$.

So, apparently, almost identical is not good enough!

#102 MDBU; N-BUTYL-MDA; 3,4-METHYLENEDIOXY-N-BUTYLAMPHETAMINE

SYNTHESIS: A total of 30 mL butylamine was introduced under the surface of 33 mL concentrated HCl, and the mixture stripped of volatiles under vacuum. The resulting glassy solid was dissolved in 160 mL MeOH and treated with 7.2 g 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation). To this there was added 50% NaOH dropwise until the pH was at about 6 as determined by the use of external dampened universal pH paper. The solution was vigorously stirred and 2.8 g sodium cyanoborohydride was added. Concentrated HCl was added as needed, to keep the pH constant at about 6. The addition required about two days, during which time the reaction mixture first became quite cottage-cheese like, and then finally thinned out again. All was dumped into 1 L H_2O acidified with HCl, and extracted with 3x100 mL CH_2Cl_2. These extracts were combined, extracted with 2x100 mL dilute H_2SO_4, which was combined with the aqueous fraction above. This latter mixture was made basic with 25% NaOH, and extracted with 3x150 mL CH_2Cl_2. Evaporation of the solvent yielded 4.0 g of an amber oil which, on distillation at 90-100 °C at 0.15 mm/Hg, yielded 3.2 g of a white clear oil. This was dissolved in 20 mL IPA, neutralized with 30 drops of concentrated HCl, and the spontaneously formed crystals were diluted with sufficient anhydrous Et_2O to allow easy filtration. After Et_2O washing and air drying, there was obtained 2.8 g of 3,4-methylenedioxy-N-butylamphetamine hydrochloride (MDBU) as white crystals with a mp of 200-200.5 °C. Anal. ($C_{14}H_{22}ClNO_2$) N.



DOSAGE: greater than 40 mg.

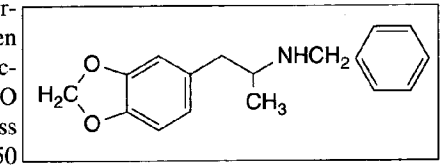
DURATION: unknown.

EXTENSIONS AND COMMENTARY: Straight chain homologues on the nitrogen atom of MDA longer than two carbons are probably not active. This butyl compound provoked no interest, and although the longer chain counterparts were made by the general sodium cyanoborohydride method (see under MDBZ), they were not tasted. All mouse assays that compared this homologous series showed a consistent decrease in action (anesthetic potency and motor activity) as the alkyl chain on the nitrogen atoms was lengthened.

This synthetic procedure, using the hydrochloride salt of the amine and sodium cyanoborohydride in methanol, seems to be quite general for ketone compounds related to 3,4-methylenedioxyphenylacetone. Not only were most of the MD-group of compounds discussed here made in this manner, but the use of phenylacetone (phenyl-2-propanone, P-2-P) itself appears to be equally effective. The reaction of butylamine hydrochloride in methanol, with phenyl-2-propanone and sodium cyanoborohydride at pH of 6, after distillation at 70-75 °C at 0.3 mm/Hg, produced N-butylamphetamine hydrochloride (23.4 g from 16.3 g P-2-P). And, in the same manner with ethylamine hydrochloride there was produced N-ethylamphetamine (22.4 g from 22.1 g P-2-P) and with methylamine hydrochloride there was produced N-methylamphetamine hydrochloride (24.6 g from 26.8 g P-2-P). The reaction with simple ammonia (as ammonium acetate) gives consistently poor yields in these reactions.

#103 MDBZ; N-BENZYL-MDA; 3,4-METHYLENEDIOXY-N-BENZYLAMPHETAMINE

SYNTHESIS: To a suspension of 18.6 g benzylamine hydrochloride in 50 mL warm MeOH there was added 2.4 g of 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 1.0 g sodium cyanoborohydride. Concentrated HCl in MeOH was added over several days as required to maintain the pH at about 6 as determined with external, dampened universal paper. When the demand for acid ceased, the reaction mixture was added to 400 mL H_2O and made strongly acidic with an excess of HCl. This was extracted with 3x150 mL CH_2Cl_2 (these extracts must be saved as they contain the product) and the residual aqueous phase made basic with 25% NaOH and again extracted with 4x100 mL CH_2Cl_2. Removal of the solvent under vacuum and distillation of the 8.7 g pale yellow residue at slightly reduced pressure provided a colorless oil that was pure, recovered benzylamine. It was best characterized as its HCl salt (2 g in 10 mL IPA neutralized with about 25 drops concentrated HCl, and dilution with anhydrous Et_2O gave beautiful white crystals, mp 267-268 °C). The saved CH_2Cl_2 fractions



above were extracted with 3x100 mL dillute H_2SO_4. These pooled extracts were back-washed once with CH_2Cl_2, made basic with 25% NaOH, and extracted with 3x50 mL CH_2Cl_2. The solvent was removed from the pooled extracts under vacuum, leaving a residue of about 0.5 g of an amber oil. This was dissolved in 10 mL IPA, neutralized with concentrated HCl (about 5 drops) and diluted with 80 mL anhydrous Et_2O. After a few min, 3,4-methylenedioxy-N-benzylamphetamine hydrochloride (MDBZ) began to appear as a fine white crystalline product. After removal by filtration, Et_2O washing and air drying, this weighed 0.55 g, and had a mp of 170-171 °C with prior shrinking at 165 °C. Anal. ($C_{17}H_{20}ClNO_2$) N.

DOSAGE: greater than 150 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: The benzyl group is a good ally in the synthetic world of the organic chemist, in that it can be easily removed by catalytic hydrogenation. This is a trick often used to protect (for a step or series of steps) a position on the molecule, and allowing it to become free and available at a later part in a synthetic scheme. In pharmacology, however, it is often a disappointment. With most centrally active alkaloids, there is a two-carbon separation between the weak base that is called the aromatic ring, and the strong base that is called the nitrogen. This is what makes phenethylamines what they are. The phen- is the aromatic ring (this is a shortened form of prefix phenyl which is a word which came, in turn, from the simplest aromatic alcohol, phenol); the ethyl is the two carbon chain, and the amine is the basic nitrogen. If one carbon is removed, one has a benzylamine, and it is usually identified with an entirely different pharmacology, or is most often simply not active. A vivid example is the narcotic drug, Fentanyl. The replacement of the phenethyl group, attached to the nitrogen atom with a benzyl group, virtually eliminates its analgesic potency.

Here too, there appears to be little if any activity in the N-benzyl analogue of MDA. A number of other variations had been synthesized, and none of them ever put into clinical trial. With many of them there was an ongoing problem in the separation of the starting amine from the product amine. Sometimes the difference in boiling points could serve, and sometimes their relative polarities could be exploited. Sometimes, ion-pair extraction would work wonders. But occasionally, nothing really worked well, and the final product had to be purified by careful crystallization.

Several additional N-homologues and analogues of MDA are noted here. The highest alkyl group on the nitrogen of MDA to give a compound that had been assayed, was the straight-chain butyl homologue, MDBU. Six other N-alkyls were made, or attempted. Isobutylamine hydrochloride and 3,4-methylenedioxyphenylacetone were reduced with sodium cyanoborohydride in methanol to give 3,4-methylenedioxy-N-(i)-butylamphetamine boiling at 95-105 °C at 0.15 mm/Hg

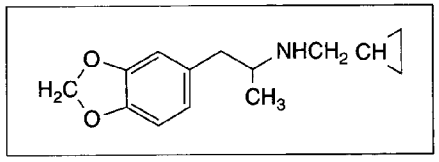
and giving a hydrochloride salt (MDIB) with a mp of 179-180 °C. Anal. ($C_{14}H_{22}ClNO_2$) N. The reduction with sodium cyanoborohydride of a mixture of (t)-butylamine hydrochloride and 3,4-methylenedioxyphenylacetone in methanol produced 3,4-methylenedioxy-N-(t)-butylamphetamine (MDTB) but the yield was miniscule. The amyl analog was similarly prepared from (n)-amylamine hydrochloride and 3,4-methylenedioxyphenylacetone in methanol to give 3,4-methylenedioxy-N-amylamphetamine which distilled at 110-120 °C at 0.2 mm/Hg and formed a hydrochloride salt (MDAM) with a mp of 164-166 °C. Anal. ($C_{15}H_{24}ClNO_2$) N. A similar reaction with (n)-hexylamine hydrochloride and 3,4-methylenedioxyphenylacetone in methanol, with sodium cyanoborohydride, produced after acidification with dilute sulfuric acid copious white crystals that were water and ether insoluble, but soluble in methylene chloride! This sulfate salt in methylene chloride was extracted with aqueous sodium hydroxide and the remaining organic solvent removed to give a residue that distilled at 110-115 °C at 0.2 mm/Hg to give 3,4-methylenedioxy-N-(n)-hexylamphetamine which, as the hydrochloride salt (MDHE) had a mp of 188-189 °C. Anal. ($C_{16}H_{26}ClNO_2$) N. An attempt to make the 4-aminoheptane analogue from the primary amine, 3,4-methylenedioxyphenylacetone, and sodiumcyanoborohydride in methanol seemed to progress smoothly, but none of the desired product 3,4-methylenedioxy-N-(4-heptyl)-amphetamine could be isolated. This base has been named MDSE, with a SE for septyl rather than HE for heptyl, to resolve any ambiguities about the use of HE for hexyl. In retrospect, it had been assumed that the sulfate salt would have extracted into methylene chloride, and the extraordinary partitioning of the sulfate salt of MDHE mentioned above makes it likely that the sulfate salt of MDSE went down the sink with the organic extracts of the sulfuric acid acidified crude product. Next time maybe ether as a solvent, or citric acid as an acid. With (n)-octylamine hydrochloride and 3,4-methylenedioxyphenylacetone in methanol, with sodium cyanoborohydride, there was obtained 3,4-methylenedioxy-N-(n)-octylamphetamine as a water-insoluble, ether-insoluble sulfate salt. This salt was, however, easily soluble in methylene chloride, and with base washing of this solution, removal of the solvent, and distillation of the residue (130-135 °C at 0.2 mm/Hg) there was eventually gotten a fine hydrochloride salt (MDOC) as white crystals with a mp of 206-208 °C. Anal. ($C_{18}H_{30}ClNO_2$) N.

As to N,N-dialkylhomologues of MDA, the N,N-dimethyl has been separately entered in the recipe for MDDM. Two efforts were made to prepare the N,N-diethyl homologue of MDA. The reasonable approach of reducing a mixture of diethylamine hydrochloride and 3,4-methylenedioxyphenylacetone in methanol with sodium cyanoborohydride was hopelessly slow and gave little product. The reversal of the functionality was successful. Treatment of MDA (as the amine) and an excess of acetaldehyde (as the carbonyl source) with sodium borohydride in a cooled acidic medium gave, after acid-base workup, a fluid oil that distilled at 85-90 °C at 0.15 mm/Hg and was converted in isopropanol with concentrated hydrochloric acid to 3,4-methylenedioxy-N,N-diethylamphetamine (MDDE) with a mp of 177-178 °C. Anal. ($C_{14}H_{22}ClNO_2$) N.

And two weird N-substituted things were made. Aminoacetonitrile sulfate and 3,4-methylenedioxyphenylacetone were reduced in methanol with sodium cyanoborohydride to form 3,4-methylenedioxy-N-cyanomethylamphetamine which distilled at about 160 °C at 0.3 mm/Hg and formed a hydrochloride salt (MDCM) with a mp of 156-158 °C after recrystallization from boiling isopropanol. Anal. ($C_{12}H_{15}ClN_2O_2$) N. During the synthesis of MDCM, there appeared to have been generated appreciable ammonia, and the distillation provided a fore-run that contained MDA. The desired product had an acceptable NMR, with the N-cyanomethylene protons as a singlet at 4.38 ppm. A solution of t-butylhydrazine hydrochloride and 3,4-methylenedioxyphenylacetone in methanol was reduced with sodium cyanoborohydride and gave, after acid-basing and distillation at 95-105 °C at 0.10 mm/Hg, a viscous amber oil which was neutralized in isopropanol with concentrated hydrochloric acid to provide 3,4-methylenedioxy-N-(t)-butylaminoamphetamine hydrochloride (MDBA) with a mp of 220-222 °C with decomposition. Anal. ($C_{14}H_{23}ClN_2O_2$); N: calcd, 9.77; found, 10.67, 10.84.

#104 MDCPM; CYCLOPROPYLMETHYL-MDA; 3,4-METHYLENEDIOXY-N-CYCLOPROPYLMETHYLAMPHETAMINE

SYNTHESIS: A solution of 9.4 g cyclopropylmethylamine hydrochloride in 30 mL MeOH was treated with 1.8 g 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 0.5 g sodium cyanoborohydride. Concentrated HCl was added as needed to keep the pH constant at about 6. After several days stirring, the reaction mixture was added to H_2O, acidified with HCl, and washed with 2x100 mL CH_2Cl_2. The aqueous phase was made basic with 25% NaOH, and extracted with 3x150 mL CH_2Cl_2. Removal of the solvent from these extracts under vacuum yielded 2.8 g of a crude product which, on distillation at 90-100 °C at 0.1 mm/Hg, yielded 0.4 g of a clear white oil. This was dissolved in a small amount of IPA, neutralized with a few drops of concentrated HCl, and diluted with anhydrous Et_2O to the point of turbidity. There was obtained a small yield of crystalline 3,4-methylenedioxy-N-cyclopropylmethylamphetamine hydrochloride (MDCPM) which was filtered off, Et_2O washed and air dried. The mp was 218-220 °C, with extensive darkening just prior to melting. Anal. ($C_{14}H_{20}ClNO_2$) N.



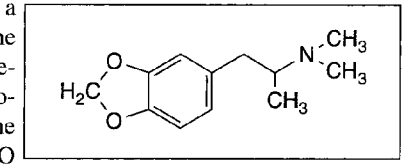
DOSAGE: greater than 10 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: The record of the tasting assay of this compound is pretty embarrassing. The highest level tried was 10 milligrams, which showed no hint of activity. But in light of the rather colorful activities of other cyclopropylmethyl things such as CPM and 2C-T-8, this compound might someday warrant reinvestigation. It is a certainty that the yield could only be improved with a careful resynthesis.

#105 MDDM; N,N-DIMETHYL-MDA; 3,4-METHYLENEDIOXY-N,N-DIMETHYLAMPHETAMINE

SYNTHESIS: To a well stirred solution of 9.7 g dimethylamine hydrochloride in 50 mL MeOH there was added 3.56 g of 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 0.88 g sodium cyanoborohydride. A 1:1 mixture of concentrated HCl and MeOH was added as required to maintain the pH at about 6 as determined with external, dampened universal paper. Twenty drops were called for over the first four h, and a total of 60 drops were added over the course of two days at which time the reduction was complete. After the evaporation of most of the MeOH solvent, the reaction mixture was added to 250 mL H_2O and made strongly acidic with an excess of HCl. After washing with 2x100 mL CH_2Cl_2 the aqueous phase was made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent under vacuum yielded a nearly colorless oil that was distilled at 85-90 °C at 0.3 mm/Hg. There was obtained 1.5 g of a water-white oil that was dissolved in 8 mL IPA, neutralized with concentrated HCl and then diluted with 10 mL anhydrous Et_2O. The slightly turbid solution deposited a light lower oily layer which slowly crystallized on scratching. With patience, an additional 75 mL of Et_2O was added, allowing the formation of a white crystalline mass. This was removed by filtration and washed with additional Et_2O. After air drying there was obtained 1.3 g of 3,4-methylenedioxy-N,N-dimethylamphetamine hydrochloride (MDDM) with a mp of 172-173 °C. The NMR spectrum (60 mH) of the hydrochloride salt (in D_2O and with external TMS) was completely compatible with the expected structure. The signals were: 1.25, 1.37 (d) CCH_3, 3H; $ArCH_2$ under the $N(CH_3)_2$, 2.96, 8H; CH (m) 3.65; CH_2O_2 (s) 6.03 2H; ArH 6.93 (3H). Anal: ($C_{12}H_{18}ClNO_2$) N.



DOSAGE: greater than 150 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 150 mg) " No effects whatsoever."

(with 150 mg) "The effects, if any, were so-so. Perhaps a threshold. But my libido was non-existent for three days."

(with 550 mg) "I took 550 milligrams of it Saturday night and I had a pretty bad trip. On a scale of positive 10 to negative 10 it was about a negative 6. It really downed me. Two other friends took 200 milligrams. They found it very pleasant after about 20 minutes. It was a plus 3 [on the -10 to +10 scale]. Then it wore off a little bit; and then, 4 hours later, it hit them even stronger and was about a plus 5."

(with 1000 mg) "I took up to a gram of it and absolutely nothing."

EXTENSIONS AND COMMENTARY: I cannot attest for the actual drug that had been used in the two larger-dose reports above. These are from an anonymous source associated with clandestine syntheses. If this material does eventually prove to be active, it is going to require a pretty hefty dose. But it may well have some activity, as there have been reports in the forensic literature of its preparation, or at least its intended preparation, in illicit laboratories. It seems unlikely that much effort would be directed towards the synthesis of a completely inactive compound.

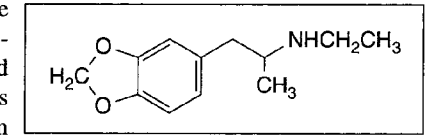
The reduced potency of MDDM has been exploited in an unexpected way. Based on the premise that the dialkylation of the amine group of amphetamine makes the parent compound intrinsically less active but without interfering with its ability to enter the brain, a large number of materials have been explored to take advantage of this very property. There is a need in medical diagnosis for agents that can allow various organs of the body to be visualized. One of the most powerful modalities for this work is the positron camera, and the use of the unusual properties of the positron that allow it to work. In the art of positron emission tomography (PET), an emitted positron (from a radioactive and thus unstable atom) will quickly interact with a nearby electron and all mass disappears with the complete conversion to energy. The detection of the produced pair of annihilation gamma rays will establish with great exactness the line along which this interaction occurred. So if one were to put an unstable atom into a compound that went to the tissue of the brain, and this atom were to decay there, the resulting gamma rays would allow a "photograph" to be made of the brain tissue. One could in this way visualize brain tissue, and observe abnormalities.

But what is needed is a molecule that carries the unstable atom (and specifically one that emits positrons) and one which goes to the brain as well. One of the very best unstable atoms for the formation of positrons is iodine, where there is an isotope of mass 122 which is perfect for these needs. And, of course, the world of the psychedelic drugs is tailor-made to provide compounds that go to the brain. But, the last thing that the physician wants, with the diagnostic use of such tools, would be to have the patient bouncing around in some turned-on altered state of consciousness.

So the completely logical union of these requirements is to take a compound such as DOI (carrying the needed atom and certainly going to the brain) and put two methyl groups on the nitrogen (which should reduce the chances for conspicuous biological activity). This compound was made, and it does label the brain, and it has shown promise as a flow indicator in the brain, and it and several of its close relatives are discussed in their own separate recipe, called IDNNA.

#106 MDE; MDEA; EVE; N-ETHYL-MDA; 3,4-METHYLENEDIOXY-N-ETHYLAMPHETAMINE

SYNTHESIS: (from MDA) To a solution of 3.6 g of the free base of 3,4-methylenedioxyamphetamine (MDA) in 20 g pyridine, there was added 2.3 g acetic anhydride, and the mixture stirred at room temperature for 0.5 h. This was then poured into 250 mL H_2O and acidified with HCl. This aqueous phase was extracted with 3x75 mL CH_2Cl_2, the extracts pooled and washed with dilute HCl, and the solvent removed under vacuum. The pale amber residue of N-acetyl-3,4-methylenedioxyamphetamine weighed 5.2 g as the crude product, and it was reduced without purification. On standing it slowly formed crystals. Recrystallization from a mixture of EtOAc/hexane (1:1) gave white crystals with a mp of 92-93 °C.



A stirred suspension of 4.8 g LAH in 400 mL anhydrous THF was brought up to a reflux, and then treated with a solution of 5.0 g of the impure N-acetyl-3,4-methylenedioxyamphetamine in 20 mL anhydrous THF. Reflux conditions were maintained for 3 days, and then after cooling in an ice bath, the excess hydride was destroyed with the careful addition of H_2O. The 4.8 mL H_2O (in a little THF) was followed with 4.8 mL of 15% NaOH, and finally an additional 15 mL H_2O. The white, granular, basic mass of inorganic salts was removed by filtration, the filter cake washed with additional THF, and the combined filtrate and washings stripped of solvent under vacuum. The residue was dissolved in 20 mL IPA, made acidic with 40 drops of concentrated HCl, and diluted with 150 mL anhydrous Et_2O. The crystalline product was removed by filtration, washed with 80% Et_2O (containing IPA) followed by Et_2O itself, and then air dried to provide 3.0 g of 3,4-methylenedioxy-N-ethylamphetamine hydrochloride (MDE) as fine white crystals with a mp of 198-199 °C.

(from 3,4-methylenedioxyphenylacetone with aluminum amalgam) To 40 g of thin aluminum foil cut in 1 inch squares (in a 2 L wide mouth Erlenmeyer flask) there was added 1400 mL H_2O containing 1 g mercuric chloride. Amalgamation was allowed to proceed until there was the evolution of fine bubbles, the formation of a light grey precipitate, and the appearance of occasional silvery spots on the surface of the aluminum. This takes between 15 and 30 min depending on the freshness of the surfaces and the temperature of the H_2O. The H_2O was removed by decantation, and the aluminum was washed with 2x1400 mL of fresh H_2O. The

residual H_2O was removed as thoroughly as possible by shaking, and there was added, in succession and with swirling, 72.5 g ethylamine hydrochloride dissolved in 60 mL warm H_2O, 180 mL IPA, 145 mL 25% NaOH, 53 g 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation), and finally 350 mL IPA. The exothermic reaction was kept below 60 °C with occasional immersion into cold water and, when it was thermally stable, it was allowed to stand until it had returned to room temperature and all the insolubles settled to the bottom as a grey sludge. The clear yellow overhead was decanted and the sludge removed by filtration and washed with MeOH. The combined decantation, mother liquors, and washes, were stripped of solvent under vacuum, the residue suspended in 1500 ml of H_2O, and sufficient HCl added to make the phase distinctly acidic. This was then washed with 2x100 mL CH_2Cl_2, made basic with 25% NaOH, and extracted with 3x100 mL of CH_2Cl_2. After removal of the solvent from the combined extracts, there remained 59.5 g of an amber oil which was distilled at 145-150 °C at 0.5 mm/Hg, producing 40.3 g of an off-white oil. This was dissolved in 600 mL IPA, neutralized with about 20 mL of concentrated HCl and then treated with 300 mL anhydrous Et_2O. After filtering off the white crystals, washing with a IPA/Et_2O (2:1) mixture, with Et_2O and air drying, the final 3,4-methylenedioxy-N-ethylamphetamine hydrochloride (MDE) weighed 37.4 g.

(from 3,4-methylenedioxyphenylacetone with $NaBH_3CN$) To a well stirred solution of 31.0 g ethylamine hydrochloride in 110 mL MeOH there was added 6.6 g of 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 3.0 g sodium cyanoborohydride. Concentrated HCl in MeOH was added as required to maintain the pH at about 6 as determined with external, dampened universal pH paper. About 2 days were required for the reduction to be complete as determined by the final stabilization of the pH. The reaction mixture was added to 1 L H_2O and made strongly acidic with an excess of HCl. After washing with 2x100 mL CH_2Cl_2 the aqueous phase was made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent under vacuum yielded 8.3 g of a pale amber oil that was distilled at 85-100 °C at 0.2 mm/Hg. There was obtained 6.0 g of a water-white oil that was dissolved in 65 mL IPA and neutralized with 75 drops of concentrated HCl which produced crystals spontaneously. These were diluted with some 20 mL of anhydrous Et_2O removed by filtration, washed first with IPA/Et_2O (2:1), and then with Et_2O. After air drying there was obtained 6.1 g of 3,4-methylenedioxy-N-ethylamphetamine hydrochloride (MDE) with a mp of 201-202 °C. Anal. ($C_{12}H_{18}ClNO_2$) N.

DOSAGE: 100 - 200 mg.

DURATION: 3 - 5 h.

QUALITATIVE COMMENTS: (with 100 mg) "There was a warm light all about me. And a gentle, almost alcohol-like, intoxication. The drug seems to change my state of awareness, but it does nothing else. The world is as intense or as dull as I choose to make it. At the 1.5 hour point I was clearly dropping, and an hour later yet, completely without residue."

(with 160 mg) "The first effects were felt in forty minutes and I seemed to be completely there by the end of that first hour. There was an initial slightly dizzy intoxication, and then I felt very nice. A good intoxication, with maybe a little motor incoordination. There was absolutely no appetite at all. The next morning there was still some feeling of elation but I was still very relaxed. High marks for the quality of the experience."

(with 160 mg) "Overall this was a wonderful experience. I felt that the effect was stronger and smoother than MDMA, but perhaps the group enhancement may be partly responsible. I felt definitely fewer physiological side-effects than with MDMA, particularly the urinating problem; although there was dehydration, there was less burning annoyance."

(with 160 mg) "I was hard hit, to the extent that there was difficulty in verbalizing and following other people's thoughts. I entered the experience with some cold symptoms, and my sore throat disappeared. I felt quite intoxicated and tranquilized."

(with 200 mg) "Very stoned. There was some nausea in the beginning of the experience. As it developed I found it very difficult to concentrate on what I was thinking or saying simply due to the extraordinary nature of coming on to this material. There is noticeable jaw-clenching and rice crispies in the ears. This is a meditative material not unlike MDMA except there are more difficulties in forming words. And there is a problem in focusing the eyes, what I want to call 'eye-romp.' My anorexia was extremely long-lived—perhaps a total of 72 hours. This may have been too high a dosage."

EXTENSIONS AND COMMENTARY: This immediate homologue of MDMA has a very similar chronology but requires a slightly larger dose. Another similarity is the occasional report of teeth clenching, especially following the use of supplemental dosages intended to extend the effects of the drug. These supplements have been explored in the 50 to 75 milligram range, usually at the two hour point. In one unpublished clinical experiment with MDMA, an extension was attempted at the 1 hour 45 minute point with MDE rather than with MDMA, to see if there was any change in the qualitative character of the experience. The effective time of intoxication was extended, but the group fell surprisingly quiet, with a drop in the usual urge to converse and interact.

The effects of MDE are similar in many ways to those of MDMA, but there are believable differences. The particular magic, and affective transference, does not appear to be there. There is a stoning intoxication, as there is with MDA, and there is a seemingly unrewarding aspect to the upping of the dosages, again similar to MDA, and the properties of unusually easy communication and positive self-viewing of MDMA seem to be absent. Maybe the "S" isomer would have these

properties, and they are lost in the racemate due to something coming from a more potent "intoxicating" "R" isomer. The optical isomers have never been evaluated separately in man.

There are only two ways in which two drugs can interact to produce a result that is not obvious from the summing of their individual actions. One is the process of synergism, where two active materials are allowed to interact within a single individual and at one time, and the consequence of this interaction is different than that which would have been expected. The other is the process of potentiation, where only one drug is active, but the presence of the second (and inactive) drug enhances the observed action of the first. MDE seems to fall in the first category.

The "piggy-back" or "window exploitation" studes were first discovered and explored with MDE, and have subsequently been extended most successfully with MDMA. The earliest procedure used was to assay modest quantities of active materials at the drop-off period of MDE, to exploit the open and benign state that was present. Usually, only a fraction of the standard dosage of the following drug was necessary to evoke a full experience. In psychotherapy applications, this sequence has been frequently used with MDMA followed by a second material that has been chosen to modify and expand the opening that the MDMA produced.

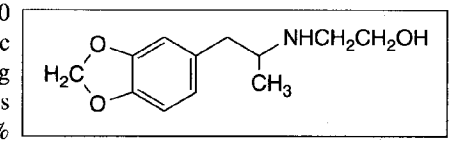
With the placement of MDMA under legal control in 1985, MDE occasionally appeared in the illicit street trade. It had been called EVE, which carries some perverse logic in light of the nickname used occasionally for MDMA, which was ADAM. The term INTELLECT has been used for it as well, but there has been no apparent reason advanced for this. And a final note on nomenclature. An old literature use of the code MDE was for the compound 3,4-methylenedioxyethanolamine. See the discussion on this under the recipe for DME.

I have been told of an analogue of MDE that has been synthesized, and explored by the researcher who synthesized it. It contains the N-trifluoroethyl group common to several pharmaceuticals such as Quazepam. The analogue is 3,4-methylenedioxy-N-(2,2,2-trifluoroethyl)amphetamine hydrochloride (mp 207-209 °C) which was made from 2,2,2-trifluoroethylamine and 3,4-methylenedioxyphenylacetone and sodium cyanoborohydride in methanol. The best final line for this compound is that it is "possibly active." The most heroic dosage schedule mentioned was a total of 500 milligrams, taken in three approximately equal portions over the course of five or six hours, with only a very mild intoxication and little or no sympathomimetic effects. And what little there might have been was quickly gone. A collection of totally unexplored N-substituted homologues and analogues of MDE is gathered at the end of the recipe for MDBZ.

Another direction that has been used to homologate the MDMA and MDE structure is with the length of the aliphatic chain that carries the phenyl ring and the amine function. "H" shows the two-carbon chain, "I" shows the amphetamine chain length, and MDE can be called ETHYL-I. The four-carbon chain is the "J" group, and this entire Muni-Metro concept is explained under METHYL-J.

#107 MDHOET; HYDROXYETHYL-MDA; 3,4-METHYLENEDIOXY-N-(2-HYDROXYETHYL)AMPHETAMINE

SYNTHESIS: To a well stirred solution of 25 g ethanolamine hydrochloride in 75 mL MeOH there was added 4.45 g of 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 1.1 g sodium cyanoborohydride. Concentrated HCl in MeOH was added as required, over the next few days, to maintain the pH at about 6 as determined with external, dampened universal pH paper. The reaction mixture was added to 300 mL H_2O and made strongly acidic with an excess of HCl. After washing with 3x100 mL CH_2Cl_2 the aqueous phase was made basic with 25% NaOH, and extracted with 4x100 mL CH_2Cl_2. Removal of the solvent under vacuum yielded 3.5 g of a viscous off-white oil that was distilled at 160 °C at 1.3 mm/Hg to give 2.0 g of a white viscous oil. The pot residue remained fluid, but was discarded. This distillate was dissolved in 8.0 mL IPA to give, eventually, a clear solution. This was neutralized with concentrated HCl and diluted with 100 mL anhydrous Et_2O. The loose white crystals of 3,4-methylenedioxy-N-(2-hydroxy-ethyl)amphetamine hydrochloride (MDHOET) that formed were removed by filtration, washed with Et_2O, and air dried. These weighed 2.3 g, and had a mp of 147-148 °C. Anal. ($C_{12}H_{18}ClNO_3$) N.



DOSAGE: greater than 50 mg.

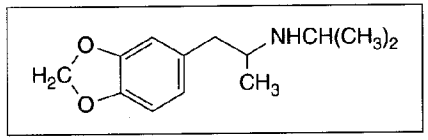
DURATION: unknown.

EXTENSIONS AND COMMENTARY: Most compounds with bare, exposed polar groups like hydroxyls are not centrally active, as they simply do not have any way of getting into the brain. MDHOET is certainly not very active, if it is active at all.

There was one report that at very high doses some central effects were indeed observed. With quantities in the several hundreds of milligrams a picture emerged of changes in perceived color and depth perception, but without euphoria. It was said to resemble a mild dose of ketamine. This is an interesting comment, in that ketamine has found its major medical use as an anesthetic, and MDHOET is among the most effective of all the N-substituted MDA derivatives assayed in several animal analgesia models.

#108 MDIP; N-ISOPROPYL-MDA; (3,4-METHYLENEDIOXY-N-ISOPROPYLAMPHETAMINE)

SYNTHESIS: To a well stirred and cooled solution of 14.75 g isopropylamine in 100 mL MeOH there was added 4.45 g of 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by a 1:1 mixture of concentrated HCL and MeOH, sufficient to bring the pH to about 4. This was followed with 1.1 g sodium cyanoborohydride, and stirring was continued overnight. When the pH increased to over 6 there was added an additional 0.5 g of the borohydride, and additional methanolic HCl was added as needed to maintain the pH there. When the pH became stable, the reaction mixture was brought soundly acid with the addition of yet additional HCl, and all solvents were removed under vacuum. The residues were added to 500 mL H_2O and washed with 3x100 mL CH_2Cl_2. The aqueous phase was made basic with 25% NaOH, and extracted with 4x100 mL CH_2Cl_2. Removal of the solvent under vacuum yielded 2.8 g of an amber liquid that was distilled at 95-110 °C at 0.3 mm/Hg. There was obtained about 2 mL of a white oil that was dissolved in 10 mL of IPA, neutralized with about 20 drops of concentrated HCl producing spontaneous crystals. These were diluted with some 40 mL of anhydrous Et_2O, removed by filtration, washed with Et_2O, and then air dried. There was obtained 1.6 g of 3,4-methylenedioxy-N-isopropylamphetamine hydrochloride (MDIP) with a mp of 186-186.5 °C with prior sintering at 185 °C. Anal. ($C_{13}H_{20}ClNO_2$) N.



DOSAGE: greater than 250 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 250 mg) "At 35 minutes there was an extremely slight head disturbance which increased over the next few minutes. I would have missed it if there had been any sensory input at all. At the one hour point there was a slight physical malaise, but no 'open window' of any kind, either like MDMA or like LSD. At the most, this was a threshold, and in another half hour, I was completely baseline."

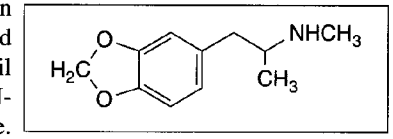
EXTENSIONS AND COMMENTARY: The structure of MDIP can be looked at as exactly that of MDE but with an additional methyl group (one carbon) hanging off the ethyl that is on the nitrogen. And with that slight additional weight, the activity has disappeared. On those occasions where research has shown a compound to be inactive, there has been some study made that could be called a "primer" experiment. Why not take advantage of the fact that an "inactive" compound might well be sitting in some receptor site in the brain without doing anything? Might its presence, wherever it might be, have some effect if only a person were to explore it in the correct way? Might it augment or interfere with the action of another compound? Many experiments of this kind have been performed, geared to milk additional information out of a new trial of a new material.

Here is an example of a primer experiment that involved MDIP. Some five hours following an inactive trial with 120 milligrams of MDIP (maybe a slight disturbance at one hour, nothing at two hours) a calibration dose of 80 milligrams of MDMA was taken. The effects of the MDMA were noted at the 33 minute point, and an honest plus one was achieved at one hour. At this point a second 80 milligrams was added to the inventory that was already on board, and the general intoxication and the eye effects that followed were completely explained by the MDMA alone. It was obvious that the two drugs did not see one-another.

Sometimes an experiment can involve the assay of an unknown material at the supplement time of an active drug. This has been called "piggybacking." Here is an example. At the five hour point of an experiment with 140 milligrams of MDE (this had been a light experience, a plus one which had not laster more than two hours) a dosage of 200 milligrams of MDIP rekindled a +1 experience, a pleasant intoxication of the MDE sort, but one that was quite invested with tremor and some feelings of eye-popping. It was almost as if the physical toxic effects outweighed the mental virtues. Imagine an iceberg, with the bulk of its mass underwater. The MDE had had its own modest effects, and had submerged into invisibility, and the response to a little bit of an otherwise inactive MDIP was to refloat a bit of the otherwise unseeable MDE.

#109 MDMA; MDM; ADAM; ECSTASY; 3,4-METHYLENEDIOXY-N-METHYLAMPHETAMINE

SYNTHESIS: (from MDA) A solution of 6.55 g of 3,4-methylenedioxyamphetamine (MDA) as the free base and 2.8 mL formic acid in 150 mL benzene was held at reflux under a Dean Stark trap until no further H_2O was generated (about 20 h was sufficient, and 1.4 mL H_2O was collected). Removal of the solvent gave an 8.8 g of an amber oil which was dissolved in 100 mL CH_2Cl_2, washed first with dilute HCl, then with dilute NaOH, and finally once again with dilute acid. The solvent was removed under vacuum giving 7.7 g of an amber oil that, on standing, formed crystals of N-formyl-3,4-methylenedioxyamphetamine. An alternate process for the synthesis of this amide involved holding at reflux for 16 h a solution of 10 g of MDA as the free base in 20 mL fresh ethyl formate. Removal of the volatiles yielded an oil that set up to white crystals, weighing 7.8 g.



A solution of 7.7 g N-formyl-3,4-methylenedioxyamphetamine in 25 mL

148-153 °C. The variously hydrated polymorphs have distinct infrared spectra, but have broad mps that depend on the rate of heating.

DOSAGE: 80 - 150 mg.

DURATION: 4 - 6 h.

QUALITATIVE COMMENTS: (with 100 mg) "MDMA intrigued me because everyone I asked, who had used it, answered the question, 'What's it like?' in the same way: 'I don't know.' 'What happened?' 'Nothing.' And now I understand those answers. I too think nothing happened. But something seemed changed. Before the 'window' opened completely, I had some somatic effects, a tingling sensation in the fingers and temples — a pleasant sensation, not distracting. However, just after that there was a slight nausea and dizziness similar to a little too much alcohol. All these details disappeared as I walked outside. My mood was light, happy, but with an underlying conviction that something significant was about to happen. There was a change in perspective both in the near visual field and in the distance. My usually poor vision was sharpened. I saw details in the distance that I could not normally see. After the peak experience had passed, my major state was one of deep relaxation. I felt that I could talk about deep or personal subjects with special clarity, and I experienced some of the feeling one has after the second martini, that one is discoursing brilliantly and with particularly acute analytical powers."

(with 100 mg) "Beforehand, I was aware of a dull, uncaring tiredness that might have reflected too little sleep, and I took a modest level of MDMA to see if it might serve me as a stimulant. I napped for a half hour or so, and woke up definitely not improved. The feeling of insufficient energy and lack of spark that I'd felt before had become something quite strong, and might be characterized as a firm feeling of negativity about everything that had to be done and everything I had been looking forward to. So I set about my several tasks with no pleasure or enjoyment and I hummed a little tune to myself during these activities which had words that went: 'I shouldn't have done that, oh yes, I shouldn't have done that, oh no, I shouldn't have done that; it was a mistake.' Then I would start over again from the beginning. I was stuck in a gray space for quite a while, and there was nothing to do but keep doing what I had to do. After about 6 hours, I could see the whole mental state disintegrating and my pleasant feelings were coming back. But so was my plain, ornery tiredness. MDMA does not work like Dexedrine."

(with 120 mg) "I feel absolutely clean inside, and there is nothing but pure euphoria. I have never felt so great, or believed this to be possible. The cleanliness, clarity, and marvelous feeling of solid inner strength continued throughout the rest of the day, and evening, and through the next day. I am overcome by the profundity of the experience, and how much more powerful it was than previous experiences, for no apparent reason, other than a continually improving state of being. All the next day I felt like 'a citizen of the universe' rather than a citizen of the planet, completely disconnecting time and flowing easily from one activity to the next."

(with 120 mg) "As the material came on I felt that I was being enveloped, and my attention had to be directed to it. I became quite fearful, and my face felt cold and ashen. I felt that I wanted to go back, but I knew there was no turning back. Then the fear started to leave me, and I could try taking little baby steps, like taking first steps after being reborn. The woodpile is so beautiful, about all the joy and beauty that I can stand. I am afraid to turn around and face the mountains, for fear they will overpower me. But I did look, and I am astounded. Everyone must get to experience a profound state like this. I feel totally peaceful. I have lived all my life to get here, and I feel I have come home. I am complete."

(with 100 mg of the "R" isomer) "There were the slightest of effects noted at about an hour (a couple of paresthetic twinges) and then nothing at all."

(with 160 mg of the "R" isomer) "A disturbance of baseline at about forty minutes and this lasts for about another hour. Everything is clear by the third hour."

(with 200 mg of the "R" isomer) "A progression from an alert at thirty minutes to a soft and light intoxication that did not persist. This was a modest +, and I was at baseline in another hour."

(with 60 mg of the "S" isomer) "The effects began developing in a smooth, friendly way at about a half-hour. My handwriting is OK but I am writing faster than usual. At the one hour point, I am quite certain that I could not drive, time is slowing down a bit, but I am mentally very active. My pupils are considerably dilated. The dropping is evident at two hours, and complete by the third hour. All afternoon I am peaceful and relaxed, but clear and alert, with no trace of physical residue at all. A very successful ++."

(with 100 mg of the "S" isomer) "I feel the onset is slower than with the racemate. Physically, I am excited, and my pulse and blood pressure are quite elevated. This does not have the 'fire' of the racemate, nor the rush of the development in getting to the plateau."

(with 120 mg of the "S" isomer) "A rapid development, and both writing and typing are impossible before the end of the first hour. Lying down with eyes closed eliminates all effects; the visual process is needed for any awareness of the drug's effects. Some teeth clenching, but no nystagmus. Excellent sleep in the evening."

EXTENSIONS AND COMMENTARY: In clinical use, largely in psychotherapeutic sessions of which there were many in the early years of MDMA study, it became a common procedure to provide a supplemental dosage of the drug at about the one and a half hour point of the session. This supplement, characteristically 40 milligrams following an initial 120 milligrams, would extend the expected effects for about an additional hour, with only a modest exacerbation of the usual physical side-effects, namely, teeth clenching and eye twitching. A second supplement (as, for instance, a second 40 milligrams at the two and a half hour point) was rarely felt to be warranted. There are, more often than not, reports of tiredness and lethargy

on the day following the use of MDMA, and this factor should be considered in the planning of clinical sessions.

With MDMA, the usual assignments of activity to optical isomers is reversed from all of the known psychedelic drugs. The more potent isomer is the "S" isomer, which is the more potent form of amphetamine and methamphetamine. This was one of the first clear distinctions that was apparent between MDMA and the structurally related psychedelics (where the "R" isomers are the more active). Tolerance studies also support differences in mechanisms of action. In one study, MDMA was consumed at 9:00 AM each day for almost a week (120 milligrams the first day and 160 milligrams each subsequent day) and by the fifth day there were no effects from the drug except for some mydriasis. And even this appeared to be lost on the sixth day. At this point of total tolerance, there was consumed (on day #7, at 9:00 AM) 120 milligrams of MDA and the response to it was substantially normal with proper chronology, teeth clench, and at most only a slight decrease in mental change. A complete holiday from any drug for another 6 days led to the reversal of this tolerance, in that 120 milligrams of MDMA had substantially the full expected effects. The fact that MDMA and MDA are not cross-tolerant strengthens the argument that they act in different ways, and at different sites in the brain.

A wide popularization of the social use of MDMA occurred in 1984-1985 and, with the reported observation of serotonin nerve changes in animal models resulting from the administration of the structurally similar drug MDA, an administrative move was launched to place it under legal control. The placement of MDMA into the most restrictive category of the Federal Controlled Substances Act has effectively removed it from the area of clinical experimentation and human research. The medical potential of this material will probably have to be developed through studies overseas.

A word of caution is in order concerning the intermediate 3,4-methylenedioxyphenylacetone, which has also been called piperonylacetone. A devilish ambiguity appeared in the commercial market for this compound, centered about its name. The controversy focused on the meaning of the prefix, piperonyl, which has two separate chemical definitions. Let me try to explain this fascinating chaos in non-chemical terms. Piperonyl is a term that has been used for a two-ring system (the methylenedioxyphenyl group) either without, or with, an extra carbon atom sticking off of the side of it. Thus, piperonylacetone can be piperonyl (the two-ring thing without the extra carbon atom attached) plus acetone (a three carbon chain thing); the total number of carbons sticking out, three. Or, piperonylacetone can be piperonyl (the two-ring thing but with the extra carbon atom attached) plus acetone (a three carbon chain thing); the total number of carbons sticking out, four.

Does this make sense?

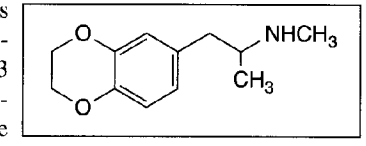
The three carbon sticking out job gives rise to MDA and to MDMA and to many homologues that are interesting materials discussed at length in these Book II comments. This is the usual item of commerce, available from both domestic and foreign suppliers. But the four-carbon sticking out job will produce totally weird

stuff without any apparent relationship to psychedelics, psychoactives or psychotropics whatsoever. I know of one chemical supply house which supplied the weird compound, and they never did acknowledge their unusual use of the term piperonyl. There is a simple difference of properties which might be of value. The three carbon (correct) ketone is an oil with a sassafras smell that is always yellow colored. The four carbon (incorrect) ketone has a weak terpene smell and is white and crystalline. There should be no difficulties in distinguishing these two compounds. But unprincipled charlatans can always add mineral oil and butter yellow to otherwise white solids to make them into yellow oils. Caveat emptor.

#110 MDMC; EDMA; 3,4-ETHYLENEDIOXY-N-METHYL-AMPHETAMINE

SYNTHESIS: To a solution of 27.6 g protocatechualdehyde (3,4-dihydroxybenzaldehyde) in 250 mL acetone there was added 57 g finely powdered anhydrous K_2CO_3 and 43 g 1,2-dibromoethane. The mixture was held at reflux for 16 h, and then the acetone removed by evaporation. The remaining tar-like goo was distributed between equal volumes of H_2O and CH_2Cl_2, and the phases separated by centrifugation. The organic phase was washed with 2x50 mL 5% NaOH, and the solvent removed under vacuum. The residue (22.0 g with the smell of the starting halide) was distilled to give a fraction that boiled at 110 °C at 0.25 mm/Hg to yield 3,4-ethylenedioxybenzaldehyde (1,4-benzodioxane-6-carboxaldehyde) as a white oil weighing 6.88 g. This spontaneously crystallized to give white solids that melted at 50-51 °C.

A solution of 6.64 g 3,4-ethylenedioxybenzaldehyde in 40 mL nitroethane was treated with 0.26 g anhydrous ammonium acetate and held at reflux for 3 days. TLC analysis showed that there was much aldehyde remaining unreacted, so an additional 0.7 g ammonium acetate was added, and the mixture held at reflux for an additional 6 h. The excess nitroethane was removed under vacuum. The residue was dissolved in 30 mL hot MeOH which, with patience and slow cooling, finally deposited a heavy yellow-gold powder. This product 1-(3,4-ethylenedioxyphenyl)-2-nitropropene melted at 95-96 °C and weighed 6.03 g when air dried to constant weight. Recrystallization from either MeOH or EtOAc gave the product as a yellow solid, but without any improvement in mp.



A solution of 4.0 g of 1-(3,4-ethylenedioxyphenyl)-2-nitropropene was made in 30 mL warm acetic acid. This was added to a suspension of 16 g elemental electrolytic iron in 75 mL acetic acid. The mixture was heated on the steam bath, and an exothermic reaction set in at about 70 °C. Heating was continued and the

reaction allowed to proceed until the mass was a thick gray color and a dirty scum had been formed on the surface. After about 2 h, the entire mix was poured into 2 L H_2O and filtered free of a little residual unreacted iron which was washed with CH_2Cl_2. The filtrate and washes were extracted with 3x100 mL CH_2Cl_2 and the pooled organic extracts washed with 2x50 mL 5% NaOH. Removal of the solvent gave 3.38 g of an amber oil which was distilled. The product 1-(3,4-ethylenedioxyphenyl)-2-propanone distilled as a white oil, at 105-110 °C at 0.2 mm/Hg. It weighed 2.74 g.

To 2.0 g. of 1 inch squares of light-weight aluminum foil there was added a solution of 50 mg mercuric chloride in 70 mL water. After standing at room temperature for 30 min, the H_2O was drained away, and the amalgamated aluminum washed twice with H_2O, and shaken as dry as possible. There was then added, promptly and in immediate sequence, a solution of 3 g methylamine hydrochloride in 3 mL H_2O, 9 mL IPA, 7.25 mL 25% NaOH, 2.70 g of 1-(3,4-ethylenedioxyphenyl)-2-propanone, and 18 mL IPA. The mixture was heated on the steam bath until an exothermic reaction set in, and then it was continuously swirled as the reaction proceeded. When the aluminum was consumed, there was a colorless gray sludge, and this was filtered and washed with 2x10 mL MeOH. The combined mother liquors and washes were stripped of solvent under vacuum. The two phase residue was suspended in 400 mL H_2O containing sufficient H_2SO_4 to make the resulting water solution acidic to pH paper. This was washed with 3x50 mL CH_2Cl_2, made basic with 25% NaOH, and the product extracted with 3x50 mL CH_2Cl_2. The resulting 3.01 g slightly amber residue oil was distilled at 110-120 °C at 0.25 mm/Hg to give 2.53 g of a white oil, which did not appear to absorb carbon dioxide. This was dissolved in 12 mL IPA, neutralized with 1 mL concentrated HCl and diluted with anhydrous Et_2O to the point of initial turbidity. There separated white crystals of 3,4-ethylenedioxy-N-methylamphetamine hydrochloride (MDMC) which weighed, when air dried to constant weight, 2.53 g.

DOSAGE: 200 or more mg.

DURATION: 3 - 5 h.

QUALITATIVE COMMENTS: (with 150 mg) "A flood of paresthesia at the 30 minute point, and then nothing. There was the development of a plus one-and-a half effect over the next hour with the tendency to drift into a dozing state with hypnogogic imagery. There were colored letters in the periphery of my visual field. There was no appetite loss nor was there any blood pressure rise. And no eye jiggle or teeth clenching. I was out of the experience in 4 to 5 hours. A repeat of this level a few days later gave a bare possible threshold with no other effects."

(with 200 mg) "There was something unmistakable at 45 minutes, with hints of nystagmus. Possibly MDMA-like, with no indicators of anything psychedelic. Subtle return to baseline, and there were no after-effects."

(with 250 mg) "Alert at 40 minutes, and to a clear ++ at an hour. Slight something in the eye muscles. Dropping thirty minutes later, and baseline at three hours."

(with 250 mg) "I am at a bare threshold at best."

EXTENSIONS AND COMMENTARY: What a strange and completely unsatisfactory compound! In the original run-up from low levels to increasing higher levels, there never was a dosage that was a minus, that had no effect. At every level, something was thought to be there, usually at a level of a single plus or thereabouts. But with different people, different responses. There is no way of guessing what an active level might be, or how consistent that level might be between different people, or for that matter what the responses are that might be expected at that level.

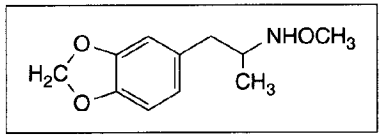
This was yet one more effort to find an MDMA-like substitute by the miniscule manipulation of the MDMA molecule. Perhaps a small molecular change might leave the particular magic of the MDMA action alone, but eliminate the serotonin neuron problem in test animals. Maybe the serotonin neuron change is essential for MDMA to have the action it has. Who can tell?

The original name that this compound got, during the several explorations of MDMA analogues, was based on the nickname for MDMA which was Adam. HAD'EM was mentioned with the hydroxy compound, MADAM with the 6-methyl homologue, and FLADAM with the 6-fluoro analogue. This compound got the sobriquet MACADAM from that horrible black gooey mess generated at the aldehyde stage. This was shortened to "C" and eventually the "C" was added to the MDMA parent name. Thus, MDMC. It doesn't really make sense; EDMA is more reasonable. But then there is no reason why MDMC should make sense.

#111 MDMEO; N-METHOXY-MDA; 3,4-METHYLENEDIOXY-N-METHYOXYAMPHETAMINE

SYNTHESIS: To a solution of 20.9 g methoxyamine hydrochloride in 75 mL MeOH (a strongly acidic solution) there was added 4.45 g 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 1.10 g sodium cyanoborohydride. There was the immediate formation of a solid phase, and the evolution of what appeared to be hydrogen cyanide. To this there were added about 4 mL 5% NaOH which brought the pH to the vicinity of 3 or 4. Another 1.0 g of sodium cyanoborohydride was added (no gas evolution this time) and stirring was continued at ambient temperature for 6 days. All was added to 500 mL H_2O, acidified with 10 mL HCl, and extraction with 3x100 mL CH_2Cl_2 removed almost all the color. The aqueous phase was made basic with 25% NaOH, and extracted with 4x100 mL CH_2Cl_2. Evaporation of the solvent from these extracts yielded 1.8 g of a pale yellow oil which, on distillation at 90-95 °C at 0.5 mm/Hg, gave a 1.6

g fraction of an absolutely white, viscous, clear oil. This was dissolved in 8 mL IPA and neutralized with concentrated HCl. The product was an exceptionally weak base, and appropriate end points must be respected on the external pH paper (yellow to red, rather than purple to orange). Anhydrous Et_2O was added to the point of turbidity, and as soon as crystallization had actually started, more Et_2O was added with stirring, for a net total of 200 mL. After a couple of h standing, the fine white crystalline 3,4-methylenedioxy-N-methoxyamphetamine hydrochloride (MDMEO) was removed by filtration, Et_2O washed, and air dried to constant weight. There was obtained 1.7 g of a product with a mp of 143-146 °C. The proton NMR was excellent with the N-methoxyl group a sharp singlet at 4.06 ppm. Anal. ($C_{11}H_{16}ClNO_3$) N.



DOSAGE: greater than 180 mgs.

DURATION: unknown

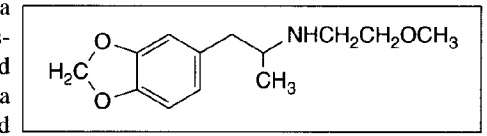
EXTENSIONS AND COMMENTARY: Why the interest in the N-methoxy analogue of MDA? There are several reasons. One, this is an isostere of MDE and it would be interesting to see if it might serve as a primer to the promotion of the effectiveness of other drugs (see primer discussion under MDPR). In one experiment, wherein a 60 microgram dosage of LSD was used an hour and a half after a 180 milligram load of MDMEO, there was no augmentation of effects. Thus, it would appear not to be a primer. Another reason for interest was that the material, although having an extremely similar overall structure to most of the active MD-series compounds, is very much a weaker base. And MDOH, which is also a very much weaker base than MDA, still shows the action and potency of MDA. And, as this compound appears to be inactive, base strength is not a sole predictor of activity.

The ultimate reason for making MDMEO was, of course, that it could be made. That reason is totally sufficient all by itself.

#112 MDMEOET; N-METHOXYETHYL-MDA; 3,4-METHYLENEDIOXY-N-(2-METHOXYETHYL)AMPHETAMINE

SYNTHESIS: A crude solution of methoxyethylamine hydrochloride was prepared from 17.7 g methoxyethylamine and 20 mL concentrated HCl with all volatiles removed under vacuum. This was dissolved in 75 mL MeOH and there was added 4.45 g of 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 1.3 g sodium cyanoborohydride. Concentrated HCl in MeOH was added as required to maintain the pH at about 6 as determined with external,

dampened universal pH paper. About 4.5 mL were added over the course of 5 days, at which time the pH had stabilized. The reaction mixture was added to 400 mL H_2O and made strongly acidic with an excess of HCl. After washing with 2x100 mL CH_2Cl_2 the aqueous phase was made basic with 25% NaOH, and extracted with 4x75 mL CH_2Cl_2. Removal of the solvent under vacuum yielded 6.0 g of an amber oil that was distilled at 110-120 °C at 0.2 mm/Hg. There was obtained 4.7 g of a crystal-clear white oil that was dissolved in 30 mL IPA and neutralized with 45 drops of concentrated HCl producing a heavy mass of spontaneous crystals that had to be further diluted with IPA just to be stirred with a glass rod. These were diluted with 200 mL of anhydrous Et_2O, removed by filtration, and washed with additional Et_2O. After air drying there was obtained 4.9 g of 3,4-methylenedioxy-N-(2-methoxyethyl)amphetamine hydrochloride (MDMEOET) with a mp of 182.5-183 °C. Anal. ($C_{13}H_{20}ClNO_3$) N.



DOSAGE: greater than 180 mg.

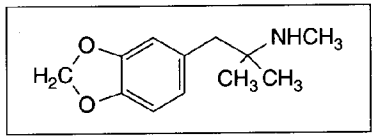
DURATION: unknown.

EXTENSIONS AND COMMENTARY: This is another example of the replacement of a neutral atom out near the end of a chain, with a more basic and a more polar one. MDMEOET would be called an isostere of MDBU in that it has the same shape, with a methylene unit (the CH_2) replaced by an oxygen atom. No activity turned up with either compound, so nothing can be learned from this particular example of change of polarity.

#113 MDMP; α,α,N-TRIMETHYL-3,4-METHYLENEDIOXY-PHENETHYLAMINE; METHYLENEDIOXYMEPHENTERMINE

SYNTHESIS: To a well stirred solution of 1.64 g of 1-(N-(benzyloxycarbonyl)amino)-1,1-dimethyl-2-(3,4-methylenedioxyphenyl)ethane (see under MDPH for its preparation) in 10 mL anhydrous THF there was added a suspension of 0.38 g LAH in 25 mL THF. All was held at reflux for 24 h, the excess hydride was destroyed by the addition of 1.5 mL H_2O, and sufficient aqueous NaOH was added to make the reaction mixture basic and flocculant enough to be filterable. The inorganic solids were removed by filtration and, following washing with THF, the combined filtrate and washings were stripped of organic solvent under vacuum. The residue was dissolved in 100 mL Et_2O and washed with 2x50 mL saturated aqueous $NaHCO_3$. After drying the organic phase with anhydrous $MgSO_4$, the solvent

was removed under vacuum to give a yellow oil. This was dissolved in 50 mL absolute EtOH and neutralized with concentrated HCl. Removal of the solvent under vacuum yielded an off-white solid that was recrystallized from an EtOH/EtOAc mixture to provide 0.84 g of α,α,N-trimethyl-3,4-methylenedioxyphenethylamine hydrochloride (MDMP) with a mp of 206-208 °C. The NMR spectrum showed the α,α-dimethyl pair as a singlet at 1.38 ppm. Anal. ($C_{12}H_{18}ClNO_2$) C,H,N.



DOSAGE: above 110 mg.

DURATION: perhaps 6 hours.

QUALITATIVE COMMENTS: (with 60 mg) "There was a faint, dull alerting at just over a half hour. The time sense was out of order, and an absence of visuals but a generalized attentiveness to my surroundings was suggestive of MDMA. Nothing remained at the six hour point."

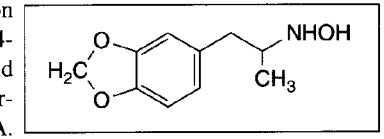
(with 110 mg) "There was a light-headedness, and a complete absence of libido. Nothing in any way psychedelic, but there are hints of discomfort (jaw tension) that will bear close watching at higher dosages. It might evolve at higher levels into something like MDMA."

EXTENSIONS AND COMMENTARY: This is one of several candidates for clinical use as a substitute for MDMA, but there will have to be a much broader study of its qualitative action in man. It is clearly not psychedelic at these modest levels, and in *in vitro* animal studies it was apparently inactive as a serotonin releaser. The warped logic for looking at phentermine analogs was discussed in the comments that concerned MDPH. The initials used here have been chosen with care. MDM should not be used as it has found some currency as an abbreviation for MDMA (Methylene-Dioxy-Methamphetamine). MDMP fits neatly with Methylene-Dioxy-Me-Phentermine.

#114 MDOH; N-HYDROXY-MDA; 3,4-METHYLENEDIOXY-N-HYDROXYAMPHETAMINE

SYNTHESIS: To a well stirred solution of 14.8 g hydroxylamine hydrochloride in 120 mL MeOH there was added 3.6 g of 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 1.0 g sodium cyanoborohydride. The oxime, prepared from the ketone and hydroxylamine in MeOH with pyridine, may

be substituted for these two components. Concentrated HCl was added over the course of a couple of days, to keep the pH near neutrality. When the reaction was complete, it was added to H_2O, made strongly acidic with HCl, and washed with 3x100 mL CH_2Cl_2. The aqueous phase was made basic with 25% NaOH, and reextracted with 3x100 mL of CH_2Cl_2. The extracts were pooled, and the solvent removed under vacuum to give 1.7 g of an oily residue which, with pumping under a hard vacuum for a few minutes, changed to a white solid. This can be Kugelrohred if the vacuum is sufficiently good to keep the temperature during the distillation below 100 °C. The extremely viscous distillate formed crystals immediately upon wetting with IPA. It was dissolved in 20 mL of warm IPA and neutralized with concentrated HCl, with the titration end-point being red rather than orange on universal pH paper. Modest addition of Et_2O allowed the formation of 3,4-methylenedioxy-N-hydroxyamphetamine hydrochloride (MDOH) as white crystals, which weighed 1.4 g when air dried. If the temperature of distillation exceeded 100 °C, there was extensive decomposition during distillation, with the formation of 3,4-methylenedioxyamphetamine (MDA) and the oxime of the ketone. Under these circumstances, the only base isolated was MDA.



The surest isolation procedure was to obtain MDOH as the free base, as a crystalline solid which could be recrystallized from 5 volumes of boiling IPA. The free base had a mp of 94-95 °C (and should not be confused with the oxime of 3,4-methylenedioxyphenylacetone which has a mp of 86-88 °C since the mixed mp is depressed, mp 56-62 °C, or with the free base of MDA which is an oil). Anal. ($C_{10}H_{13}NO_3$) N. The hydrochloride salt had a mp of 149-150 °C (and should not be confused with the hydrochloride of MDA which has a mp of 185-186 °C since the mixed mp is depressed, mp 128-138 °C). Anal. ($C_{10}H_{14}ClNO_3$) N. Acetic anhydride can serve as a useful tool for distinguishing these materials. MDA gives an N-acetyl derivative with an mp of 92-93 °C. MDOH gives an N,O-diacetyl derivative with a mp of 72-74 °C. Methylenedioxyphenylacetone oxime gives an O-acetyl derivative that is an oil.

DOSAGE: 100 - 160 mg.

DURATION: 3 - 6 h.

QUALITATIVE COMMENTS: (with 100 mg) "I felt hampered the first hour by some internal barrier, which prevented total enjoyment. However, this began to break through in a wonderful way just before the supplement was offered. Since I felt I was beginning to move through the barrier, I declined the supplement, particularly since I was anxious to compare the after-effects with my first experience. I had found the first time very remarkable, but felt unusually tired for several days following. I feel it is important to know whether this is a specific drug-induced

effect, or the result of psychological phenomena. The experience continued in a rich, meaningful way. There was a marvelous inner glow, the warmth from all the other participants was wonderful to feel, nature was most beautiful. There were no dramatic breakthroughs, or rushes of insight or energy, but just a wonderful contemplative space where things gently unfolded as you put your attention on them."

(with 100 mg) "The material came on fairly rapidly. In about 30 minutes, I was intensely intoxicated, and more deeply than with MDMA. It was a glorious feeling, and beauty was everywhere enhanced. With eyes closed it felt marvelous, and it was appealing to pursue the inner experience. I did notice an internal dryness which was characteristic of MDMA, and I had similar difficulty in urinating, but not as intense as with MDMA."

(with 120 mg) "The colors of the market-place, of all the fresh foods, constituted a beautiful mosaic. Nothing practical, simply a real treasure to be used with individual intention and enjoyment. Everything was seen with new eyes, new meanings, faces, figures, the colors of the rainbow subconsciously individually applied. A 'soul-scape'. The following day very exhausted, tired, back-pain."

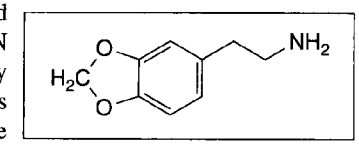
EXTENSIONS AND COMMENTARY: The first time that MDOH was synthesized, it had inadvertently and unknowingly been converted to MDA. And the search for proper dosage and characterization of effects of this product was, of course, the rediscovery of the dosage and the effects of MDA. It is one of the world's most remarkable coincidences that after the second synthesis of MDOH, when MDOH had really and truly been actually prepared, the brand new search for proper dosage and characterization of effects revealed that they were almost identical to the earlier observations for (the inadvertently produced) MDA.

This reminds me of my speculations in the discussion of both FLEA and the HOT compound where they also showed paired molecular structures with their prototypes that differ only by a single oxygen atom. Again, might there be some metabolic interconversion within the body? The immediate thought would be that the oxygen atom (the hydroxy group) might be metabolically removed, and the effects of either drug are due to the action of MDA. But the opposite direction is in many ways more appealing, the *in vivo* conversion of MDA to MDOH. Why more appealing? For one thing, oxidative changes are much more common in the body than reductive changes. For another, the conversion of amphetamine to N-hydroxyamphetamine is an intermediate in the conversion of amphetamine to phenylacetone, a known metabolic process in several animal species. And that intermediate, N-hydroxyamphetamine, is a material that gives the famous cytochrome P-450 complex that has fascinated biochemists studying the so-called NADPH-dependent metabolism.

I would put my money on the likelihood of MDA going to MDOH if it should turn out that the two drugs interconvert in the body. And in that case, it would be MDOH, or another metabolite on down the line that is common to both MDA and MDOH, that is the factor intrinsic to the intoxication that is produced. Human metabolic studies are needed, and they have not yet been done.

#115 MDPEA; 3,4-METHYLENEDIOXYPHENETHYLAMINE; HOMOPIPERONYLAMINE

SYNTHESIS: A suspension of 4.0 g LAH in 300 mL anhydrous Et_2O was stirred and heated to a gentle reflux in an inert atmosphere. There was added 3.9 g 3,4-methylenedioxy-ß-nitrostyrene (see under BOH for its preparation) by allowing the condensing Et_2O to leach it out from a Soxhlet thimble. After the addition was complete, the reaction mixture was held at reflux for an additional 48 h. It was then cooled and the excess hydride was destroyed by the cautious addition of 300 mL of 1.5 N H_2SO_4. When both phases were completely clear, they were separated, and the aqueous phase washed once with 50 mL Et_2O. There was then added 100 g potassium sodium tartrate, followed by sufficient base to bring the pH >9. This was extracted with 3x75 mL CH_2Cl_2, and the solvent from these pooled extracts was removed under vacuum. The residue was dissolved in 150 mL anhydrous Et_2O and saturated with anhydrous HCl gas. There was a heavy crystallization of 3,4-methylenedioxyphenethylamine hydrochloride (MDPEA) which weighed 3.0 g and had a mp of 212-213 °C.



DOSAGE: greater than 300 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 200 mg) "It was taken twice at different times in a dosage of 200 milligrams each time, without the slightest peripheral or central effects."

(with 300 mg) "My tinnitus had disappeared. Probably nothing."

EXTENSIONS AND COMMENTARY: How strange. Even more than DMPEA, this cyclic analogue MDPEA is a potential prodrug to dopamine, and would be a prime candidate for central activity. So why is this drug not active? The usual reason advanced by the pharmacologists is that the body is full of potent enzymes known as monoamine oxidases, and this is a monoamine, and so the body simply chews away on it in an oxidative manner, inactivating it before it ever makes it to some target receptor.

That is the pitch given in the textbooks. Phenethylamines are subject to easy enzymatic oxidation, hence they are not active. The presence of an alpha-

methyl group (the corresponding amphetamines) blocks the compound from easy access to the enzyme, and since that protects them from oxidative destruction, they are active. The oft-quoted exception is mescaline, and even it is largely destroyed, as evidenced by the large amount needed for activity (a fraction of a gram). Sorry, I can't buy it. This entire book is peppered with phenethylamines that are active at the few-milligram area. Why aren't they also destroyed as well? The textbooks simply are not right.

MDPEA was one of the seven compounds evaluated as to toxicity and animal behavi[illegible] he University of Michigan under contract from the Army Chemical Cente[illegible] Edgewood Arsenal code number was EA-1297. The number for MDA itself was EA-1298.

The beta-hydroxy analogue of MDPEA is the ethanolamine MDE, standing for methylenedioxyethanolamine. This is an old term, and in the more recent literature, since 1975 certainly, MDE has been used to represent methylenedioxyethylamphetamine. The ethanolamine compound is discussed in the recipe for DME.

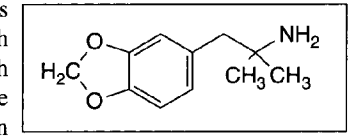
There is a family of compounds, to be discussed elsewhere, that is called the Muni-Metro (see under METHYL-J). The simplest member is this compound, MDPEA, and under its chemically acceptable synonym, homopiperonylamine, it can be called "H". Following that code, then, the N-methyl homologue of MDPEA is METHYL-H, and it has been looked at, clinically, as an antitussive agent. N-METHYL-MDPEA, or METHYL-H, or N-methyl-3,4-methylenedioxyphenethylamine is effective in this role at dosages of about 30 milligrams, but I have read nothing that would suggest that there were any central effects. I have tried it at this level and have found a little tightness of the facial muscles, but there was nothing at all in the mental area.

#116 MDPH; α,α-DIMETHYL-3,4-METHYLENEDIOXYPHENETHYLAMINE; 3,4-METHYLENEDIOXYPHENTERMINE

SYNTHESIS: To 150 mL of THF, under an atmosphere of nitrogen, there was added 11.2 g diisopropylamine, and the solution was cooled with external dry ice/IPA. There was then added 48 mL of a 2.3 M solution of butyllithium in hexane, dropwise, with good stirring. This was warmed to room temperature, stirred for a few min, and then all was cooled again in the dry ice bath. Following the dropwise addition of 4.4 g of isobutyric acid there was added 10.5 mL hexamethylphosphoramide. Again, the stirred reaction mixture was brought to room temperature for about 0.5 h. There was then added, drop-wise, 8.5 g 3,4-methylenedioxybenzyl chloride and the mixture allowed to stir overnight at room temperature. The reaction mixture was poured into 100 mL 10% HCl, and the excess THF was removed under vacuum. The acidic aqueous residue was extracted with 2x150 mL Et_2O. These

extracts were pooled, washed with 10% HCl, and then extracted with 3x75 mL of 4 N Na_2CO_3. These extracts were pooled, made acidic with HCl, and again extracted with Et_2O. After drying the pooled extracts with anhydrous $MgSO_4$, the solvent was removed under vacuum to give a residue that spontaneously crystallized. Recrystallization from hexane yielded 6.5 g of 2,2-dimethyl-3-(3,4-methylenedioxyphenyl)propionic acid as white crystals with a mp of 71-73 °C. The NMR spectrum in $CDCl_3$ showed the alpha-dimethyl groups as a sharp singlet at 1.18 ppm. Anal. ($C_{12}H_{14}O_4$) C,H.

The triethylamine salt of 2,2-dimethyl-3-(3,4-methylenedioxyphenyl)-propionic acid (5.4 g amine, 11.4 g acid) was dissolved in 10 mL H_2O and diluted with sufficient acetone to maintain a clear solution at ice-bath temperature. A solution of 6.4 g ethyl chloroformate in 40 mL acetone was added to the 0 °C solution over the course of 30 min, followed by the addition of a solution of 4.1 g sodium azide in 30 mL H_2O. Stirring was continued for 45 min while the reaction returned to room temperature. The aqueous phase was extracted with 100 mL toluene which was washed once with H_2O and then dried with anhydrous $MgSO_4$. This organic solution of the azide was heated on a steam bath until nitrogen evolution had ceased, which required about 30 min. The solvent was removed under vacuum and the residue was dissolved in 30 mL benzyl alcohol. This solution was heated on the steam bath overnight. Removal of the excess benzyl alcohol under vacuum left a residue 13.5 g of 1-(N-(benzyloxycarbonyl)amino)-1,1-dimethyl-2-(3,4-methylenedioxyphenyl)ethane as an amber oil. The dimethyl group showed, in the NMR, a sharp singlet at 1.30 ppm in $CDCH_3$. Anal. ($C_{19}H_{21}NO_4$) C,H. This carbamate was reduced to the primary amine (below) or to the methylamine (see under MDMP).



A solution of 3.27 g of 1-[N-(benzyloxycarbonyl)amino]-1,1-dimethyl-2-(3,4-methylenedioxyphenyl)ethane in 250 mL absolute ethanol was treated with 0.5 g 10% palladium on carbon. This mixture was shaken under hydrogen at 35 pounds pressure for 24 h. The carbon was removed by filtration through Celite, and the filtrate titrated with HCl. The solvent was removed under vacuum, and the residue allowed to crystallize. This produce was recrystallized from an EtOH/EtOAc mixture to provide α,α-dimethyl-3,4-methylenedioxyphenethylamine hydrochloride (MDPH). The white crystals weighed 1.63 g and had a mp of 180-181 °C. Anal. ($C_{11}H_{16}ClNO_2$) C,H,N.

DOSAGE: 160 - 240 mg.

DURATION: 3 - 5 h.

QUALITATIVE COMMENTS: (with 120 mg) "The alert was felt in forty minutes and I was pretty much there at an hour and twenty. Quite like MDA, simple, with

no lines, no colors, no motion, no fantasy. I am pleasantly stoned. The anorexia is real, as is the impotency. The drop from the 4th to the 6th hour was softened by a modest amount of wine, and this proved to be extremely intoxicating. My speech was slurred, and there was later amnesia for the rather aggressive and uninhibited behavior that occurred. I felt that there was more drug than alcohol contributing to this episode. My dream patterns were disturbingly unreal."

(with 160 mg) "A very quiet development. There was no body load whatsoever. And no visual, and I saw it fading away all too soon. This might be a good promoter, like MDPR. I felt refreshed and relaxed on the following morning."

(with 200 mg) "This has an inordinately foul taste. I felt slightly queasy. There were short daydreams which were quickly forgotten. I see no values that are worth the hints of physical problems, a little eye mismanagement and some clenching of teeth, and a tendency to sweat. I was able to sleep at only five hours into it, but there were a couple of darts. This is not as rewarding (stoning) as MDA, and has none of the magic of MDMA. It was a short-lived plus two."

EXTENSIONS AND COMMENTARY: What is the train of thought that leads from the structure of a known compound (which is active) to the structure of an unknown one (which may or may not be active)? Certainly the extrapolations involve many what-if's and maybe's. The path can be humorous, it certainly can be tortuous, and it often calls for special things such as faith, insight, and intuition. But can one say that it is logical?

Logic is a tricky thing to evaluate. One of the earliest approaches was laid down by Aristotle, in the form of the syllogism. In it there are three lines consisting of two premises and a conclusion, a form that is called a "mood." All are statements of relationships and, if the premises are true, there are only certain conclusions that may logically follow. For example:

Every man is a lover.
Every chemist is a man.
Therefore, every chemist is a lover.

Letting lover be the major term "a" and letting chemist be the minor term "b" and letting man be the middle term "m", this reduces to:

Every m is a,
Every b is m.
Therefore, every b is a

and it is a valid mood called Barbara.

Of the 256 possible combinations of all's and some's and none's and are's and are-not's, only 24 moods are valid. The reasoning here with MDPH goes:

Some stimulants when given a methylenedioxy ring are MDMA-like.
Some ring-unsubstituted 1,1-dimethylphenylethylamines are stimulants.
Therefore, some ring-unsubstituted 1,1-dimethylphenylethyl amines when given a methylenedioxy ring are MDMA-like.

In symbolic form this is:

Some m is a, and
Some b is m, then
Some b is a

and this is not one of the 24 valid moods. Given the first premise as some m is a, there is only one valid syllogism form that can follow, and this is known as Disamis, or:

Some m is a, and
Every m is b, then
Some b is a

which translates as:

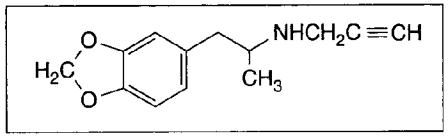
Some stimulants when given a methylenedioxy group are MDMA-like.
Every stimulant is a ring-unsubstituted 1,1-dimethylphenyl ethylamine.
Therefore, some ring-unsubstituted 1,1-dimethylphenylethyl amines when given a methylenedioxy group are MDMA-like.

The conclusion is the same. But the second premise is false so the entire reasoning is illogical. What is the false second premise? It is not a fact that every stimulant is a phentermine. There are lots of stimulants that are not phentermines.

So much for applying syllogistics to pharmacology.

#117 MDPL; N-PROPARGYL-MDA; N-PROPYNYL-MDA; 3,4-METHYLENEDIOXY-N-PROPARGYLAMPHETAMINE)

SYNTHESIS: A solution of 10.5 g propargylamine hydrochloride in 40 mL MeOH was treated with 2.0 g 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 0.55 g sodium cyanoborohydride. Concentrated HCl was added as needed, to keep the pH constant at about 6. The reaction seemed to progress very slowly. After about five days, the reaction mixture was added to 400 of H_2O, acidified with HCl, and extracted with 3x100 mL CH_2Cl_2. The aqueous phase was made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. Evaporation of the solvent from these extracts yielded 1.6 g of a clear amber, strong smelling oil which, on distillation at 105-110 °C at 0.2 mm/Hg, yielded 1.0 g of an almost colorless oil. This was dissolved in 20 mL IPA, neutralized with about 10 drops of concentrated HCl, and the spontaneously formed crystals were diluted with 50 mL anhydrous Et_2O. After filtration, Et_2O washing and air drying, there was obtained 1.1 g white crystals of 3,4-methylenedioxy-N-propargylamphetamine hydrochloride (MDPL) with a mp of 189-190 °C. Anal. ($C_{13}H_{16}ClNO_2$) N.



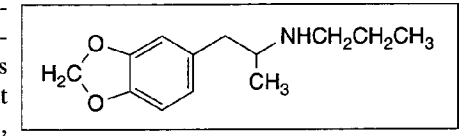
DOSAGE: greater than 150 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: There is a continuing uncertainty about the name for the three-carbon radical that contains a triple bond. The hydrocarbon is propyne, although it has been referred to as methylacetylene in the older literature. The adjective, going from the triple bond out to the point of attachment, is called propargyl, as in propargyl chloride. When the adjective must be built on the parent hydrocarbon, the double bond is on the outside and one reads away from it, as in 2-propynyl something. However, when the hydrocarbon is essentially the entire structure, then things get named going towards the triple bond, as in 3-chloro-1-propyne. Wait. I'm not done yet! When the actual hydrocarbon name becomes distorted into the derivative, then the triple bond is again at the high end of the numbering scheme. Propynol is 2-propyn-1-ol, which is, of course, the same as 3-hydroxypropyne, or propargyl alcohol. The code MDPL takes the first and last letter of the two of them, both propargyl and propynyl.

#118 MDPR; N-PROPYL-MDA; 3,4-METHYLENEDIOXY-N-PROPYLAMPHETAMINE

SYNTHESIS: A total of 20 mL concentrated HCl was added beneath the surface of 20 mL propylamine, and when the addition was complete, the mixture was stripped of volatiles under vacuum. The slightly yellow residual oil weighed 20.7 g and set up to crystals on cooling. It was dissolved in 75 mL MeOH, and there was added 4.45 g of 3,4-methylenedioxyphenylacetone (see under MDMA for its preparation) followed by 1.1 g sodium cyanoborohydride. Concentrated HCl in MeOH was added as required to maintain the pH at about 6 as determined with external, dampened universal pH paper. When the generation of base had stopped, the MeOH was allowed to evaporate and the residue was suspended in 1 L water. This was made strongly acidic with an excess of HCl. After washing with CH_2Cl_2, the aqueous phase was made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent from the pooled extracts under vacuum yielded 3.3 g of a pale amber oil that was distilled at 85-90 °C at 0.2 mm/Hg. This fraction was water-white and weighed 2.3 g. It was dissolved in 10 mL IPA and neutralized with 25 drops concentrated HCl which produced crystals spontaneously. These were diluted with anhydrous Et_2O, removed by filtration, washed with additional Et_2O, and air dried. In this way there was obtained 2.3 g of 3,4-methylenedioxy-N-propylamphetamine hydrochloride (MDPR) with a mp of 190-192 °C. Recrystallization from IPA gave a mp of 194-195 °C. The NMR spectrum was completely consistent with the assigned chemical structure. Anal. ($C_{13}H_{20}ClNO_2$) N.



DOSAGE: greater than 200 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 200 mg) "There are the slightest hints of physical response, maybe a smidgin of a lightheadedness at the one hour point. Perhaps a slight teeth clench. Certainly there is no central mental effect."

EXTENSIONS AND COMMENTARY: This particular drug, considering that it was without activity, has proven one of the richest veins of pharmacological raw material. Two clues suggested its potential value. A number of reports in the 150 to 200 milligram area suggested that something was taking place in the periphery even without any clear central effects. The term "body window" was used occasionally by experimenters, an outgrowth of the term "window" that was used (at that time, the mid-1970's) to describe the mental effects of MDMA. It was as if the body was opened up and made receptive, instead of the mind. The second clue

came from many anecdotal reports that methedrine (a potent central nervous system stimulant) would augment the effects of an LSD dosage which followed it. The putting of a drug on top of an inactive drug is the "primer" concept. It turned out that MDPR was an extraordinary primer to some following psychedelic, especially LSD, even at modest doses. The putting of a drug on top of an active drug, usually during the latter part of its effectiveness is, as previously stated, called "piggy-backing." A third drug-drug interaction has also been studied; the simultaneous administration of two active drugs, to study synergism. There may be an enhancement, or an inhibition, of one with the other. Let's now re-enter the subsection "Qualitative Comments" again, with this primer concept in mind.

QUALITATIVE COMMENTS: (with 160 mg followed at 2 h by 60 µgs LSD) "The visual phenomena were extraordinary. We were at the beach just south of Mendocino. In anything that had ever been living, there was an endlessly deep microcosm of detail. Endless, and forever more microscopic in intricacy. A sea urchin shell, a bit of driftwood, a scrap of dried seaweed, each was a treasure of jewels. I have never had such wealth of visual eroticism and bliss before. Later, we visited the pygmy forest, but these living fossils were not as magical.

(with 160 mg followed at 2 h by 60 µgs LSD) "We both felt the first effects at about 30 minutes, and an hour later we found ourselves in a startling folie-a-deux, involved in reliving the origins of man's arrival on earth. We were deep in a tropic environment, defending ourselves against the nasties of nature (insects, threatening things, blistering heat) and determining that man could indeed live here and perhaps survive. A shared eyes-closed fantasy that seemed to be the same script for both of us."

(with 160 mg followed at 2 h by100 µgs LSD) "This proved to be almost too intoxicating, and a problem arose that had to have a solution. The entire research group was here, and all were following this same regimen. Two hours into the second half of the experiment a telephone call came that reminded me of a promise I had made to perform in a social afternoon with the viola in a string quartet. Why did I answer the phone? My entire experience was, over the course of about 20 minutes, pushed down to a fragile threshold, and I drove about 10 minutes to attend a swank afternoon event and played an early Beethoven and a middle Mozart with an untouched glass of expensive Merlot in front of me. I could always blame the booze. I declined the magnificent food spread, split, and returned to my own party. Safely home, and given 20 more minutes, I was back into a rolling +++ and I now know that the mind has a remarkable ability to control the particular place the psyche is in."

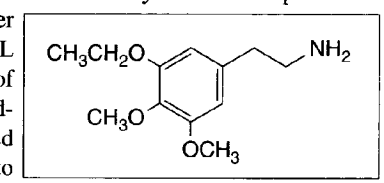
(with 200 mg followed at 2 h by 60 µgs LSD) "There was a steady climb from the half-hour point to about 2 hours. There was not the slightest trace of anything sinister. There was simply a super tactile person-to-person window. I had an overpowering urge to go out and interact with other people. To see, to talk, to be with others. There are unending fantasies of things erotic. Perhaps being with others should be circumspect. By evening the effects had largely worn off, but this was an incredible day, beautiful and unexpectedly relaxing."

EXTENSIONS AND COMMENTARY: There is need for more commentary. It must be noted that all of the above comments used rather modest dosages of LSD. The notes of this period, some two years of exploring interactions of the MD series of compounds as preludes to true psychedelics, are difficult to distill into a simple pattern. Most of these studies used LSD in the 60-100 microgram range which is fundamentally a modest level. Many trials were made where the challenge of acid plopped right on top of an active residue of another drug was more in keeping with the "piggyback" argument. An illustration of this is a trial in which the primer was MDMA followed at 5 hours (this is at a time of almost no effect) with a larger dose of LSD (250 micrograms). The LSD overwhelmed the residual numbing of the MDMA, and the generated state was overwhelmingly erotic and out of body. There can be no way of analytically organizing such a gemisch of drug-drug interactions with any logic that would allow a definitive interpretation. And LSD is not the only agent that can be used to challenge the "body window" such as that produced by MDPR. 2C-B, 2C-T-2 and 2C-T-7 have all been used with fine success as well.

In general, the use of an MD compound (looking at it as a stimulant and primer) followed by a psychedelic, brings about an exaggeration and enhancement of the latter compound. Much work must be done in this area to make sense of it all.

#119 ME; METAESCALINE; 3,4-DIMETHOXY-5-ETHOXY-PHENETHYLAMINE

SYNTHESIS: To a vigorously stirred suspension of 18.6 g of 5-bromobourbonal in 100 mL CH_2Cl_2 there was added 14.2 g methyl iodide, 1.0 g decyltriethylammonium iodide, and 120 mL 5% NaOH. The color was a deep amber, and within 1 min the top phase set up to a solid. This was largely dispersed with the addition of another 50 mL of water. The reaction was allowed to stir for 2 days. The lower phase was washed with H_2O, and saved. The upper phase was treated with another 100 mL CH_2Cl_2, 50 mL of 25% NaOH, another g of decyltriethylammonium iodide, and an additional 50 mL of methyl iodide. The formed solids dispersed by themselves in a few h to produce two relatively clear layers. Stirring was continued for an additional 3 days. The lower phase was separated, washed with H_2O, and combined with the earlier extract. The solvent was removed under vacuum to give 20.3 g of an amber oil that was distilled at 120-133 °C at 0.4 mm/Hg to yield 15.6 g of 3-bromo-4-methoxy-



5-ethoxybenzaldehyde as a white crystalline solid with a mp of 52-53 °C.

A mixture of 15.6 g 3-bromo-4-methoxy-5-ethoxybenzaldehyde and 10 mL cyclohexylamine was heated with an open flame until it appeared free of H_2O. The residue was put under a vacuum (0.5 mm/Hg) and distilled at 148-155 °C yielding 19.2 g 3-bromo-N-cyclohexyl-4-methoxy-5-ethoxybenzylidenimine as an off-white crystalline solid with a melting point 66-68.5 °C. Recrystallization from 100 mL boiling MeOH gave a mp of 67-68.5 °C. The C=N stretch in the infra-red was at 1640 cm^{-1}. Anal. ($C_{16}H_{22}BrNO_2$) C,H.

A solution of 17 g 3-bromo-N-cyclohexyl-4-methoxy-5-ethoxybenzylidenimine in 200 mL anhydrous Et_2O was placed in an atmosphere of He, stirred magnetically, and cooled with an external dry-ice acetone bath. Then 38 mL of a 1.55 M solution of butyllithium in hexane was added over 2 min, producing a clear yellow solution. There was then added 25 mL of butyl borate at one time, and the stirred solution allowed to return to room temperature. This was followed with 100 mL of saturated aqueous ammonium sulfate. The Et_2O layer was separated, washed with additional saturated ammonium sulfate solution, and evaporated under vacuum The residue was dissolved in 200 mL of 50% MeOH and treated with 12 mL of 30% hydrogen peroxide. This reaction was mildly exothermic, and was allowed to stir for 15 min, then added to an aqueous solution of 50 g ammonium sulfate. This was extracted with 2x100 mL CH_2Cl_2, the pooled extracts washed once with H_2O, and the solvent removed under vacuum. The residue was suspended in dilute HCl, and heated on the steam bath for 0.5 h. Stirring was continued until the reaction was again at room temperature and then it was extracted with 2x100 mL CH_2Cl_2. These extracts were pooled and in turn extracted with 2x100 mL dilute NaOH. The aqueous extracts were reacidified with HCl, and reextracted with 2x100 mL CH_2Cl_2. After pooling, the solvent was removed under vacuum to yield an oily residue. This was distilled at 118-130 °C at 0.2 mm/Hg to yield 7.5 g of 3-ethoxy-5-hydroxy-4-methoxybenzaldehyde as a distillate that set to white crystals. Recrystallization from cyclohexane gives a product with a mp of 77-78 °C. Anal. ($C_{10}H_{12}O_4$) C,H.

A solution of 7.3 g of 3-ethoxy-5-hydroxy-4-methoxybenzaldehyde in 100 mL acetone was treated with 5 mL methyl iodide and 8.0 g finely powdered anhydrous K_2CO_3, and held at reflux on a steam bath for 6 h. The solvent was removed under vacuum, and the residue was suspended in H_2O. After making this strongly basic, it was extracted with 3x50 mL CH_2Cl_2, the extracts were pooled, and the solvent removed under vacuum. The residual amber oil was distilled at 110-120 °C at 0.4 mm/Hg to yield 7.3 g of a white oil. This spontaneously set to white crystals of 3,4-dimethoxy-5-ethoxybenzaldehyde which had a mp of 49-49.5 °C. Anal. ($C_{11}H_{14}O_4$) C,H. This same aldehyde can be obtained, but in a less satisfactory yield, by the ethylation of 3,4-dimethoxy-5-hydroxybenzaldehyde described under the preparation of metaproscaline (MP).

A solution of 7.2 g 3,4-dimethoxy-5-ethoxybenzaldehyde in 100 mL nitromethane containing 0.1 g anhydrous ammonium acetate was held at reflux for 50 min. The excess nitromethane was removed under vacuum producing 6.8 g of a red oil which was decanted from some insoluble material. Addition of 10 mL hot MeOH to the decantings, gave a homogeneous solution that spontaneously crystallized on cooling. The yellow crystals were removed by filtration, washed sparingly with MeOH and air dried yielding 3.5 g yellow crystals of 3,4-dimethoxy-5-ethoxy-ß-nitrostyrene, with a mp of 89.5-90 °C after recrystallization from MeOH. Anal. ($C_{12}H_{15}NO_5$) C,H.

A solution of 2.0 g LAH in 100 mL anhydrous THF under He was cooled to 0 °C and vigorously stirred. There was added, dropwise, 1.3 mL of 100% H_2SO_4, followed by the dropwise addition of a solution of 3.1 g 3,4-dimethoxy-5-ethoxy-ß-nitrostyrene in 50 mL anhydrous THF, over the course of 10 min. The mixture was stirred at 0 °C for a while, and then brought to a reflux on the steam bath for 30 min. After cooling again, the excess hydride was destroyed with IPA in THF, followed by the addition of 20 mL 10% NaOH which was sufficient to convert the solids to a white and granular form. These were removed by filtration, the filter cake washed with IPA, the mother liquor and filtrates combined, and the solvents removed under vacuum. The residue was added to 150 mL dilute H_2SO_4, and the cloudy suspension washed with 2x75 mL CH_2Cl_2 which removed much of the color. The aqueous phase was made basic with 25% NaOH, and extracted with 3x50 mL CH_2Cl_2. The solvent was removed from these pooled extracts and the residue distilled at 103-116 °C at 0.25 mm/Hg to provide 2.3 g of a colorless viscous liquid. This was dissolved in 10 mL IPA, neutralized with about 25 drops of concentrated HCl, which produced an insoluble white solid. This was diluted with 40 mL anhydrous Et_2O added slowly with continuous stirring. The white crystalline 3,4-dimethoxy-5-ethoxyphenethylamine hydrochloride (ME) was isolated by filtration, washed with Et_2O, and air dried, and weighed 2.4 g. It had a mp of 202-203 °C which increased by one degree upon recrystallization from boiling IPA. Anal. ($C_{12}H_{20}ClNO_3$) C,H.

DOSAGE: 200 - 350 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 200 mg) "It tasted pretty strong. However, the taste was soon gone, and an energetic feeling began to take over me. It continued to grow. The feeling was one of great camaraderie, and it was very easy to talk to people. Everyone was talking to everyone else. I found it most pleasant, energetic and at the same time relaxing, with my defenses down. This material did not seem to lead to introspection; however, it might if one took it without other people around. Heightened visual awareness was mild, but the audio awareness was quite heightened. The feeling of being with everyone was intense."

(with 250 mg) "Initially I took 200 milligrams of metaescaline, and the experience developed for me very gradually at first, and very pleasantly. After about one half hour I became aware of a wall that seemed to shut me in, not

unpleasantly. The wall slowly dissolved, but I was afraid I might get into a negative experience. I felt immediate relief (from this isolation) upon taking the additional 50 mg (at 2:23 into the experiment) as though glad of the decision. I lay down outside on a blanket. There was a marvelous feeling inside, although no imagery. I felt the wall dissolve completely, and I desired to join the group. From this point on the experience was most enjoyable, euphoric. Although not dramatic like some psychedelics, it was most rewarding for me personally. I felt a marvelous bond with everyone present, with clear-headed, excellent thinking, and excellent communication. All in all, a most rewarding and enjoyable experience. Afterwards I felt much strengthened, with good energy and good insight. I have a strong feeling that the group tailored the nature of the experience, and that I and others were most desirous of group interaction. I feel that one could do a lot of other things with it if one turned one's attention to it."

(with 275 mg) "Onset of both physical and mental change was slow relative to other psychochemicals. Very gradual internal stirrings were felt at about the hour-and-a-half point. These were mostly feelingful rather than cognitive, and were quite pleasurable. At about the two-and-a-half hour point I grew quite thirsty, and drank a pint of beer. Almost immediately, and quite unexpectedly, I tomsoed to a much higher level and remained there for another three hours until the whole experience waned. [The verb, to tomso, means a sudden rekindling of the drug-induced altered state with a small amount of alcohol. It is explained in the recipe for TOMSO.] During the experience heights, and in fact before it reached its height, talking was easy and unimpeded. The transference feelings so characteristic of MDMA were basically not there. But for purposes of psychotherapy, there were some advantages: fluent associations, undefended positions, and general bonaise."

(with 400 mg) "Ingested 300 milligrams at about 1:30 in the afternoon. Very quiet climb. Occasional yawns. Matter-of-fact view of the world. No rosy glow. At the end of the second hour, I seem to be stuck at a ++. Take another 100 milligrams at 3:45 PM. Still tastes awful. Feel a small head-rush fifteen minutes after taking the supplement, and within a half hour I am completely +3. For a while this was a sterner mescaline. Saw the eternal, continual making of choices, all opposites continually in motion with each other. Yin and yang everywhere, giving life to every molecule. The universe itself keeps alive by the action-reaction, the yes-no, the black-white, male-female, plus-minus. All life is a continual making of choices on all levels. Then I closed my eyes, and I found myself floating up to the very top of a temple, where there was radiant light and a sense of homecoming. Making love is a clear stream over and through rocks and canyons — the earth and sky make love, and the rocks make love to other rocks, and the water is the teasing, fondling, living and moving actions of loving. To realize that, on some level, all existence makes love to all other existence. The Japanese Garden: a structured way of laying out a small glimpse into cosmic love-making, so that it can be read by other human souls. All loving, when direct and free and undemanding, is a touching of the Source. The hardest lesson, of course, is how to love yourself that same way.

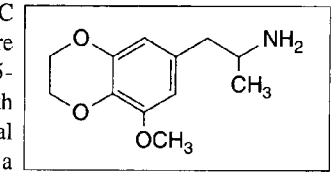
And it remains both the first lesson of Kindergarten and the Ph.D. final. I was able to drift into sleep at about 4:00 AM."

EXTENSIONS AND COMMENTARY: The reorientation of the single ethyl group of escaline (E) to the meta-position produces metaescaline (ME). In cats, in studies of over 50 years ago, the two compounds produced similar effects at similar dosages. In man, ME also appears to be similar to mescaline in potency. However, a subtle difference is apparent between ME and Peyote, the natural source of mescaline. With Peyote itself, the initial taste of the crude cactus is more than just foul; it might better be described as unbelievably foul. But in the middle of a Peyote experience, the taste of the cactus is truly friendly. When ME was retasted in the middle of an experience, the taste was still foul.

There are other distinctions from mescaline. Unlike mescaline or Peyote, there is rarely any body discomfort during the early phase of intoxication, no nausea and only an occasional comment suggesting hyperreflexia. And, also unlike mescaline, most subjective reports on ME claim that music produces little imagery, and the exaggeration of color perception is more reserved. Appetite is normal, the tastes and textures of food are unusually rewarding. No subject has ever expressed a reluctance to repeat the experience. Sleep is easy, refreshing, and the following day seems free from residue.

#120 MEDA; 3-METHOXY-4,5-ETHYLENEDIOXY-AMPHETAMINE

SYNTHESIS: To a solution of 50 g 3,4-dihydroxy-5-methoxybenzaldehyde in 100 mL distilled acetone there was added 70 g ethylene bromide and 58 g finely powdered anhydrous K_2CO_3. The mixture was held at reflux for 5 days. This was then poured into 1.5 L H_2O and extracted with 4x100 mL CH_2Cl_2. Removal of the solvent from the pooled extracts gave a residue which was distilled at 19 mm/Hg. Several of the fractions taken in the 203-210 °C range spontaneously crystallized, and they were pooled to give 18.3 g of 3-methoxy-4,5-ethylenedioxybenzaldehyde as white solids with a mp of 80-81 °C. A small sample with an equal weight of malononitrile in EtOH treated with a few drops of triethylamine gave 3-methoxy-4,5-ethylenedioxybenzalmalononitrile as pale yellow crystals from EtOH with a mp of 153-154 °C.



A solution of 1.50 g 3-methoxy-4,5-ethylenedioxybenzaldehyde in 6 mL acetic acid was treated with 1 mL nitroethane and 0.50 g anhydrous ammonium acetate, and held on the steam bath for 1.5 h. To the cooled mixture H_2O was

cautiously added until the first permanent turbidity was observed, and once crystallization had set in, more H_2O was added at a rate that would allow the generation of additional crystals. When there was a residual turbidity from additional H_2O, the addition was stopped, and the beaker held at ice temperature for several h. The product was removed by filtration and washed with a little 50% acetic acid, providing 0.93 g 1-(3-methoxy-4,5-ethylenedioxyphenyl)-2-nitropropene as dull yellow crystals with a mp of 116-119 °C. Recrystallization of an analytical sample from MeOH gave a mp of 119-121 °C.

A stirred suspension of 6.8 g LAH in 500 mL anhydrous Et_2O under an inert atmosphere was brought up to a gentle reflux. A total of 9.4 g 1-(3-methoxy-4,5-ethylenedioxyphenyl)-2-nitropropene in warm Et_2O was added over the course of 0.5 h. Refluxing was maintained for 6 h, and then the reaction mixture was cooled and the excess hydride destroyed by the cautious addition of 400 mL 1.5 N H_2SO_4. The two clear phases were separated, and the aqueous phase was brought to pH of 6 by the addition of a saturated Na_2CO_3 solution. This was filtered free of a small amount of insolubles, and the clear filtrate was heated to 80 °C. To this there was added a solution of 9.2 g picric acid (90% material) in 100 mL boiling EtOH, and the clear mixture allowed to cool in an ice bath. Scratching generated yellow crystals of the picrate salt. This salt was filtered free of the aqueous environment, treated with 50 mL of 5% NaOH, and stirred until the picric acid was totally in the form of the soluble sodium salt. This was then extracted with 3x100 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. The residue weighed 6.0 g, and was dissolved in 100 mL anhydrous Et_2O, and saturated with dry HCl gas. The white solids that formed were filtered free of the Et_2O, and ground up under 50 mL of slightly moist acetone, providing 4.92 g of 3-methoxy-4,5-ethylenedioxyamphetamine hydrochloride monohydrate (MEDA) as white crystals.

DOSAGE: greater than 200 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: There are times when the Gods smile in unexpectedly nice ways. Having found the activity of MMDA, the "scientific" thing to do would be to compare it against the other "psychotomimetic" amphetamine that was known at that time (this was 1962), namely TMA. Comparing their structures, the only difference of any kind was that two of the adjacent methoxyl groups of TMA were replaced with a 5-membered ring, called the methylenedioxy ring.

Where does one go next? Some perverse inspiration suggested increasing the size of this ring to a 6-membered ring, the ethylenedioxy (or dioxene) homologue. Well, if you thought that getting myristicinaldehyde was a difficulty, it was nothing compared to getting this 6-membered counterpart. But I huffed and I puffed, and I did make enough to taste and to evaluate. And it was here that I got

the divine message! No activity!! So, rather than being condemned forever *a la* Sisyphus to push ever larger rings up my psyche, I gave myself permission to pursue another path. The message was: "Don't change the groups. Leave them as they are, but relocate them instead." And that led directly to TMA-2 and its story.

A couple of diversions may be mentioned here. Before the blessed inactivity of MEDA was established, the 7-membered ring counterpart, 3-methoxy-4,5-trimethylenedioxyamphetamine (MTDA) was prepared by essentially the same procedure. The above 3-methoxy-4,5-dihydroxybenzaldehyde with trimethylene bromide gave 3-methoxy-4,5-trimethylenedioxybenzaldehyde, white solids, with a malononitrile derivative with a mp of 134-135 °C; the aldehyde with nitroethane gave the nitropropene with a mp of 86-87 °C; and this with LAH gave MTDA as the hydrochloride (mp 160-161 °C) again isolated first as the picrate. It had been tasted at up to an 8 milligram dosage (no activity, but none expected) before being abandoned. And, an initial effort was made to synthesize a five-member ring (methylenedioxy) with a methyl sticking out from it. This ethylidine homologue got as far as the aldehyde stage. The reaction between 3,4-dihydroxy-5-methoxy–benzaldehyde and 1,1-dibromoethane in acetone containing anhydrous potassium carbonate gave a minuscule amount of a product that was a two-component mixture. This was resolved by dozens of separate injections into a preparatory gas chromatography system, allowing the isolation of the second of the two components in a quantity sufficient to demonstrate (by NMR spectroscopy) that it was the desired 3-methoxy-4,5-ethylidinedioxybenzaldehyde. Starting with the pre-prepared dipotassium salt or the lead salt of the catecholaldehyde gave nothing. With no activity being found with MEDA, all was abandoned.

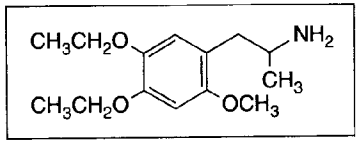
There are some comments made under MDA for successful chemistry (using a different approach) along these lines when there is no methoxyl group present. These are the compounds EDA and IDA. But the pharmacology was still not that exciting.

#121 MEE; 4,5-DIETHOXY-2-METHOXYAMPHETAMINE

SYNTHESIS: To a solution of 166 g bourbonal in 1 L MeOH there was added a solution of 66 g KOH pellets in 300 mL H_2O. There was then added 120 g ethyl bromide, and the mixture was held at reflux on the steam bath for 3 h. The reaction was quenched with three volumes of H_2O, and made strongly basic by the addition of 25% NaOH. This was extracted with 3x300 mL CH_2Cl_2, and the pooled extracts stripped of solvent under vacuum. There remained 155 g of 3,4-diethoxybenzaldehyde as a fluid oil that had an infra-red spectrum identical (except for being slightly wet) to that of a commercial sample from the Eastman Kodak Company.

A solution of 194 g 3,4-diethoxybenzaldehyde in 600 g glacial acetic acid was arranged in a flask that could be magnetically stirred, yet cooled as needed with

an external ice bath. A total of 210 g of 40% peracetic acid in acetic acid was added at a rate such that, with ice cooling, the exothermic reaction never raised the internal temperature above 26 °C. The reaction developed a deep red color during the 2 h needed for the addition. At the end of the reaction the mixture was quenched by the addition of three volumes of H_2O, and the remaining acidity was neutralized by the addition of solid Na_2CO_3 (700 g was required). This aqueous phase was extracted several times with CH_2Cl_2, and the solvent was removed from the pooled extracts under vacuum. The residue was a mixture of the intermediate formate ester and the end product phenol. This was suspended in 800 mL 10% NaOH, and held on the steam bath for 1.5 h. After cooling, this was washed once with CH_2Cl_2 (discarded) and then acidified with HCl. There was the formation of an intensely hydrated complex of the product phenol, reminiscent of the problem encountered with 3-ethoxy-4-methoxyphenol. This was worked up in three parts. The entire acidified aqueous phase was extracted with Et_2O (3x200 mL) which on evaporation gave 80 g of an oil. The hydrated glob was separately ground up under boiling CH_2Cl_2 which, on evaporation, gave an additional 30 g of oil, and the aqueous mother liquor from the glob was extracted with 2x200 mL CH_2Cl_2 which provided, after removal of the solvent, an additional 10 g. These crude phenol fractions were combined and distilled at 1.5 mm/Hg. Following a sizeable forerun, a fraction boiling at 158-160 °C was the anhydrous product, 3,4-diethoxyphenol. It was a clear, amber oil, and weighed 70.0 g. The slightest exposure to H_2O, even moist air, give a solid hydrate, with mp of 63-64 °C. This phenol can be used for the synthesis of MEE (this recipe) or for the preparation of EEE (see the separate recipe). A solution of 2.0 g of this phenol in 5 mL CH_2Cl_2 was diluted with 15 mL hexane. This was treated with 2 g methyl isocyanate followed by a few drops of triethylamine. After about 5 min, white crystals formed of 3,4-diethoxyphenyl-N-methyl carbamate, with a mp of 90-91 °C.



A solution of 26.6 g 3,4-diethoxyphenol in 50 mL MeOH was mixed with another containing 9.6 g KOH pellets dissolved in 200 mL hot MeOH. There was then added 21.4 g methyl iodide, and the mixture was held at reflux for 2 h on the steam bath. This was then quenched in 3 volumes of water, made strongly basic with 25% NaOH, and extracted with 3x150 mL CH_2Cl_2. Evaporation of the solvent from the pooled extracts gave 19.3 g of 1,2-diethoxy-4-methoxybenzene (3,4-diethoxyanisole) as a clear, pale amber oil that solidified when cooled. The mp was 20-21 °C.

A mixture of 32.0 g N-methyl formanilide and 36.2 g $POCl_3$ was allowed to stand until it was a deep red color (about 0.5 h). To this there was added 18.3 g 1,2-diethoxy-4-methoxybenzene and the exothermic reaction was heated on the steam bath for 2.5 h. This was then poured over 600 mL chipped ice, and the dark oily material slowly began lightening in color and texture. A light oil was formed which, on continued stirring, became crystalline. After the conversion was

complete, the solids were removed by filtration producing, after removal of as much H_2O as possible by suction, 26.9 g of crude aldehyde. A small sample pressed on a porous plate had a mp of 87.5-88.5 °C. Recrystallization of the entire damp crop from 50 mL boiling MeOH gave, after cooling, filtering, and air drying, 17.7 g of 4,5-diethoxy-2-methoxybenzaldehyde as fluffy, off-white crystals with a mp of 88-88.5 °C. A solution of 1.0 g of this aldehyde and 0.5 g of malononitrile dissolved in warm absolute EtOH was treated with 3 drops triethylamine. There was the immediate formation of crystals which were filtered and air dried to constant weight. The product, 4,5-diethoxy-2-methoxybenzalmalononitrile, was a bright yellow crystalline material, which weighed 1.0 g and had a mp of 156-157 °C.

To a solution of 14.7 g 4,5-diethoxy-2-methoxybenzaldehyde in 46 g glacial acetic acid, there was added 8.0 g nitroethane and 5.0 g anhydrous ammonium acetate. The mixture was heated on the steam bath for 2 h, becoming progressively deeper red in color. The addition of a small amount of H_2O to the hot, clear solution produced a slight turbidity, and all was allowed to stand overnight at room temperature. There was deposited a crop of orange crystals that was removed by filtration and air dried. There was obtained 7.0 g 1-(4,5-diethoxy-2-methoxyphenyl)-2-nitropropene as brilliant orange crystals that had a mp of 89-90.5 °C. This was tightened up, but not improved, by trial recrystallization from acetic acid, mp 89-90 °C, and from hexane, mp 90-90.5 °C. Anal. ($C_{14}H_{19}NO_5$) C,H.

To a gently refluxing suspension of 5.0 g LAH in 400 mL anhydrous Et_2O under a He atmosphere, there was added 6.5 g 1-(4,5-diethoxy-2-methoxyphenyl)-2-nitropropene by allowing the condensing Et_2O to drip into a shunted Soxhlet thimble containing the nitrostyrene. This effectively added a warm saturated solution of the nitrostyrene dropwise. Refluxing was maintained for 5 h, and the reaction mixture was cooled with an external ice bath. The excess hydride was destroyed by the cautious addition of 400 mL of 1.5 N H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated, and 100 g of potassium sodium tartrate was dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was >9, and this was extracted with 3x200 mL CH_2Cl_2. Removal of the solvent under vacuum produced an off-white oil that was dissolved in anhydrous Et_2O and saturated with anhydrous HCl gas. The crystals of 4,5-diethoxy-2-methoxyamphetamine hydrochloride (MEE) that formed were very fine and slow to filter, but finally were isolated as a white powder weighing 5.4 g and melting at 178.5-180 °C. Anal. ($C_{14}H_{24}ClNO_3$) C,H,N.

DOSAGE: greater than 4.6 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: There were early trials made with MEE, before it became known what direction the ethoxy substitution results would take. A number of progressive trials, up to a dosage of 4.6 milligrams, were without any

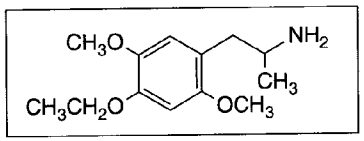
central effects at all.

There is an instinct in structure-activity studies to think of a change as a success or a failure, depending on whether there is an increase or a decrease in the desired activity. But if one were to look at the effects of putting an ethoxy group onto TMA-2 in place of a methoxy group as a way of decreasing the effectiveness, then the 4-position becomes the worst position (MEM is equipotent to TMA-2), and the 5-position is perhaps a little less bad (MME is almost as potent) and the 2-position is the best by far (EMM is out of it, potency-wise). In other words, in the comparison of the 2- and the 5-positions, the lengthening of the 5-position gives modest loss of activity, and the lengthening of the whatever in the 2-position is the most disruptive. With this as a basis for prediction, then MEE (which differs from MEM only by a lengthening of the 5-position substituent) might be only a little less active than MEM and, as MEM is about the same as TMA-2, it is distinctly possible that MEE may show activity in the area at dosages that are not much above the 25 to 50 milligram area. Of all the diethoxy homologues, it would be the most promising one to explore.

Which brings to mind a quotation of a hero of mine, Mark Twain. "I like science because it gives one such a wholesome return of conjecture from such a trifling investment of fact."

#122 MEM; 2,5-DIMETHOXY-4-ETHOXYAMPHETAMINE

SYNTHESIS: A solution of 83 g bourbonal (also called ethyl vanillin, or vanillal, or simply 3-ethoxy-4-hydroxybenzaldehyde) in 500 mL MeOH was treated with a solution of 31.5 g KOH pellets (85% material) dissolved in 250 mL H_2O. There was then added 71 g methyl iodide, and the mixture was held under reflux conditions for 3 h. All was added to 3 volumes of H_2O, and this was made basic with the addition of 25% NaOH. The aqueous phase was extracted with 5x200 mL CH_2Cl_2. The pooling of these extracts and removal of the solvent under vacuum gave a residue of 85.5 g of the product 3-ethoxy-4-methoxybenzaldehyde, with a mp of 52-53 °C. When this product was recrystallized from hexane, its mp was 49-50 °C. When the reaction was run with the same reactants in a reasonably anhydrous environment, with methanolic KOH, the major product was the acetal, 3-ethoxy-α,α,4-trimethoxytoluene. This was a white glistening product which crystallized readily from hexane, and had a mp of 44-45 °C. Acid hydrolysis converted it to the correct aldehyde above. The addition of sufficient H_2O in the methylation completely circumvents this by-product. A solution of 1.0 g of this aldehyde and 0.7 g malononitrile in 20 mL warm absolute EtOH, when treated with a few drops of triethylamine, gave immediate yellow color followed,



in a few min by the formation of crystals. Filtration, and washing with EtOH, gave bright yellow crystals of 3-ethoxy-4-methoxybenzalmalononitrile with a mp of 141-142 °C.

A well stirred solution of 125.4 g 3-ethoxy-4-methoxybenzaldehyde in 445 mL acetic acid was treated with 158 g 40% peracetic acid (in acetic acid) at a rate at which, with ice cooling, the internal temperature did not exceed 27 °C. The addition required about 45 min. The reaction mixture was then quenched in some 3 L H_2O. There was the generation of some crystals which were removed by filtration. The mother liquor was saved. The solid material weighed, while still wet, 70 g and was crude formate ester. A small quantity was recrystallized from cyclohexane twice, to provide a reference sample of 3-ethoxy-4-methoxyphenyl formate with a mp of 63-64 °C. The bulk of this crude formate ester was dissolved in 200 mL concentrated HCl which gave a deep purple solution. This was quenched with water which precipitated a fluffy tan solid, which was hydrated phenolic product that weighed about 35 g, and melted in the 80-90 °C. range. The mother liquors of the above filtration were neutralized with Na_2CO_3, then extracted with 3x100 ml Et_2O. Removal of the solvent gave a residue of about 80 g that was impure formate (containing some unoxidized aldehyde). To this there was added 500 mL 10% NaOH, and the dark mixture heated on the steam bath for several h. After cooling, the strongly basic solution was washed with CH_2Cl_2, and then treated with 200 mL Et_2O, which knocked out a heavy semi-solid mass that was substantially insoluble in either phase. This was, again, the crude hydrated phenol. The Et_2O phase, on evaporation, gave a third crop of solids. These could actually be recrystallized from MeOH/H_2O, but the mp always remained broad. When subjected to distillation conditions, the H_2O was finally driven out of the hydrate, and the product 3-ethoxy-4-methoxyphenol distilled as a clear oil at 180-190 °C at 0.8 mm/Hg. This product, 45.1 g, gave a fine NMR spectrum, and in dilute CCl_4 showed a single OH band at 3620 cm^{-1}, supporting the freedom of the OH group on the aromatic ring from adjacent oxygen. Efforts to obtain an NMR spectrum in D_2O immediately formed an insoluble hydrate. This phenol can serve as the starting material for either MEM (see below) or EEM (see separate recipe).

To a solution of 12.3 g 3-ethoxy-4-methoxyphenol in 20 mL MeOH, there was added a solution of 4.8 g flaked KOH in 100 mL heated MeOH. To this clear solution there was then added 10.7 g methyl iodide, and the mixture held at reflux on the steam bath for 2 h. This was then quenched in 3 volumes H_2O, made strongly basic with 10% NaOH, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent from the pooled extracts under vacuum gave 9.4 g of an amber oil which spontaneously crystallized. The mp of 1,4-dimethoxy-2-ethoxybenzene was 42-43.5 °C, and was used, with no further purification, in the following step.

A mixture of 17.3 g N-methylformanilide and 19.6 g $POCl_3$ was allowed to stand for 0.5 h, producing a deep claret color. To this there was added 9.2 g 1,4-dimethoxy-2-ethoxybenzene, and the mixture was held on the steam bath for 2 h. It was then poured into chipped ice and, with mechanical stirring, the dark oily phase

slowly became increasingly crystalline. This was finally removed by filtration, providing a brown solid mat which showed a mp of 103.5-106.5 °C. All was dissolved in 75 mL boiling MeOH which, on cooling, deposited fine crystals of 2,5-dimethoxy-4-ethoxybenzaldehyde that were colored a light tan and which, after air drying to constant weight, weighed 8.5 g and had a mp of 108-109.5 °C. Search was made by gas chromatography for evidence of the other two theoretically possible positional isomers, but none could be found. The NMR spectrum showed the two para-protons as clean singlets, with no noise suggesting other isomers. There was a single peak by GC (for the recrystallized product) but the mother liquors showed a contamination that proved to be N-methylformanilide. A 0.3 g sample, along with 0.3 g malononitrile, was dissolved in 10 mL warm absolute EtOH, and treated with a drop of triethylamine. There was the immediate formation of a yellow color followed, in 1 min, by the deposition of fine yellow needles. Filtering and air drying gave 0.25 g of 2,5-dimethoxy-4-ethoxybenzalmalononitrile, with a mp of 171-172 °C.

A solution of 7.3 g 2,5-dimethoxy-4-ethoxybenzaldehyde in 25 g glacial acetic acid was treated with 3.6 g nitroethane and 2.25 g anhydrous ammonium acetate, and heated on the steam bath. After two h, the clear solution was diluted with an equal volume of H_2O, and cooled in an ice bucket. There was the formation of a heavy crop of orange crystals which were removed by filtration. The dry weight of 1-(2,5-dimethoxy-4-ethoxyphenyl)-2-nitropropene was 4.8 g and the mp was 120-124 °C. Recrystallization of an analytical sample from MeOH gave a mp of 128-129 °C. Anal. ($C_{13}H_{17}NO_5$) C,H.

To a gently refluxing suspension of 3.3 g LAH in 400 mL anhydrous Et_2O under a He atmosphere, there was added 4.3 g 1-(2,5-dimethoxy-4-ethoxy)-2-nitropropene by allowing the condensing Et_2O to drip into a shunted Soxhlet thimble apparatus containing the nitrostyrene, thus effectively adding a warm saturated ether solution of it to the hydride mixture. The addition took 2 h. Refluxing was maintained for 5 h, and then the reaction mixture was cooled to 0 °C with an external ice bath. The excess hydride was destroyed by the cautious addition of 300 mL of 1.5 N H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated, and 100 g of potassium sodium tartrate was dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was >9, and this was then extracted with 3x100 mL CH_2Cl_2. Evaporation of the solvent from the pooled extracts produced an almost white oil that was dissolved in 100 mL anhydrous Et_2O and saturated with anhydrous HCl gas. There was deposited a white crystalline solid of 2,5-dimethoxy-4-ethoxyamphetamine hydrochloride (MEM) which weighed 3.1 g and had a mp of 171-172.5 °C. Anal. ($C_{13}H_{22}ClNO_3$) C,H,N.

DOSAGE: 20 - 50 mg.

DURATION: 10 - 14 h.

QUALITATIVE COMMENTS: (with 20 mg) "I experienced some physical discomfort, but doesn't that tell us about the work to be done, rather than the property of the material? The breakthrough I had was the following day (and this seems to be the way MEM operates, i.e., first the energy and expansion, next day insight) was of the highest value and importance for me. I was given a methodology for dealing with my shadow parts. No small gift. And I did it all alone and the results were immediate. I am so grateful."

(with 20 mg, at 1.5 h following 120 mg MDMA) "The transition was very smooth, with no obvious loss of the MDMA experience. I felt less of a need to talk, but the intimate closeness with the others was maintained. The experience continues to grow more profound and euphoric and I prayed, in the latter part of the afternoon, that it wouldn't stop. It continued until midnight with marvelous feelings, good energy, and much hilarity. And it abated very little over the next several days leaving me with the feeling of lasting change with important insights still coming to mind one week later."

(with 25 mg, at 2 h following 120 mg MDMA) "I found that sounds in general were distracting. No, they were out-and-out annoying. I may have been in an introspective mood, but I really wanted to be alone. No body problems at all. Felt good. I developed some color changes and some pattern movement. Not much, but then I didn't explore it much. The wine party afterwards was certainly most pleasant. The soup was a great pleasure. And that hard bread was good. The material was clearly not anorexic, or at least I overcame whatever anorexia there might have been."

(with 30 mg) "I was aware of this in thirty minutes and it slowly developed from there to an almost +++ in the following hour. There were visual phenomena, with some color enhancement and especially a considerable enhancement of brights and darks. The first signs of decline were at about six hours, but there was something still working there after another six hours had passed. A slow decline, certainly."

(with 50 mg) "I came into the experience knowing that yesterday had been a very fatiguing and tense day. I felt this material within the first ten minutes which is the fastest that I have ever felt anything. The ascent was rapid and for the first hour I tended to an inward fantasying with a distinct sensual tinge. There was a persistent queasiness that never left me, and it contrasted oddly with a good feeling of outward articulation and lucidity which succeeded in coming to the fore after the introverted first hour. Sleep was difficult, but the next day was calm and clear."

(with 50 mg) "Lots of energy, best directed into activity. Clear imaging, thinking. Intense yet serene. Good feeling of pleasantness and some euphoria. I felt the need to keep moving. Hard to stay still."

(with 70 mg, in two parts) "The effects of the 40 milligrams were muted by another drug experiment yesterday morning, and I never got much over a plus 1. There is an erotic nature, tactile sensitivity perhaps not as delicate as with 2C-B, but it is there. At the 2 hour point, an additional 30 milligrams increased the body impact (a distinct tremor and sensitivity) but somehow not a lot more mental. I have

been compromised by yesterday."

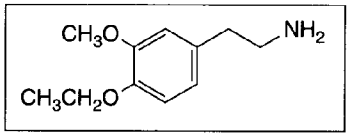
EXTENSIONS AND COMMENTARY: MEM was both a valuable and dramatic compound, as well as a drug that played a watershed role. The completion of all the possible trimethoxyamphetamines (the TMA's) showed that only two of them combined the values of dependability of positive psychedelic effects with a reasonably high potency. Both TMA-2 and TMA-6 are treasures, both active in similar dosages, and both offer methoxyl groups that are begging to be replaced by other things. The first focus was on TMA-2, partly because the needed synthetic chemistry was better known, and partly because I had discovered its activity earlier. But there were three entirely different and distinct methoxyl groups to work on, in TMA-2. There is one at the 2-position, one at the 4-position, and one at the 5-position. The most obvious thing to do, it seemed, was to make each of them one carbon longer. Replace a methoxy with an ethoxy. And a logical naming pattern could follow the use of M for methoxy, and E for ethoxy, in sequence right around the ring from the 2- to the 4- to the 5-positions. The first group to be compared, then, would be EMM, MEM, and MME. And of these three, it was only MEM that was right up there in drama and in potency. But, by the time that became apparent, I had already completed the diethoxy possibilities (EEM, EME, and MEE) as well as the triethoxy homologue, EEE. With the discovery that the 4-position was the magic leverage point, and that the homologues at positions 2- and 5- were clearly less interesting, all emphasis was directed at this target, and this has led to the many 4-substituted families that are now known to be highly potent and felt by many to be personally valuable.

Why put such emphasis on potency, I am frequently asked? Why should it matter how much of a compound you take, as long as the effective level is much lower than its toxic level? Well, in a sense, that is the very reason. There are no guides as to what the toxic levels of any of these many compounds might really be in man. There is simply no way of determining this. Only a few have been explored in animals in the pursuit of an LD-50 level. Most of them are similar to one-another, in that they are, in mice, of relatively low toxicity and, in rat, of relatively high toxicity. But this toxicity appears not to be related to potency in man. So, if one might extrapolate that they are of more or less the same risk to man (from the toxic point of view) then the lower the dosage, the greater the safety. Maybe. In the absence of anything factual, it makes a reasonable operating hypothesis.

Many of the reports of MEM effects have been with experiments in which an effective dose of MDMA had been taken shortly earlier. There has developed a concept, embraced by a number of researchers, that the ease and quietness usually seen with the development of the MDMA experience can mitigate some of the physically disturbing symptoms sometimes seen with other psychedelics. This may be partly due to a familiar entry into a altered place, and partly due to a lessening of dosage usually required for full effects. MEM seems to have had more trials using this combination than many of the other psychedelic drugs.

#123 MEPEA; 3-METHOXY-4-ETHOXYPHENETHYLAMINE

SYNTHESIS: A solution of 10.0 g 3-methoxy-4-ethoxybenzaldehyde in 150 mL nitromethane was treated with 1.7 g anhydrous ammonium acetate, and heated on the steam bath for 1 h. The excess nitromethane was removed under vacuum, yielding a loose, yellow crystalline mass that was filtered and modestly washed with cold MeOH. The 8.0 g of damp yellow crystals thus obtained were dissolved in 50 mL of vigorously boiling CH_3CN, decanted from a small amount of insolubles (probably ammonium acetate residues) and cooled in an ice bath. The crystals so obtained were removed by filtration, washed with 2x5 mL cold CH_3CN, and air dried to constant weight. The yield of 4-ethoxy-3-methoxy-ß-nitrostyrene was 6.3 g of beautiful yellow crystals.



A solution of 2.3 g LAH in 70 mL anhydrous THF was cooled, under He to 0 °C with an external ice bath. With good stirring there was added 2.3 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 6.2 g 3-ethoxy-4-methoxy-ß-nitrostyrene in anhydrous THF. After a few min further stirring, the temperature was brought up to a gentle reflux on the steam bath, and then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of IPA followed by sufficent 10% NaOH to give a white granular character to the oxides, and to assure that the reaction mixture was basic. The reaction mixture was filtered and the filter cake well washed with THF. The filtrate and washes were combined and stripped of solvent under vacuum. The residue was dissolved in dilute H_2SO_4. This was washed with 2x75 mL CH_2Cl_2, which removed the residual yellow color. The remaining aqueous phase was made basic with NaOH, and extracted with 3x75 mL CH_2Cl_2. These extracts were combined and the solvent removed under vacuum. The residue was distilled at 108-115 °C at 0.4 mm/Hg to give 4.2 g of a mobile, colorless liquid. This was dissolved in 12 mL IPA, neutralized with 60 drops concentrated HCl, and diluted with 100 mL anhydrous Et_2O. There was deposited a fine white crystalline product which, after removal by filtration, ether washing, and air drying, yielded 3.8 g of 3-methoxy-4-ethoxyphenethylamine hydrochloride (MEPEA).

DOSAGE: 300 mg or greater.

DURATION: short.

QUALITATIVE COMMENTS: (with 120 mg) "I am at perhaps a +1, a very slight effect of lightness, without any body awareness at all. And then in another hour, I was completely baseline again."

(with 300 mg) "Whatever changes took place were complete at the end of an hour. The effects were very quiet, very pleasant, and very light. There was

nothing psychedelic here, but rather a gentle lifting of spirits. No sensory enhancement or other expected changes."

EXTENSIONS AND COMMENTARY: This is one of the very few phenethylamines with only two substituents that shows even a hint of central activity. And there is an interesting story attached. I got a call out of absolutely nowhere, from a Stanislov Wistupkin, that he had discovered a number of new psychedelic drugs which he would like to share with me. Two of them were simple phenethylamines, one with an ethoxy group at the 4-position, and one with an allyloxy group there. Both, he said, were mood elevators active between 100 and 300 milligrams. One of them was this material, here called MEPEA, and the other one was 3-methoxy-4-allyloxyphenethylamine, or MAPEA. When I did meet him in person, he gave me a most remarkable publication which had been authored some ten years earlier, by a person named Leminger, now dead. It was all in Czech, but quite unmistakably, right there on the third page, were the structures of MEPEA and MAPEA, and the statement that they were active at between 100 and 300 milligrams. I have not yet made the allyloxy compound, but I feel that it too might be a gentle mood elevator similar to the ethoxy.

A most appealing extension of these materials would be the amphetamine derivatives, things with a 3-methoxy group, and something small and terse on the 4-position. The immediate analogies of MEPEA and MAPEA would be 3-methoxy-4-ethoxy- (and 3-methoxy-4-allyloxy)-amphetamine. And equally interesting would be the 4-hydroxy analogue. This would be an easily made compound from vanillin, one of our most enjoyable spices in the kitchen cabinet, and it would be directly related to the essential oils, eugenol and isoeugenol. This amphetamine compound has already been synthesized, but it is still unexplored in man.

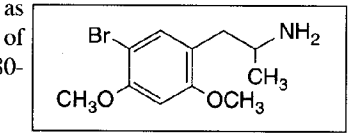
Some years ago a report appeared in the forensic literature of Italy, of the seizure of a small semitransparent capsule containing 141 milligrams of a white powder that was stated to be a new hallucinogenic drug. This was shown to contain an analogue of DOM, 3-methoxy-4-methylamphetamine, or MMA. The Italian authorities made no mention of the net weight contained in each dosage unit, but it has been found that the active level of MMA in man is in the area of 40-60 milligrams. The compound can apparently be quite dysphoric, and long lived.

In the Czechoslovakian publication that presented MEPEA and MAPEA. there were descriptions of escaline (E), proscaline (P), and the allyloxy analogue (AL). These are all active in man, and have been entered elsewhere. This is the only published material dealing with psychedelic drugs I have ever been able to find, from the laboratory of Otakar Leminger. What sort of man was this chemist? He worked for years in industry, and only at the time of his retirement did he publish this little gem. He lived at Usti, directly north of Praha, on the Labe river (which is called by the better known name, the Elbe, as soon as it enters Germany). Might there be other treasures that he had discovered, and never published? Was young Wistupkin a student of his? Are there unrecognized notes of Otakar Leminger

sitting in some farm house attic in Northern Czechoslovakia? I extend my heartfelt salute to an almost unknown explorer in the psychedelic drug area.

#124 META-DOB; 5-BROMO-2,4-DIMETHOXYAMPHETAMINE

SYNTHESIS: The reaction of 2,4-dimethoxyamphetamine (2,4-DMA) with elemental bromine proceeded directly to the formation of 5-bromo-2,4-dimethoxyamphetamine which was isolated as the hydrobromide salt with a melting point of 204.5-205.5 °C and in a 67% yield. A mp of 180-181 °C has also been published.



DOSAGE: 50 - 100 mg.

DURATION: 5 - 6 h.

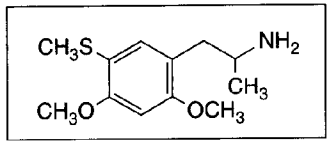
EXTENSIONS AND COMMENTARY: There is very little synthetic information available, and some of it is contradictory. The initial human report in the medical literature says only that a dosage of about 100 milligrams produced effects that were similar to those produced by MDA. Both the quality of the experience and the potency of the compound have been modified in more recent publications by the originators of this compound. A 40 milligram dose, after an induction period of an hour, produced a vague uneasiness that was interpreted originally as a threshold psychedelic effect. At doses in the 60 to 90 milligram range, there were produced feelings of anxiety and paranoid fantasies, and distinct toxic signs such as flushing, palpitations, and occasional nausea, vomiting and diarrhea. Any psychedelic effects seem to have been blurred by the more obvious toxic actions of the drug. I have been told that their final conclusion was that the drug appears toxic in the 50 to 60 milligram range. I have not personally explored this positional isomer of DOB.

The positional isomer of DOB with the bromine in the ortho-position is 4,5-dimethoxy-2-bromoamphetamine and is called, not surprisingly, ORTHO-DOB. It has been made by the condensation of 2-bromo-4,5-dimethoxybenzaldehyde with nitroethane to give 1-(2-bromo-4,5-dimethoxyphenyl)-2-nitropropene with a mp of 105-106 °C. Reduction to the amphetamine had to be conducted at a low temperature and using only an equimolar amount of lithium aluminum hydride, to minimize reductive removal of the bromo group. The hydrochloride salt of 2-bromo-4,5-dimethoxyamphetamine (ORTHO-DOB) had a mp of 214-215.5 °C, and the hydrobromide salt a melting point of 196-197 °C or of 210 °C. Both have been reported. The yield from the direct bromination of 3,4-DMA was apparently very bad. I do not think that the compound has ever gone into man.

There are three other dimethoxyamphetamine isomers known, and each has been explored chemically as to its reactivity with elemental bromine. With 2,3-DMA, a mixture of the 5-Br-2,3-DMA and 6-Br-2,3-DMA was formed; with 2,6-DMA, 3-Br-2,6-DMA was formed; and with 3,5-DMA, a mixture of 2-Br-3,5-DMA and the 2,6-dibromo product was produced. The bromination of 2,5-DMA is, of course, the preferred procedure for the synthesis of 4-Br-2,5- DMA, or DOB, q.v. None of these positional isomers has ever been put into man, but 3-Br-2,6-DMA and the iodo-counterpart have been explored as potential radio-fluorine carriers into the brain. This is all discussed in the 3,4-DMA recipe.

#125 META-DOT; 2,4-DIMETHOXY-5-METHYLTHIO-AMPHETAMINE

SYNTHESIS: To 27 g 1,3-dimethoxybenzene that was being well stirred, there was added, dropwise, 29 g concentrated H_2SO_4 over a period of 15 min. Stirring was continued for 1 hour, and then the mixture was poured slowly into 250 mL of saturated aqueous K_2CO_3. The precipitate that formed was removed by filtration, and dried at 125 °C to give 59.6 g crude potassium 2,4-dimethoxybenzenesulfonate. This was finely ground, and 30 g of it was treated with 35 g of $POCl_3$ and the mixture heated on the steam bath for 2 h. This was cooled to room temperature, and then poured over 300 mL crushed ice. When all had thawed, this was extracted with 2x150 mL Et_2O. The extracts were pooled, washed with saturated brine, and the solvent removed under vacuum to give a residue which solidified. There was thus obtained 14.2 g 2,4-dimethoxybenzenesulfonyl chloride as white solids with a mp of 69-72 °C. Heating of a small portion with concentrated ammonium hydroxide gave the corresponding sulfonamide which, on recrystallization from EtOH, produced white needles with a mp of 165.5-166.5 °C.



To a stirred and gently refluxing suspension of 11 g LAH in 750 mL anhydrous Et_2O, there was added 13.2 g 2,4-dimethoxybenzenesulfonyl chloride in an Et_2O solution. The refluxing was maintained for 48 h then, after cooling externally with ice water, the excess hydride was destroyed by the slow addition of 600 mL of 10% H_2SO_4. The phases were separated, and the aqueous phase extracted with 2x200 Et_2O. The organics were pooled, washed once with 200 mL H_2O, and the solvent removed under vacuum. The residue was dried azeotropically through the addition and subsequent removal of CH_2Cl_2. Distillation of the residue provided 8.0 g 2,4-dimethoxythiophenol as a colorless oil, boiling at 89-92 °C at 0.5 mm/Hg.

To a solution of 7.8 g 2,4-dimethoxythiophenol in 40 mL absolute EtOH there was added a solution of 4 g 85% KOH in 65 mL EtOH. This was followed by the addition of 5 mL methyl iodide, and the mixture was held at reflux for 30 min.

This was poured into 200 mL H_2O, and extracted with 3x50 mL Et_2O. The pooled extracts were washed once with aqueous sodium hydrosulfite, then the organic solvent was removed under vacuum. The residue was distilled to give 8.0 g of 2,4-dimethoxythioanisole as a colorless oil with a bp of 100-103 °C at 0.6 mm/Hg.

To a mixture of 15 g $POCl_3$ and 14 g N-methylformanilide that had been warmed briefly on the steam bath there was added 7.8 g of 2,4-dimethoxythioanisole. The reaction was heated on the steam bath for an additional 20 min and then poured into 200 mL H_2O. Stirring was continued until the insolubles had become completely loose and granular. These were removed by filtration, washed with H_2O, sucked as dry as possible, and then recrystallized from boiling MeOH. The product, 2,4-dimethoxy-5-(methylthio)benzaldehyde, was an off-white solid weighing 8.6 g. It could be obtained in either of two polymorphic forms, depending on the concentration of aldehyde in MeOH at the time of crystal appearance. One melted at 109-110 °C and had a fingerprint IR spectrum including peaks at 691, 734, 819 and 994 cm^{-1}. The other melted at 124.5-125.5 °C and had major fingerprint peaks at 694, 731, 839 and 897 cm^{-1}. Anal. ($C_{10}H_{12}O_3S$) C,H.

A solution of 8.2 g 2,4-dimethoxy-5-(methylthio)benzaldehyde in 30 mL nitroethane was treated with 1.8 g anhydrous ammonium acetate and heated on the steam bath for 4 h. Removal of the excess nitroethane under vacuum gave a colored residue which crystallized when diluted with MeOH. Recrystallization of the crude product from boiling EtOH gave, after filtration, washing and air drying to constant weight, 8.3 g 1-(2,4-dimethoxy-5-methylthiophenyl)-2-nitropropene with a mp of 112-113 °C. Anal. ($C_{12}H_{15}NO_4S$) C,H,N.

A suspension of 6.5 g LAH in 250 mL anhydrous THF was placed under a N_2 atmosphere and stirred magnetically and brought to reflux. There was added, dropwise, 8.0 g of 1-(2,4-dimethoxy-5-methylthiophenyl)-2-nitropropene in 50 mL THF. The reaction mixture was maintained at reflux for 18 h. After being brought to room temperature, the excess hydride was destroyed by the addition of 6.5 mL H_2O in 30 mL THF. There was then added 6.5 mL of 3N NaOH, followed by an additional 20 mL H_2O. The loose, white, inorganic salts were removed by filtration, and the filter cake washed with an additional 50 mL THF. The combined filtrate and washes were stripped of solvent under vacuum yielding a residue that was distilled. The free base boiled at 125-128 °C at 0.1 mm/Hg and was a white oil which solidified on standing. It weighed 5.1 g and had a mp of 47-48.5 °C. This was dissolved in 50 mL IPA, neutralized with concentrated HCl (until dampened universal pH paper showed a deep red color) and diluted with anhydrous Et_2O to the point of turbidity. There was a spontaneous crystallization providing, after filtering, washing with Et_2O, and air drying, 2,4-dimethoxy-5-methylthioamphetamine hydrochloride (META-DOT) with a mp of 140.5-142 °C. Anal. ($C_{12}H_{20}ClNO_2S$) C,H,N.

DOSAGE: greater than 35 mg.

DURATION: unknown.

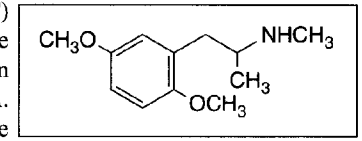
QUALITATIVE COMMENTS: (with 35 mg) "There was a vague awareness of something all afternoon, something that might be called a thinness. Possibly some brief cardiovascular stimulation, but nothing completely believable. This is a threshold level at the very most."

EXTENSIONS AND COMMENTARY: Again, as with the studies with ORTHO-DOT, it is apparent that the activity of META-DOT is going to be way down from the most interesting of these isomers, PARA-DOT (ALEPH-1, or just ALEPH). In the rectal hyperthermia assay (which calculates the psychedelic potential of compounds by seeing how they influence the body temperature of experimental animals in comparison to known psychedelics) the three DOT's were compared with DOM. And the results fell into line in keeping with the activities (or loss of activities) found in man. PARA-DOT was about half as active as DOM, but both ORTHO-DOT and the compound described here, META-DOT, were down by factors of 50x and 30x respectively. These animal studies certainly seem to give results that are reasonable with a view to other known psychedelic drugs, in that mescaline was down from DOM by a factor of more than 1000x, and LSD was some 33x more potent than DOM.

I have a somewhat jaundiced view of this rabbit rectal hyperthermia business. One is presumably able to tell whether a compound is a stimulant or a psychedelic drug by the profile of the temperature rise, and how potent it will be by the extent of the temperature rise. But the concept of pushing thermocouples into the rear ends of restrained rabbits somehow does not appeal to me. I would rather determine both of these parameters from human studies.

#126 METHYL-DMA; DMMA; 2,5-DIMETHOXY-N-METHYLAMPHETAMINE

SYNTHESIS: To a stirred solution of 28.6 g methylamine hydrochloride in 120 mL MeOH there was added 7.8 g 2,5-dimethoxyphenylacetone followed by 2.6 g sodium cyanoborohydride. HCL was added as needed to maintain the pH at about 6. The reaction was complete in 24 h, but was allowed to stir for another 3 days. The reaction mixture was poured into 600 mL H_2O, acidified with HCl (HCN evolution, caution) and washed with 3x100 mL CH_2Cl_2. Aqueous NaOH was added, making the solution strongly alkaline, and this was then extracted with 3x100 mL CH_2Cl_2. Removal of the solvent from the pooled extracts under vacuum gave 8.3 g of a clear, off-white oil that distilled at 95-105 °C. at 0.25 mm/Hg. The 6.5 g of colorless distillate was dissolved in 25 mL IPA, neutralized with concentrated HCl, and then diluted with anhydrous Et_2O to the point of cloudiness. As crystals formed, additional Et_2O was added in small increments, allowing clearing crystallization between each addition. In all, 200 mL Et_2O was used. After filtering, Et_2O washing, and air drying, there was obtained 6.2 g of 2,5-dimethoxy-N-methylamphetamine hydrochloride (METHYL-DMA) as fine white crystals with a mp of 117-118 °C. The mixed mp with 2,5-DMA (114-116 °C) was depressed to 96-105 °C. An alternate synthesis gave the same overall yield of an identical product, but started with 2,5-DMA. It required two synthetic steps. The free base amine was converted to the crystalline formamide with formic acid in benzene using a Dean Stark trap, and this intermediate was reduced to METHYL-MDA with LAH.



DOSAGE: above 250 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 250 mg) "There is a slight paresthesia at about 45 minutes, an awareness on the surface of the skin as if I had been touched by a cold draft of air. But nothing more. At three hours, I am completely out, if I was ever in. In the evening I assayed 120 milligrams of MDMA, and it barely produced a threshold effect, so the two materials might be seeing one another."

EXTENSIONS AND COMMENTARY: This is a difficult compound to pin down in the anthology of drugs. For some reason it has intrigued several independent, quiet researchers, and I have accumulated a number of interesting reports over the years. One person told me that he had felt nothing at up to 60 milligrams. Another had found a threshold at 50 milligrams, and had complete and thorough experiences at both 150 and 200 milligrams. Yet another person described two incidents involving separate individuals, with intravenous administrations of 0.2 mg/Kg, which would be maybe 15 or 20 milligrams. Both claimed a real awareness in a matter of minutes, one with a tingling in the genitalia and the other with a strange presence in the spine. Both subjects reported increases in body temperature and in blood pressure. Apparently the effects were felt to persist for many hours.

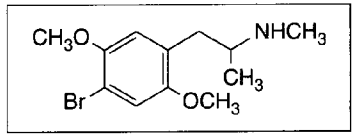
There is an interesting, and potentially informative, convergence of the metabolite of one drug with the structure of another. Under 4-MA, mention was made of a bronchodilator that has been widely used in the treatment of asthma and other allergenic conditions. This compound, 2-methoxy-N-methylamphetamine is known by the generic name of methoxyphenamine, and a variety of trade names with Orthoxine (Upjohn) being the best known. The typical dosage of methoxyphenamine is perhaps 100 milligrams, and it may be used several times a day. It apparently produces no changes in blood pressure and only a slight cardiac stimulation. And one of the major metabolites of it in man is the analogue with a hydroxyl group at the 5-position of the molecule. This phenolic amine, 5-hydroxy-2-methoxy-N-methylamphetamine is just a methyl group away from METHYL-DMA; it could either be methylated to complete the synthesis, or METHYL-DMA

could be demethylated to form this phenol. There is plentiful precedent for both of these reactions occuring in the body. It is always intriguing when drugs which show distinctly different actions can, in principle, intersect metabolically at a single structure. One wonders just what the pharmacology of that common intermediate might be.

Three additional N-methylated homologues of known psychedelics warrant mention, but do not really deserve separate recipes. This is because they have had only the most cursory assaying, which I have learned about by personal correspondence. All three were synthesized by the reduction of the formamide of the parent primary amine with LAH. METHYL-TMA (or N-methyl-3,4,5-trimethoxyamphetamine) had been run up in several trials to a maximum of 240 milligrams, with some mental disturbances mentioned only at this highest level. METHYL-TMA-2 (or N-methyl-2,4,5-trimethoxyamphetamine) had been tried at up to 120 milligrams without any effects. METHYL-TMA-6 (or N-methyl-2,4,6- trimethoxyamphetamine) had been tried at up to 30 milligrams and it, too, was apparently without effects. These are reports that I have heard from others, but I have had no personal experience with them. Those that I can describe from personal experience are entered separately as recipes of their own. And there are many, many other N-methyl homologues which have been prepared and characterized in the literature, and have yet to be tasted. So far, however, the only consistent thing seen is that, with N-methylation, the potency of the psychedelics is decreased, but the potency of the stimulants appears to be pretty much maintained.

#127 METHYL-DOB; 4-BROMO-2,5-DIMETHOXY-N-METHYLAMPHETAMINE

SYNTHESIS: To a solution of 6.0 g of the free base of 2,5-dimethoxy-N-methylamphetamine (see recipe under METHYL-DMA) in 30 mL glacial acetic acid there was added, dropwise and with good stirring, a solution of 5.5 g bromine in 15 mL acetic acid. The reaction became quite warm, and turned very dark. After stirring an additional 45 min, the mixture was poured into 200 mL H_2O and treated with a little sodium hydrosulfite which lightened the color of the reaction. There was added 20 mL concentrated HCl, and the reaction mixture was washed with 2x100 mL CH_2Cl_2 which removed most of the color. The aqueous. phase was made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. The removal of the solvent from the pooled extracts under vacuum gave 1.8 g of an oil which was dissolved in 10 mL IPA, neutralized with concentrated HCl, and diluted with 100 mL anhydrous Et_2O. No crystals were obtained, but rather an oily and somewhat granular insoluble lower phase. The Et_2O was decanted, and the residue



washed by grinding up under 3x100 mL Et_2O. The original decanted material was combined with the three washes, and allowed to stand for several h. The product 4-bromo-2,5-dimethoxy-N-methylamphetamine hydrochloride (METHYL-DOB) separated as fine white crystals which weighed, after filtering and air drying, 0.3 g and had a mp of 149-150 °C. The Et_2O-insoluble residue finally set up to a pale pink mass which was finely ground under a few mL acetone. Filtration and air drying gave a second crop of product as 0.9 g of pale lavender solids, with a mp of 143-145 °C.

DOSAGE: greater than 8 mg.

DURATION: probably rather long.

QUALITATIVE COMMENTS: (with 8.0 mg) "At an hour and twenty minutes, I was suddenly quite light headed. An hour later I must say that the effects are real, and generally good. I am spacey — nothing tangible. And a couple of hours yet later I am still aware. My teeth are somewhat rubby, and as things have been pretty steady for the last three hours, this will prove to be long lasting. There are a lot of physical effects that may be kidding me into providing myself some of the mental. At the sixth hour, I find that this is almost entirely physical. My teeth are tight, there is a general physical tenseness, my reflexes seem exaggerated, and my eyes are quite dilated. All of these signs are lessened by the eighth hour, and do not interfere with sleep at the twelfth hour. There is no desire to proceed any further, at least at the present time. Mental (+) physical (++). Next day, slight impression of persistence of toxicity."

(with 10 mg) "Nothing psychedelic, but awfully hard on the bod. The next day (24 hours later) I had a severe response to 5 milligrams of psilocybin."

EXTENSIONS AND COMMENTARY: The mention above, of the 10 milligrams of METHYL-DOB followed by 5 milligrams of psilocybin, leads to some interesting speculation. The usual pattern that is seen when two psychedelic drugs are taken too closely together is that the second experience is less effective than would have been expected. This is the property that is called tolerance, and it is frequently seen in pharmacology. The two exposures may be to a single drug, or they may be to two different drugs which usually have some properties in common. It is as if the spirit of the receptor site had become a little tired and needed a while to rest up and recuperate. When there is a demand for a repeat of full effectiveness, the user will customarily increase the dosage of the drug that is used. It is one of the built-in protections, in the area of psychedelics that, after one experience, you must wait for a period of time to lose the refractoriness that has set in.

The measure of the degree of tolerance that can be shared between different drugs, called cross-tolerance, can be used as an estimate of the similarities of their mechanisms of action. In other words, if A and B are somehow seen by the

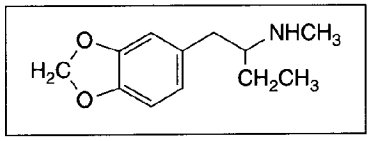
body as being similar, then a normally effective dose of A will make a next-day's normally effective dose of B weaker than expected. Or not active at all. And B will do the same job on A. If two drugs are different in their ways of doing things in the body, there is most often no cross-tolerance seen. This was described for MDMA and MDA, and is the basis of the argument that they act by distinctly separate mechanisms. A person who used what would be held as an active dose of MDMA for several days lost all response to the drug. He was tolerant to its effects. But an exposure to an effective dose of MDA at the time that tolerance to MDMA was complete, provided a normal response to the MDA. The drugs are not cross-tolerant and the body recognizes them as distinct individuals.

But for one drug to promote, or to exaggerate, the effect of another is called potentiation, and can be a clue to the dynamics going on in the brain or body. Here, admittedly in only a single report, METHYL-DOB had somehow sensitized the subject to a rather light dosage of psilocybin. But there have been other reports like this that I have heard of, from here and there. I have been told of an experiment with the dextro-isomer of DOM (this is the inactive optical isomer) at a level that was, not surprisingly, without any effects. The researcher had a severe reaction the following day with what was referred to as "poor" hashish. A similar form of potentiation has been commented upon under the recipe for TOMSO, where an inactive drug, and a most modest amount of alcohol, add together to create an unexpectedly intense intoxication. But note that in each of these cases, it is a phenethylamine interacting with a non-phenethylamine (psilocybin is an indole, hashish is a non-alkaloid terpene thing, and alcohol is, well, alcohol).

The bottom line with METHYL-DOB is, as with the other N-methylated psychedelics, that it is way down in potency, and probably not worth pursuing.

#128 METHYL-J; MBDB; EDEN; 2-METHYLAMINO-1-(3,4-METHYLENEDIOXYPHENYL)BUTANE; N-METHYL-1-(1,3-BENZODIOXOL-5-YL)-2-BUTANAMINE

SYNTHESIS: A solution of 0.12 g mercuric chloride in 180 mL H_2O was added to 5 g aluminum foil that had been cut into 1 inch squares, and amalgamation allowed to proceed for 0.5 h. The gray cloudy aqueous phase was decanted, and the resulting aluminum washed with 2x200 mL H_2O. After shaking as dry as possible, there was added, in sequence, a solution of 7.6 g methylamine hydrochloride in an equal weight H_2O, 23 mL IPA, 18.3 mL 25% NaOH, 6.72 g 1-(3,4-methylenedioxyphenyl)-2-butanone (see under the recipe of J for its preparation), and finally 44 mL additional IPA. The mixture was occasional swirled, and cooled externally as needed to keep the temperature below 50 °C. After



the reduction was completed (no metallic aluminum remaining, only gray sludge), it was filtered and the residues washed with MeOH. The combined filtrate and washes were stripped of organic volatiles under vacuum, the residue treated with 100 mL Et_2O, and this was extracted with 2x50 mL 3 N HCl. After washing the pooled aqueous extracts with 3x100 mL CH_2Cl_2, they were made basic with an excess of 25% NaOH and extracted with 5x50 mL CH_2Cl_2. Drying of these extracts with anhydrous $MgSO_4$ and removal of the solvent gave a residue that was distilled at 88 °C at 0.08 mm/Hg to give a colorless oil that was dissolved in IPA and neutralized with concentrated HCl. The solids that separated were removed by filtration, Et_2O washed, and air dried to provide 6.07 g 2-methylamino-1-(3,4-methylenedioxyphenyl)butane hydrochloride (METHYL-J or MBDB) as white crystals with a mp of 156 °C. Anal. ($C_{12}H_{18}ClNO_2$) C,H,N. Reductive amination of the butanone with methylamine hydrochloride in MeOH, employing sodium cyanoborohydride, gave an identical product but in a smaller yield.

DOSAGE: 180 - 210 mg.

DURATION: 4 - 6 h.

QUALITATIVE COMMENTS: (with 210 mg) "Generally very, very friendly, very quiet effect. I can read easily, but looking at pictures in most books is relatively meaningless. Distinct de-stressing effect, to the point where it's too much trouble to set out to do anything at all, really. There is just no drive, and it isn't even bothersome to be missing it. Do I like it? Yes, very much. Feel that I've just begun to explore it, though. Would I consider this material in therapy? Well, sure, it's worth trying. Destressing would be excellent, and better than MDMA in some ways, but the empathy and intuition levels have yet to be explored in a therapy setting. I feel that they may be somehow lower."

(with 210 mg) "Onset rapid. Alert 20 minutes, and to a +2.5 at 30 to 35 minutes. No physical symptoms, i.e., teeth clench, no stomach problems. Good visual enhancement; eyes open — bright colors — no visuals with eyes closed. No 'cone of silence' that I get with MDMA (and enjoy), otherwise I'm not sure I could tell which was which if I took them blind."

(with 210 mg and a 50 mg supplement) "Tasted perfectly rotten. Suspect I was getting some type of alert in 5 minutes (I often get one quickly with MDMA) and at 30 minutes, a full blown high developed rather abruptly. It would be difficult to describe the high. I suspect it is the lack of language for the phenomenon. I would describe it somewhat like an alcohol high without the disabling side effects of confusion, slurring, staggering and etc. The high never got any more intense than at that 30 minute point and with a noticeable drop in another hour, I took a 50 mg supplement. I enjoyed the high. I relaxed with the material. However, it did not seem to have the same qualities as MDMA, in that it was not as stimulating, and it had very little visual activity. I talked with others, but found it easy to lie down and

relax. There was some jaw-clenching towards the end, and I had considerable nystagmus at the peak which I could control. After the experience, I did not want to drink alcohol very much (sell it as a substitute for EtOH!)."

(with 210 mg and a 70 mg supplement) "I begin to feel the rush at 20 minutes, increasing rapidly. Very much like MDMA, only more intense intoxication. Otherwise same symptoms: intense euphoria that I call a feeling of grace, soft skin, voices, youthful appearance, animated discussions, feelings of great closeness to others. I start to drop noticeably at less than an hour and a half into it, but I delayed a supplement until the hour and fifty minute point. It does not get me back to the original intoxication. However, it is very nice, very much like MDMA. Only difference is that there seems to be more quietness, less inclination to talk than with an MDMA supplement. My conclusion: Seems an excellent substitute for MDMA, Next time may try somewhat lower amount, supplement sooner."

EXTENSIONS AND COMMENTARY: An observer who was familiar with the outwardly apparent effects with groups experimenting with MDMA felt that, although most subjects commented favorably in their comparisons of METHYL-J with MDMA, there was lacking some of the spontaneity, the warmth, and the clear intimacy of the latter drug. The dosage range explored is remarkably tight, attesting to a consistency of response. The typical supplement used, if any, was 70 milligrams or less, just before the two hour point. This indicates a chronology similar to that of MDMA, and about two thirds the potency.

The arguments that weigh the use of the code name of MBDB against the use of METHYL-J are present in the recipe for BDB (or J). But what is the source of this H, I, J, K naming thing that I have called the Muni Metro?

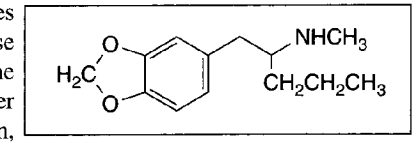
First, a little bit of local color. In San Francisco, there is a public transportation called the S.F. Municipal Metropolitan System complex that has integrated an underground street-car system that emerges above ground and connects with a bus network. A number of the street-car lines fan across the city to the outer reaches which are called the Avenues. These lines are named by sequential letters. There is the J Church Street line, the K Ingelside line, the L Taraval line, the M Ocean line, and the N Judah. And in the pharmacological complex that involved the lengthening of the aliphatic chain, there were two coincidental benchmarks in the names that were proposed. Those without an alpha-substituent (no carbon atoms at the position alpha to the amine group, the phenethylamines) were originally called the H compounds. H stood for "homopiperonylamine." And the first of those with the alpha-ethyl group there (two carbon atoms at the position alpha to the amine group) was familiarly called "Jacobamine" in recognition of a famous chemist who had set the synthetic wheels in motion.

It is quite obvious, that with one carbon atom lying on that alpha-position, you are precisely half-way between no carbons and two carbons. And there was one letter of the alphabet that lies precisely half-way between an H and a J. So, an natural naming pattern developed. The I compounds were already pretty well known by

names such as MDA and MDMA and MDE, so I, and METHYL-I, and ETHYL-I, didn't have any appeal. But for the new, the alpha-ethyl compounds, why not call them the J-compounds? If it has a methyl on the nitrogen it will be METHYL-J and if it has an ethyl group it will be ETHYL-J. And in the next longer group, the 3-carbon propyl group on the alpha-position becomes the K family, and the 4-carbon butyl group located there, the L family. Each with its METHYL and ETHYL prefixes, if the nitrogen atoms are substituted with a methyl or and ethyl group. *V'la, comme on dit en Français. Le système Muni Metro. Plus simple.*

#129 METHYL-K; 2-METHYLAMINO-1-(3,4-METHYLENEDIOXYPHENYL)PENTANE; N-METHYL-1-(1,3-BENZODIOXOL-5-YL)-2-PENTYLAMINE

SYNTHESIS: The Grignard reagent of butyl bromide was prepared in anhydrous Et_2O by the dropwise addition of 68 g n-butyl bromide to a well-stirred suspension of 14 g magnesium turnings in 500 mL anhydrous Et_2O. When the exothermic reaction had stopped, there was added a solution of 60 g piperonal in about 100 mL Et_2O, over the course of 1 h. After the exothermic addition was complete, the reaction mixture was held at reflux for several h, then cooled and decomposed by the addition of dilute HCl. The phases were separated, and the aqueous phase extracted with 2x75 mL CH_2Cl_2. The organics were combined and gave, after the removal of the solvents under vacuum, 84 g of 1-hydroxy-1-(3,4-methylenedioxyphenyl)pentane as a yellow liquid. This was used in the following dehydration step without further purification.



A mixture of 52 g of the crude 1-hydroxy-1-(3,4-methylenedioxyphenyl)-pentane and 2 g powdered $KHSO_4$ was heated with a flame until there was no more apparent generation of H_2O. The resulting dark, fluid oil was distilled at 100-110 °C at 0.3 mm/Hg to give 29.5 g of 1-(3,4-methylenedioxyphenyl)-1-pentene as a light yellow liquid. This was employed in the following oxidation step without further purification.

To 120 mL of 90% formic acid there was added, with good stirring, 15 mL H_2O, followed by 23 mL of 35% H_2O_2 To this mixture, cooled with an external ice bath, there was added a solution of 24 g crude 1-(3,4-methylenedioxyphenyl)-1-pentene in 120 mL acetone at a rate slow enough to keep the internal temperature from exceeding 35 °C. At the end of the addition, the temperature was brought up to 45 °C by heating briefly on the steam bath, and then the reaction mixture was allowed to stand and stir at ambient temperature for several h. All volatiles were removed under vacuum, with a bath temperature maintained at 45 °C. The residue was dissolved in 30 mL MeOH, then there was added 200 mL 15% H_2SO_4 and the

mixture held on the steam bath for 1.5 h. There was then added an additional 300 mL H_2O, and this was extracted with 2x250 mL of a petroleum ether/EtOAc (5:1) mixture. The extracts were pooled, and the solvents removed under vacuum to give a residue that was distilled at 115-120 °C at 0.3 mm/Hg. This light yellow liquid weighed 13.5 g and was substantially pure 1-(3,4-methylenedioxyphenyl)-2-pentanone by TLC.

To 5.0 g of aluminum foil cut into 1 inch squares, there was added a solution of 150 mg $HgCl_2$ in 200 mL H_2O. The mixture was heated briefly until there were clear signs of active amalgamation, such as fine bubbling for the aluminum surfaces and the beginning of the formation of a gray, amorphous solid phase. The $HgCl_2$ solution was decanted off and the aluminum was washed with 2x200 mL additional H_2O. After shaking as dry as possible, there was added, in sequence and with good swirling agitation between each addition, 10 g methylamine hydrochloride in 10 mL H_2O, 27 mL IPA, 22 mL of 25% NaOH, 5.0 g 1-(3,4-methylenedioxyphenyl)-2-pentanone, and finally an additional 50 mL IPA. The mixture was heated on the steam bath periodically to maintain the reaction rate at a vigorous boil. When all of the aluminum had been consumed, the cooled mixture was filtered and the solids washed with MeOH. The combined filtrate and washings were stripped of solvent under vacuum. The residue was dissolved in dilute H_2SO_4 and washed with 2x75 mL CH_2Cl_2. After making basic again with 25% NaOH, this was extracted with 2x100 mL CH_2Cl_2, and the pooled extracts were stripped of solvent under vacuum. The residue was distilled at 105-110 °C at 0.3 mm/Hg to give 2.7 g of a colorless liquid. This was dissolved in 15 mL IPA, neutralized with concentrated HCl, and diluted with 75 mL anhydrous Et_2O which allowed a delayed appearance of a fine white crystal. This was removed by filtration, Et_2O washed, and air dried to give 2.45 g 2-aminomethyl-1-(3,4-methylenedioxyphenyl)pentane hydrochloride (METHYL-K) as a white product with a mp of 155-156 °C. Anal. ($C_{13}H_{20}ClNO_2$) C,H.

DOSAGE: greater than 100 mg.

DURATION: unknown.

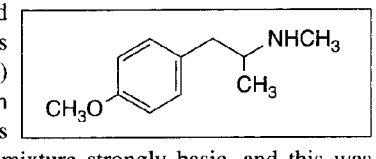
QUALITATIVE COMMENTS: (with 100 mg) "There were no effects. I was busy and totally wound up and didn't sleep until 3 AM, but this was probably unrelated to the Me-K."

EXTENSIONS AND COMMENTARY: The well appears to be running dry, with a pentane chain as a basic skeleton. METHYL-J, at this level, was already showing a number of hints and clues, largely physical such as coldness in the feet and a slight mastoidal pressure, that activity was right around the corner. But METHYL-K gave no such hints. The unmethylated homologue, 2-amino-1-(3,4-methylenedioxyphenyl)pentane (K), was also made, by the reductive amination of 1-(3,4-methylenedioxyphenyl)-2-pentanone with ammonium acetate and sodium cyanoborohydride in methanol. It was a white crystalline solid, mp 202-203 °C, but is given here in the comments only, as its human assaying had never even been initiated. Anal. ($C_{12}H_{18}ClNO_2$) C,H. The N-ethyl homologue, 2-ethylamino-1-(3,4-methylenedioxyphenyl)pentane (ETHYL-K), is entered with its own recipe, on the other hand, since testing had been started with it.

And the longest chain that has been explored in this Muni Metro series is the six-carbon hexyl chain which is, quite logically, the L-series, sort of the end of the Taraval line (see under METHYL-J for an explanation). The central compound for all the L-compounds was the ketone 1-(3,4-methylenedioxyphenyl)-2-hexanone, which was prepared by the Grignard reagent of (n)-amyl bromide with piperonal to give 1-hydroxy-1-(3,4-methylenedioxyphenyl)hexane, dehydration of this with potassium bisulfate to the olefin, and oxidation of this with hydrogen peroxide and formic acid to the L-ketone which was an orange-colored liquid with a bp of 125-135 °C at 0.3 mm/Hg. This ketone was reductively aminated with ammonium acetate and sodium cyanoborohydride in methanol to produce 2-amino-1-(3,4-methylenedioxyphenyl)hexane hydrochloride (L) as a white crystalline product with a mp of 157-158 °C. Anal. ($C_{13}H_{20}ClNO_2$) C,H. And this ketone was reductively aminated with methylamine hydrochloride and amalgamated aluminum in isopropanol to produce 2-methylamino-1-(3,4-methylenedioxyphenyl)hexane hydrochloride (METHYL-L) as a white crystalline product with a mp of 139-141 °C. Anal. ($C_{14}H_{22}ClNO_2$) C,H. The reduction of this ketone in a similar manner with ethylamine hydrochloride produced 2-ethylamino-1-(3,4-methylenedioxyphenyl)hexane (ETHYL-L). None of this series has yet been explored either as psychedelic or entactogenic materials.

#130 METHYL-MA; PMMA; DOONE; 4-MMA; 4-METHOXY-N-METHYLAMPHETAMINE

SYNTHESIS: A solution of 20 g methylamine hydrochloride in 150 mL hot MeOH was treated with 10.0 g 4-methoxyphenylacetone and stirred magnetically. After returning to room temperature, there was added 5.0 g sodium cyanoborohydride, followed by cautious addition of HCl as required to maintain the pH at about 6. The reaction was complete after a few days, and the mixture was poured into 800 mL H_2O. This was acidified with HCl (HCN evolution!) and washed with 3x75 mL CH_2Cl_2, which removed most of the yellow color. There was 25% NaOH added to make the reaction mixture strongly basic, and this was extracted with 3x75 mL CH_2Cl_2. The solvent was removed from the pooled extracts under vacuum, and the 10.3 g of residue distilled at 0.3 mm/Hg. The 9.7 g of



colorless oil that distilled at 75-90 °C was dissolved in 50 mL IPA, neutralized with 4.5 mL concentrated HCl, and then diluted with 100 mL anhydrous Et_2O. There were generated glistening crystals of 4-methoxy-N-methylamphetamine hydrochloride (METHYL-MA or DOONE) that weighed, after washing with Et_2O and air drying to constant weight, 11.0 g and which had a mp of 177-178 °C. The same base can be made by the action of ethyl chloroformate on 4-MA in the presence of triethylamine to make the carbamate, or the action of formic acid to make the formamide. These can then be reduced with LAH to this same end product.

DOSAGE: greater than 100 mg.

DURATION: short.

QUALITATIVE COMMENTS: (with 110 mg) "One hour into it, my pulse was up over 100, and I was compulsively yawning. There was some eye muscle disturbance, a little like the physical side of MDMA, but there was none of its central effects. But all the hints of the cardiovascular are there. By the fourth hour, I am pretty much back to baseline, but the yawning is still very much part of it. I might repeat this, at the same level, but with continuous close monitoring of the body."

EXTENSIONS AND COMMENTARY: Why would there be interest in this particular compound? The track record from the comparison of active compounds that are primary amines, and their N-methyl homologues, has shown that, in general, the stimulant component might be maintained, but the "psychedelic" contribution is generally much reduced. MDMA is, of course, an exception, but then, that particular compound is a one-of-a-kind thing which simply defies all the rules anyway, and I drop it from this kind of reasoning. And as 4-MA is a pretty pushy stimulant with little if any sensory sparkle, why bother with the N-methyl compound at all?

For a completely silly and romantic reason. When the MDMA story became front-page news back in mid-1985, the cartoonist-author of Doonesbury, Gary Trudeau, did a two-week feature on it, playing it humorous, and almost (but not quite) straight, in a hilarious sequence of twelve strips. On August 19, 1985 he had Duke, president of Baby Doc College, introduce the drug design team from USC in the form of two brilliant twins, Drs. Albie and Bunny Gorp. They vividly demonstrated to the enthusiastic conference that their new drug "Intensity" was simply MDMA with one of the two oxygens removed. "Voila," said one of them, with a molecular model in his hands, "Legal as sea salt." And what is MDMA with one oxygen atom removed? It is 4-methoxy-N-methylamphetamine or METHYL-MA which, according to the twins, should give the illusion of substance to one's alter ego. So, I called it Doonesamine, or simply "DOONE" for short. Maybe that was also a homonym for Frank Herbert's science fiction book, "Dune," wherein the magical drug "spice" provided a most remarkable alteration of the user's state of consciousness.

This comic strip presentation was the first nationally distributed allusion to the term "designer drugs," and perhaps it lent unexpected support for the passage, just a year later, of the Controlled Substances Analogue Enforcement Act of 1986. This intentionally vague piece of legislation makes the giving of, or the taking of, or even the possession with the intent to take, any drug that in any way alters your state of consciousness, a felony. A shameful and desperate effort by the governmental authorities to maintain the image of control in a lost situation.

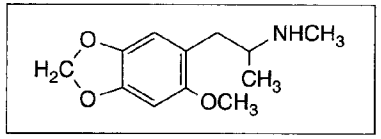
Enough editorial. Back to historic technicalities. In truth, METHYL-MA is a well studied drug, at least in animals. In both mice and rats, it is an exceptionally potent agent in creating the state of catatonia. Animal studies, prompted by the clandestine synthesis of METHYL-MA, have shown that there is indeed locomotor stimulation and some central effects, but these effects are somehow different than those of a simple amphetamine-like agent. The experimenter's conclusions, based on its structural resemblance to 4-MA and its proclivity to produce catatonia in some animal species and the ever-present possibility that there might be unsuspected neurochemical changes to be seen with its use, are that human experimentation should be discouraged. I have come to the same conclusion, but in my case this is based on a much more succinct observation: I tried it and I didn't like it.

A brief comment on two of the N,N-dimethylhomologues of methoxyamphetamine. One was 4-methoxy-N,N-dimethylamphetamine, 4-MNNA. This material, made by the reductive amination of 4-methoxyphenylacetone with dimethylamine, was a colorless oil, which distilled at 70-85 °C at 0.3 mm/Hg. The corresponding 2-methoxy-N,N-dimethylamphetamine was similarly made. 2-MNNA was also a colorless oil and had the same bp. Both of them were fluorinated with ^{18}F labelled acetyl hypofluorite (3% and 6% yields respectively) but neither of them was pursued any further in the search for a brain blood flow indicator.

#131 METHYL-MMDA-2; 2-METHOXY-N-METHYL-4,5-METHYLENEDIOXYAMPHETAMINE

SYNTHESIS: A suspension of 17.4 g electrolytic elemental iron in 100 g glacial acetic acid was heated on the steam-bath until there were the first signs of bubbling and reaction, about 60 °C. There was then added, in small portions, a suspension of 9.2 g 1-(2-methoxy-4,5-methylenedioxyphenyl)-2-nitropropene (see under MMDA-2 for its preparation) in 40 g warm glacial acetic acid. The reaction was extremely exothermic. After the color had lightened as much as possible, there was added an additional quantity of iron sufficient to completely discharge the residual yellow color. Mechanical stirring was maintained as the reaction mixture was allowed to return to room temperature. All was poured into 800 mL H_2O, and the insolubles were removed by filtration. These were washed alternately with H_2O and

with CH_2Cl_2, the combined filtrate and washes were separated, and the aqueous phase extracted with 3x100 mL CH_2Cl_2. All organics were combined, washed with 2x75 mL 5% NaOH (which removed most of the color) and the solvent removed under vacuum. The 8.7 g residue was distilled at 90-105 °C at 0.2 mm/Hg to give 6.7 g of 2-methoxy-4,5-methylenedioxyphenylacetone as a pale yellow oil.



To a magnetically stirred solution of 30 g methylamine hydrochloride in 150 mL warm MeOH, there was added 6.5 g 2-methoxy-4,5-methylenedioxyphenylacetone followed by 3.0 g sodium cyanoborohydride. Concentrated HCl was added as was required to keep the mixture at a pH of about 6. When the reaction was complete, it was added to 1 L H_2O and made strongly basic with 25% NaOH. This was extracted with 3x100 mL CH_2Cl_2, and the pooled extracts were, in turn, extracted with 2x100 mL dilute H_2SO_4. This aqueous phase was washed with CH_2Cl_2, made basic with NaOH, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent from these pooled extracts under vacuum gave 8.7 g of an amber oil. This was distilled at 110-125 °C at 0.25 mm/Hg to give 5.1 g of a colorless oil. This was dissolved in 30 mL IPA, neutralized with about 3 mL concentrated HCl, and diluted with 60 mL anhydrous Et_2O. The clear solution slowly deposited white crystals which were removed by filtration and air dried to give 4.2 g 2-methoxy-N-methyl-4,5-methylenedioxyamphetamine hydrochloride (METHYL-MMDA-2) with a mp of 168-169 °C. Anal. ($C_{12}H_{18}ClNO_3$) C,H.

DOSAGE: greater than 70 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 70 mg) "Maybe a threshold — pleasant but not possible to characterize it."

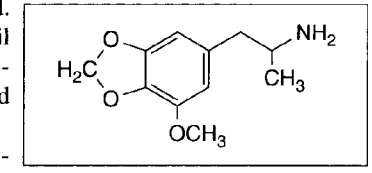
EXTENSIONS AND COMMENTARY: With the effective dosage of the unmethylated homologue being the range of 25 to 50 milligrams, this N-methyl compound is, as with the other N-methylated materials discussed here, again of reduced activity. The highest dose yet reported was 70 milligrams, and there is no way of estimating what miight be an active level nor, once there, what the quality of the effects might be.

This is the only MMDA analogue that has been explored as an N-methyl derivative. A more highly substituted analogue has also been made, the N-methyl derivative of DMMDA. Isoapiole (see its preparation under DMMDA) was oxidized with formic acid and hydrogen peroxide to the ketone (2,5-dimethoxy-3,4-methylenedioxyphenylacetone, a solid with a mp of 75-76 °C from methanol) which was reductively aminated with methylamine and amalgamated aluminum to give 2,5-dimethoxy-N-methyl-3,4-methylenedioxyamphetamine hydrobromide

monohydrate (METHYL-DMMDA, or DMMDMA) as a white crystalline solid with a mp of 91-92 °C. The hydrochloride salt was a hygroscopic solid. Anal. ($C_{13}H_{22}BrNO_5$) C,H. The above ketone has also been used in the synthesis of another methylated DMMDA, on the beta-carbon. This is described under DMMDA itself. DMMDMA has not yet been launched into an evaluation program, and I wouldn't be surprised if the needed dosage might be up there somewhere over 100 milligrams. I feel quite sure that the answers may be known in the near future. There is a surprisingly large number of inconspicuous chemical explorers out there all over the world, doing their synthetic thing in their private laboratories. They are truly the astronauts of inner space.

#132 MMDA; 3-METHOXY-4,5-METHYLENEDIOXY-AMPHETAMINE

SYNTHESIS: (from protocatechualdehyde) A solution of 18 g commercial protocatechualdehyde (3,4-dihydroxybenzaldehyde) in 200 mL warm acetic acid was filtered free of any insolubles, to provide a very dark but clear solution. With good stirring there was then added 20 g elemental bromine. The reaction spontaneously heated to about 30 °C and solids appeared in about 5 min. Stirring was continued for 1 h, and then the light gray solids that had formed were removed by filtration and lightly washed with acetic acid. These were air dried on the steam bath until free of acetic acid smell. The product, 3-bromo-4,5-dihydroxybenzaldehde, weighed 11.7 g and had a mp of 222 °C.



To a solution of 11.7 g 3-bromo-4,5-dihydroxybenzaldehyde in 36 mL DMSO there was added 29 g methylene iodide followed by 20.8 g anhydrous K_2CO_3. This was heated on the steam bath for 3 h, added to 1 L H_2O, made strongly basic with NaOH, then extracted with 3x100 mL CH_2Cl_2. These extracts were pooled, washed with H_2O, and the solvent removed under vacuum. The dark brown semi-solid residue was distilled with the major fraction (6.0 g) coming over at 120-130 °C at 0.3 mm/Hg. This, upon recrystallization from 35 g boiling MeOH, gave 1.3 g of 3-bromo-4,5-methylenedioxybenzaldehyde as an off white crystalline solid with a mp of 123-124 °C.

A mixture of 2.2 g 3-bromo-4,5-methylenedioxybenzaldehyde and 3.6 mL cyclohexylamine in a distillation flask was heated to 100 °C to effect solution, and then with an open flame until the signs of H_2O evolution were evident. This was then placed under a hard vacuum to remove the generated water and excess cyclohexylamine, and the product distilled at 120-125 °C at 0.2 mm/Hg. There was obtained 2.4 g of the Schiff base of the aldehyde and the amine, melting at 86-96 °C. Recrystallization of an analytical sample from 5 volumes of MeOH gave 3-bromo-

temperature had again been lowered to near 0 °C. The product was removed by filtration. Extraction of the filtrate with CH_2Cl_2 and removal of the solvent provided additional nitrostryrene, for a combined yield of 50.7 g with a mp of 103 °C due to the presence of a small amount of free myristicinaldehyde. A recrystallization from MeOH produced 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-nitropropene with a mp of 109-110 °C. This material was completely adequate for the above-described reduction to MMDA. The conversion of this nitropropene to myristicinaldehyde is an alternative to the lengthy synthesis given above), and can be used in the preparation of LOPHOPHINE.

A mixture of 50 g 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-nitropropene and 26 g racemic α-methylbenzylamine was heated on the steam bath. The mixture gradually formed a clear solution with the steady evolution of nitroethane. When the reaction became quiet, there was added a mixture of 20 mL concentrated HCl in 100 mL H_2O. The reaction mixture dissolved completely, and as the temperature continued to rise there was the abrupt solidification as the formed myristicinaldehyde crystallized out. This product was removed by filtration and, when combined with a second crop obtained by the hexane extraction of the filtrate, gave 36.9 g of myristicinaldehyde. The mp of 128-129 °C was raised to 133-134 °C by recrystallization from hexane.

DOSAGE: 100 - 250 mg.

DURATION: moderate.

QUALITATIVE COMMENTS: (with 100 mg) "I felt completely relaxed at one hour. Almost as if I was floating. There were no obvious effects on taste, and the relaxation and composed feeling is much like a small dose, maybe 20 mikes, of LSD. There was some dilation, and in the evening I was a little restless and slightly tired. I slept well, and awoke refreshed and happy."

(with 100 mg) "It seemed to take 45 minutes to work and then it came on very suddenly, as if my eyeballs were being pulled out and my whole head expanding. Soon a cold feeling set in with shivering — this was not unpleasant. My state in about two hours seemed to be one of empathy and passivity, compassion of an impersonal sort. The music sounded artificial and canned and tinny, in contrast to the voices, which sounded rich and full and finely articulated and melodious."

(with 150 mg) "We are on the beach at the river mouth drying seaweed, on split redwood. There is a slight nausea, slight cramps, and then my visual field starts to light up. Still vertigo but only with my eyes open, and heaviness and time stretches out; numbness in the chest as when an opiate is taken. There are geometric patterns, but the excess light on my closed eyelids interferes with this. A dance of the glittering diamond studded sea waves, increasing motion and beauty. More landscapes appear inside. This is a good introductory drug to the drugs of this class, to become familiar with the drug state in as gentle a fashion as possible. This substance seems to have a much gentler action than others of this class; perhaps more like cannabis or psilocybin. There is very little paranoia. I note hallucinations of two types: those which are strictly retinal and more minute and small and influenced by light and focused on the light ahead on the retina or lids; and the other, those deep in the visual tract and occiput which are larger and more global and dream-like and, when solid, are quite dramatic and unforgettable as in meditation."

(with 210 mg) "MMDA tastes awful. The bitter alkaloid taste is followed by a distinctively chemical laboratory flavor as if from old rubber tubing. Nothing seems to happen for about 45 minutes when rather suddenly an anvil seems to lower itself over your head; you feel disoriented, and tend to withdraw from social contact a little. The drug gives less feeling of being ill than mescaline. The effect definitely reaches a climax with a pleasant afterglow following. Apparently there are no profound motor coordination problems. MMDA yields that 'Sunday afternoon' feeling of desiring to lie down and enjoy life; a luxurious feeling of 'layback.' No enhancement of colors in visual scene (except for some greenish tinges in faces) but upon closing eyes hallucinations appear to be quite real in 3-D, like watching a movie. First these dreams appear in black and white, but later colors start appearing. Chartreuse and magenta first appear, then blue and finally red. First I had visions of large numbers on gaming tables, then people. MMDA appears to bring dreams to the conscious level; is a link between the subconscious and the conscious."

(with 225 mg) "I had a strange awareness of my hands in about 20 minutes — not a feeling in them as just that I was attracted to them somehow. Then I began to get fearful, an acute experience of aloneness. I lay face down (a depressed position for me). Next I was talking to the kids at school (an image) or to other teachers. This was very vivid. The scenes at school were more vivid that the real scenes around me here. Those people were much more real. I am actually very sleepy right now during the experiment. Of any experience I have had, this was most like a series of dreams easily remembered. When it was over, I felt as if I had had a long period of sleeping — I had gone to bed and had a series of dream-like states very vivid and colorful and real."

EXTENSIONS AND COMMENTARY: The phrase that had been used by several of the subjects in the early trials with MMDA, again and again, was "brain movies." Apparently the richest of the effects were to be had with the eyes closed. This is the compound that I had first completed in 1962, and had named it MMDA, and had begun the exploring of it when I heard that Dr. Gordon A. Alles, a professor of pharmacology at U. C. L. A. who had his own private laboratory in Los Angeles, had also synthesized it in 1962, had also named it MMDA, and had also begun exploring it. We made a date to meet and share ideas, and then he died, at the age of 62, in 1963.

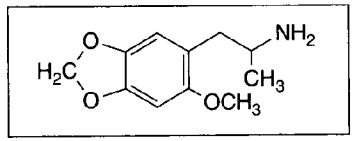
This is a material that might be a contributing factor to the pharmacology of nutmeg. The major essential oil from that spice is myristicin, and it is the easiest source of MMDA. It has been reported that the passage of this oil through the liver

of a rabbit will generate MMDA in that animal. The only difference between the two molecules, structurally, are the elements of ammonia. Myristicin plus ammonia gives MMDA. Another natural source of myristicin is Oil of Parsley, which is also an excellent source of apiole, mentioned under DMMDA. A rumor that had currency in the 1960's, that parsley could get you high, probably had its origins in the reports of myristicin being present, coupled with myristicin being the principal source of MMDA. The relationship to myristicin (an essential oil) led to the classifying of MMDA as a Essential Amphetamine. These relationships are expanded upon, under TMA.

At the time that the FDA issued its proclamation of dangerous drugs (in the mid-1960's), MMDA was being talked about, and in fact it had just become available commercially in England through the Koch Light Industries. But to my knowledge it had never appeared on the street, so its having being swept into the listings of evil drugs was simply a coincidence of bad timing. The close resemblance of initials between MMDA, and the currently notorious MDMA, has led to no small amount of confusion in the popular press. They remain totally separate and completely different drugs.

#133 MMDA-2; 2-METHOXY-4,5-METHYLENEDIOXY-AMPHETAMINE

SYNTHESIS: A solution of 11.5 g pellet KOH (85%) in 75 mL EtOH was treated with 25 g sesamol followed by 27 g methyl iodide. This was brought to reflux on the steam bath. Salt formation was apparent in 20 min, and refluxing was maintained for a total of 4 h. The solvent was removed under vacuum, and residue poured into 400 mL H_2O. This was acidified with HCl and extracted with 3x150 mL CH_2Cl_2. The pooled extracts were washed with 3x100 mL 5% NaOH, which removed most of the color. The solvent was removed under vacuum to provide 24.0 g of 3,4-methylenedioxyanisole as a pale amber oil.



A mixture of 56.4 g $POCl_3$ and 49.1 g N-methylformanilide was allowed to stand for 40 min and then it was poured into a beaker containing 64 g 3,4-methylenedioxyanisole. There was an immediate exothermic reaction with darkening and the generation of bubbles. This was heated on the steam bath for 1 h, then poured into 1 L H_2O with extremely vigorous stirring. The dark brown phase was quite opaque, and then there was a sudden lightening of color with the generation of a fine pale yellow solid. Stirring was continued for 2 h, then these crystals were removed by filtration. This crude product was recrystallized from 400 mL boiling MeOH yielding, after filtering, washing, and air drying to constant weight, 44.1 g 2-methoxy-4,5-methylenedioxybenzaldehyde with a mp of 110-111 °C. Only one

positional isomer was visible in the final product by GC, but extraction of the original mother liquors with CH_2Cl_2 produced, after evaporation of the solvent under vacuum, 2 g of a red oil that showed two earlier peaks on OV-17. These were consistent with about 1% of each of the two alternate positional isomers that could result from the Vilsmeier formylation reaction.

A solution of 43 g 2-methoxy-4,5-methylenedioxybenzaldehyde in 185 g nitroethane was treated with 9.3 g anhydrous ammonium acetate and heated on the steam bath for 4.5 h. The excess nitroethane was removed under vacuum to give a residue that spontaneously crystallized. These solids were washed out mechanically with the aid of 200 mL cold MeOH, and the brilliant orange crystals recovered by filtering and air drying to constant weight. There was obtained 35.7 g 1-(2-methoxy-4,5-methylenedioxyphenyl)-2-nitropropene with a mp of 166-167 °C. This was not improved by recrystallization from IPA. Evaporation of solvent from the methanolic washes gave yellow solids (4.6 g melting at 184-186 °C) which, on recrystallization from THF/hexane, melted at 188-190 °C. This showed a molecular weight of 416 by chemical ionization mass spectroscopy (isobutane at 0.5 torr) and is the $C_{20}H_{20}N_2O_8$ adduct of one molecule each of nitrostyrene, aldehyde, and ammonia that frequently appears as a very insoluble impurity in aldehyde-nitroethane condensations that are catalyzed by ammonium acetate.

To a refluxing suspension of 36 g LAH in 1 L anhydrous THF under an inert atmosphere, there was added 44.3 g 1-(2-methoxy-4,5-methylenedioxyphenyl)-2-nitropropene in hot THF. The solubility was very low, so that it was necessary to use a heat lamp on the dropping funnel to maintain a clear solution for addition. The addition required 2 h and the reflux was maintained for 36 h. The reaction mixture was then cooled in an ice bath and there was added, in sequence and commensurate with heat evolution, 36 mL H_2O, 36 mL 15% NaOH, and finally 108 mL H_2O. The granular solids were removed by filtration and washed with THF. The combined filtrate and washes were stripped of solvent under vacuum yielding 58.8 g of a pale amber oil. This was dissolved in 100 mL IPA, neutralized with concentrated HCl (20 mL was needed) and diluted with 500 mL anhydrous Et_2O. More IPA was required to keep an oil phase from appearing. After the crystalline product was completely formed, it was removed by filtration, washed with IPA/Et_2O, and finally with Et_2O. Air drying gave 31.1 g of 2-methoxy-4,5-methylenedioxyamphetamine hydrochloride (MMDA-2) with a mp of 186-187 °C.

DOSAGE: 25 - 50 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 25 mg) "Had some not-too-pleasant jangly effects — this is not the smoothest of drugs. Duration: onset at 1 1/2 hours (dose after lunch), acute 3 to 4 hours, seconal at 11 hours to stop residual effects so I could sleep. Occasionally from 5 to 10 hours acute abdominal distress, resembling gas

pains but unable to defecate. Abdominal muscles tight and hard. This occurred for about 15 minutes every hour or so. Rather unpleasant."

(with 30 mg) "There was the first subtle note at 45 minutes, and the slow development makes the changes easy to assimilate, but difficult to quantitate. My awareness is truly enhanced. Nothing is distorted, so there can be no misrepresentation as a result. This would be a good material to introduce someone to the slow-on slow-off type of experience. It would be impossible for any person, at this level, on this drug, to have a bad experience. This is very much like a slow MDA, perhaps 80 milligrams of it, and fully as controllable. The N-methyl of this is a must."

(with 40 mg) "The chemical is primarily a visual enhancer with only an extremely modest amount of visual distortion. The retinal activity was of a minor and non-threatening nature. The chemical seemed to facilitate empathic communication and the emotions felt strong and clean. Conversation flowed easily, without inhibitions or defensiveness. Anorexia accompanied experience. There was no impotence. There was some restless movement which dissipated with exercise (walking and playing frisbee). Next day woke feeling energetic, no muscular stiffness, alert. I would repeat this experience."

(with 50 mg) "I was coming on within 40-60 minutes, easy and slow, but the body was +3 before the mind. The mental was strange for the first 2-3 hours — I called it 'High Sierras' — realistic, dispassionate, not kind. Some dark areas are persistent. Watched last half of Circus of Dr. Lao and the whole feeling changed from pornographic to erotic. Delightful. Some fantasy. On coming down, sleep was difficult. The body feels unexpectedly depleted. Rubber legs and handwriting jerky."

EXTENSIONS AND COMMENTARY: A comparison of this material to MDA was often made by subjects who were familiar with both. But it is hard to separate that which is intellectualized from that which is felt. An awareness of the chemical structure immediately shows, of course, the close resemblance. There is the complete MDA molecule, with the addition of a methoxy group. And for the non-chemist, the name itself (MMDA-2) represents the second possible methoxy-MDA. Certainly one property that is shared with MDA is the broad variety of opinions as to the quality of its action. Some like it much, and some like it not at all. The N-methyl homologue was indeed made, for direct evaluation in comparison to N-methyl MDA (which is MDMA).

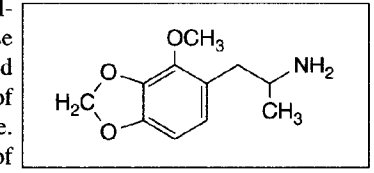
The phenethylamine analog of MMDA-2 has been prepared by the condensation of the above benzaldehyde with nitromethane (in acetic acid with ammonium acetate catalyst, giving an equal weight of the nitrostyrene as deep orange crystals with a mp of 166-167 °C from ethyl acetate) followed by lithium aluminum hydride reduction (in ether). The product, 2-methoxy-4,5-methylenedioxyphenethylamine hydrochloride (2C-2) melted at 218-219 °C. There were no effects observed at up to 2.6 milligrams, but no higher trials were made. The 4-carbon homologue was made similarly (from the aldehyde and nitropropane but

using tert-butylammonium acetate as a reagent in 100% excess and isopropanol as solvent, giving orange crystals melting at 98-99 °C from methanol) followed by reduction (with lithium aluminum hydride in ether) to give 1-(2-methoxy-4,5-methylenedioxyphenyl)-2-aminobutane hydrochloride (4C-2) with a mp of 172-174 °C. This material has never even been tasted.

The Tweetio homologue of MMDA-2 has been tasted, however. This is 2-ethoxy-4,5-methylenedioxyamphetamine, or EMDA-2. The allyl ether of sesamol (3,4-methylenedioxy-allyloxybenzene) was rearranged to the 2-allyl phenol which was, in turn, converted to the ethyl ether. Reaction with tetranitromethane gave the nitrostyrene intermediate which had a mp of 120-121 °C. The final hydrochloride salt of EMDA-2 had a mp of 188-188.5 °C. At 135 milligrams, there have been reported eyes-closed visual phenomena, with intense colors. The overall duration is similar to MMDA-2 (some 10 hours) and there are reported sleep disturbances. At 185 milligrams, the feelings were intensified, there were "marvelous eyes-closed visuals (the colors were incredible), good concentration, but distinct body-tingles and rushes." The time span was about 12 hours from start to finish, but it proved to be impossible to sleep afterwards. This homologue is thus about a third the potency of MMDA-2.

#134 MMDA-3a; 2-METHOXY-3,4-METHYLENEDIOXY-AMPHETAMINE

SYNTHESIS: To a solution of 100 g of 2,3-dihydroxyanisole in 1 L dry acetone there was added 110 g of powdered anhydrous K_2CO_3 followed by 210 g of methylene iodide. This was brought up to a reflux on the steam bath. There was a sudden appearance of a solid phase, and then a gentle reflux was maintained for three days, during which time much of the heavy solid that initially formed had redissolved. The reaction mixture was filtered to remove the insoluble salts, and these were washed with hot acetone. The combined mother liquor and washes were stripped of solvent under vacuum, leaving a solid residue. This was leached with several portions of boiling hexane. These were pooled, and removal of the solvent under vacuum provided 53.6 g of 2,3-methylenedioxyanisole as white crystals with a sharp spicy smell.



A mixture of 120 g N-methylformanilide and 137 g $POCl_3$ was allowed to incubate at ambient temperature for 0.5 h, then there was added 53 g of crude 2,3-methylenedioxyanisole. The dark reaction mixture was heated on the steam bath for 2 h and then poured into a beaker filled with shaved ice. This was stirred until hydrolysis was complete, and the black, almost crystalline gunk that separated was

removed by filtration. The 53.6 g of crude product was analyzed by GC using an ethylene glycol succinate column at 190 °C. Three peaks were apparent and had baseline separation. The major peak at 7.8 min constituted 82% of the product and was 2-methoxy-3,4-methylenedioxybenzaldehyde. A minor peak at 12.0 min represented 16% of the product and was the positional isomer 4-methoxy-2,3-methylenedioxybenzaldehyde. A trace component (2%) lay intermediate (at 9.5 min) and was myristicinaldehyde. The mps of the two major benzaldehydes were sufficiently different that they could serve as means of identification. The major product was obtained directly from the black gunk by repeated extraction with boiling cyclohexane which, upon removal of the solvent, gave 33.1 g of a yellow-colored product. This, upon one additional recrystallization from boiling cyclohexane, gave 24.4 g of 2-methoxy-3,4-methylenedioxybenzaldehyde as pale yellow crystals with a mp of 103-105 °C. The mother liquors were pooled and, after removal of all volatiles under vacuum, yielded an amber-colored solid that upon recrystallization provided a yellowish crystals. These, after yet another crystallization from cyclohexane, gave 4.1 g of 4-methoxy-2,3-methylenedioxybenzaldehyde with a mp of 85-86 °C. This latter isomer was used in the synthesis of MMDA-3b.

To a solution of 3.5 g 2-methoxy-3,4-methylenedioxybenzaldehyde in 14 g acetic acid there was added 1.4 g anhydrous ammonium acetate and 2.3 mL of nitroethane. The mixture was brought to reflux and held there for 35 min. It was then quenched by the addition of 40 mL H_2O, knocking out an orange, gummy solid. This was removed by filtration, and recrystallized from 50 mL boiling MeOH. After cooling for a few h in an ice bath, the bright yellow crystals were removed by filtration, washed with MeOH and air dried to constant weight, yielding 2.15 g 1-(2-methoxy-3,4-methylenedioxyphenyl)-2-nitropropene. The mp was 106-107 °C. Recrystallization from EtOH raised this mp to 109.5-110.5 °C.

A suspension of 2.2 g LAH in 300 mL anhydrous Et_2O under an inert atmosphere was brought to a gentle reflux. The reflux condensate was passed through a modified Soxhlet thimble containing 1.95 g 1-(2-methoxy-3,4-methylenedioxyphenyl)-2-nitropropene effectively adding it, over the course of 0.5 h, to the reaction mixture as a saturated Et_2O solution. The mixture was maintained at reflux for 16 h. After cooling to 0 °C with an ice bath, the excess hydride was destroyed by the addition of 1.5 N H_2SO_4. The phases were separated, and the aqueous phase washed with 2x100 mL Et_2O. To the aqueous phase there was added 50 g potassium sodium tartrate followed by sufficient 25% NaOH to raise the pH >9. This was then extracted with 3x100 mL CH_2Cl_2, and the solvent from the pooled extracts removed under vavuum. The residual white oil was dissolved in 250 mL anhydrous Et_2O, and saturated with anhydrous HCl gas. There was produced a crop of white microcrystals of 2-methoxy-3,4-methylenedioxyamphetamine hydrochloride (MMDA-3a) which was removed by filtration, washed with Et_2O, and air dried to a constant weight of 1.2 g. The mp was 154-155 °C.

DOSAGE: 20 - 80 mg.

DURATION: 10 - 16 h.

QUALITATIVE COMMENTS: (with 20 mg) "I became aware at about an hour, and an hour later I found myself suddenly caught up in the marvelous world of insects. Right alongside a pile of bricks I saw a measuring worm, and with great tenderness and patience I picked him up, observed his fore and aft 'feet' and finally replaced him and watched him acclimate himself. There was also a spider on the bricks, and I was compelled to watch him in action. I was grateful that I was not being observed. Time was moving slowly, and I felt I should intentionally move slowly, so as not to exhaust myself."

(with 40 mg) "This developed between one and two hours into it, and there were considerable body tremors. Talking directed the energy outwards, and I became aware of a visually sparkling world about me. I started dropping way too soon; it would have been interesting to have gone higher. By early evening I was left only with an awareness of some residual physical hypersensitivity, and there was light diarrhea. I am not at all sure just what to compare this drug to. It is gentle."

(with 60 mg) "There were visuals of a soft sort — things moved with eyes open, and with eyes closed the music was great. There seemed to be some lasting stimulation, but it didn't get in the way of sleeping. The next morning, however, I was still on. A good compound."

EXTENSIONS AND COMMENTARY: The term MMDA-3a has the feel of being complicated, but there is a reason for the code. As had been mentioned, MMDA was the initials for methoxy (the M) methylenedioxy (the MD) amphetamine (the A). And with a molecule of amphetamine there are six ways of sticking these two groupings on the aromatic ring. The numbers 1-6 had already been assigned to the six ways of sticking three methoxyl groups onto an amphetamine molecule (with the trimethoxyamphetamines, the TMA's) and I decided to hew to the same convention with the methylenedioxy counterparts. However, there are two #3's (the methoxy and the methylenedioxy can go onto the three oxygen atoms in a row in two different ways, whereas the three methoxys can go on in just one way) and there can be no #6 (since a methylenedioxy must, perforce, have two oxygens that are adjacent, and there are none to be so found in the 2,4,6-orientation of TMA-6). So, with two possible MMDA-3's it becomes reasonable, in fact essential, to name one of them "a" and the other "b". The "a" orientation occurs in nature as the essential oil croweacin, or 1-allyl-2-methoxy-3,4-methylenedioxybenzene. It thus can allow MMDA-3a to be classified as an Essential Amphetamine, since it can arise, in principle, by amination in the liver *in vivo*. But in the laboratory, croweacin is certainly not a practical starting material in this synthesis.

I have been told of a number of clinical trials that have explored MMDA-3a at considerably higher levels, but I have no explicit quotations to give, and the details are quite sketchy. Three trials at 80 milligrams, and one at 100 milligrams, all made comparisons, in both quantity and quality of the experience, to 100

micrograms of LSD. However, two events occurred that may or may not be related to these trials; one subject had a spontaneous peak experience five days after the experiment, and another made a symbolic suicide attempt.

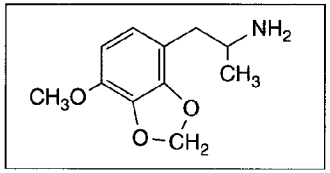
And, as with MMDA-2, both the 2-carbon "phenethylamine" analogue and the 4-carbon "ARIADNE" analogue of MMDA-3a have been made. The phenethylamine analog was prepared by the condensation of 7.6 g of the above benzaldehyde with nitromethane (in acetic acid with ammonium acetate catalyst, giving 5.4 g of the nitrostyrene with a mp of 115.5-116.5 °C from methanol) followed by lithium aluminum hydride reduction (in ether). The product, 2-methoxy-3,4-methylenedioxyphenethylamine hydrochloride (2C-3a) melted at 143-145 °C. A series of subjective evaluations were made, and there are reports of marginal effects in the 40 to 120 milligram range. At 40 milligrams, perhaps the hint of a psychic energizer; at 65 milligrams, there was a pleasant mood elevation; at 80 milligrams, there was a brief paresthetic twinge noted at about the hour and a half point, and at 120 milligrams, about the same at one hour, and then nothing. The fact that there can be such a modest change of effect over a three-fold range of dosage suggests that this compound might have some merit as an anti-depressant. It would be interesting to know if it blocks serotonin reuptake!

The 4-carbon analog was made similarly (from the aldehyde and nitropropane but using tert-butylammonium acetate as a reagent in 100% excess and isopropanol as solvent, giving bright yellow crystals melting at 105.5-106.5 °C from 25 volumes of boiling methanol) followed by reduction (with lithium aluminum hydride in ether) to give 1-(2-methoxy-3,4-methylenedioxyphenyl)-2-aminobutane hydrochloride (4C-3a) with a mp of 183-185 °C with prior sintering at 173 °C. This material has been tasted at up to 3.5 milligrams with nothing noted. There have been no trials at any higher dose.

#135 MMDA-3b; 4-METHOXY-2,3-METHYLENEDIOXY-AMPHETAMINE

SYNTHESIS: A solution of 7.0 g of 98% pure (by GC) 4-methoxy-2,3-methylenedioxybenzaldehyde (see under MMDA-3a for its preparation) in 30 mL glacial acetic acid was treated with 5 mL nitroethane and 3 g anhydrous ammonium acetate, and heated on the steam bath for 3.5 h. $H_2O$was added to the hot solution to the point of turbidity, then it was allowed to cool to room temperature with occasional stirring. A modest crop of yellow crystals formed which were removed by filtration, washed with aqueous acetic acid and air dried to constant weight. There was obtauned 4.6 g of 1-(4-methoxy-2,3-methylenedioxphenyl)-2-nitropropene, with a mp of 95-102 °C. Recrystallization from EtOH tightened this to 97-101.5 °C. The infra-red spectrum is completely different from that of its positional isomer 1-(2-methoxy-3,4-methylenedioxyphenyl)-2-nitropropene.

A suspension of 7.0 g LAH in 1 L anhydrous Et_2O under an inert atmosphere was brought to a gentle reflux. The reflux condensate was passed through a Soxhlet thimble containing 6.15 g 1-(4-methoxy-2,3-methylenedioxyphenyl)-2-nitropropene which was effectively adding the nitropropene as a saturated solution. The mixture was maintained at reflux for 16 h. After cooling to 0 °C with an ice bath, the excess hydride was destroyed by the addition of 800 mL of 1.5 N H_2SO_4. The phases were separated, and the aqueous phase washed with 2x100 mL Et_2O. To this phase there was added 175 g potassium sodium tartrate followed by sufficient 25% NaOH to raise the pH >9. This was then extracted with 3x100 mL CH_2Cl_2, and the solvent from the pooled extracts removed under vacuum. The residual off-white oil weighed 5.4 g and was dissolved in 250 mL anhydrous Et_2O and saturated with anhydrous HCl gas. There was produced a crop of slightly sticky white solids that finally became granular and loose. These were removed by filtration, washed with Et_2O, and air dried to give 5.56 g of 4-methoxy-2,3-methylenedioxyamphetamine hydrochloride (MMDA-3b) with a mp of 196-199 °C. A small sample from propanol had a mp of 199-200 °C, and a sample from nitromethane/MeOH (5:1) had a mp of 201-202 °C.



DOSAGE: greater than 80 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 60 mg) "Definitely active. Qualitatively like MDA; quantitatively perhaps less."

(with 80 mg) "No more effective than 60 mg."

EXTENSIONS AND COMMENTARY: And that's all there is known as to the activity of MMDA-3b in man. Very, very little. Nothing has ever been tried in excess of 80 milligrams that I know of, and the above trials were made over 20 years ago. There can be little argument that the 3b is less effective than the 3a, but no one can say by how much. The literature statement is that it is threefold less, but that was based on the relative responses at just-above-threshold levels. The effects here are hand-wavingly similar to those reported for MMDA-3a at 20 milligrams, but these are difficult to compare accurately as they were reported by different people. There have been absolutely no animal studies reported with MMDA-3b in the scientific literature. And neither the 2-carbon nor the 4-carbon analogues of MMDA-3b has even been prepared.

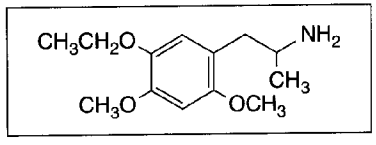
The remaining MMDA-analogue that has been prepared, is the 2,3,6-isomer. The flow diagram started with sesamol (3,4-methylenedioxyphenol) which was methylated with methyl iodide, converted to the aldehyde using butyllithium and N-methylformanilide (putting the new group directly between the two oxygen

atoms, giving 2,3-methylenedioxy-6-methoxybenzaldehyde), reaction with nitroethane to the nitrostyrene, and its reduction with lithium aluminum hydride in ether. The product, 6-methoxy-2,3-methylenedioxyamphetamine hydrochloride (MMDA-5) is practically unexplored in man. I have heard one report that 30 milligrams was modestly active, but not a particularly pleasant experience. Another person told me that he had tried 15 milligrams, but he neglected to mention if there had been any effects. I have not tried it myself. But, I have succumbed to the pressure of the experimental pharmacologists to give a number for the "Y-axis" of their animal behavior studies. So I said to myself, if this is active at 30 milligrams, and mescaline is active at 300 milligrams, why not say that it is 10x the activity of mescaline? So I did. But I have absolutely no confidence in that number.

And if the information on MMDA-5 is sparse, look at the positional isomer, MMDA-4, which I have discussed under its analogue TMA-4. Here nothing is known at all, since the compound itself is unknown. No one has yet found a way of making it.

#136 MME; 2,4-DIMETHOXY-5-ETHOXYAMPHETAMINE

SYNTHESIS: A solution was made of 166 g ethylvanillin (4-ethoxy-3-methoxybenzaldehyde) in 600 mL glacial acetic acid and arranged so that it can be stirred continuously, magnetically, and cooled as needed with an external ice bath. There was then added a total of 218 g of 40% peracetic acid in acetic acid, at a rate that permitted the temperature to stay at 25 °C with the continuous application of the ice bath. The temperature should not drop below 23 °C (the reaction stops) but it absolutely cannot be allowed to exceed 29 °C (the reaction can no longer be controlled). The addition takes about 1.5 h. At the end of the reaction, there was added 3 volumes of H_2O, and all acids were neutralized with solid K_2CO_3. The 3 or so L of black, gooey mess was extracted with 2x400 mL boiling Et_2O which, on pooling and evaporation, provided 60 g of a black oil which was a mixture containing mainly the intermediate formate and the product phenol. This was treated with 300 mL 10% NaOH, and heated on the steam bath for 1 h. After cooling, this was washed with 2x150 mL CH_2Cl_2 (discarded), acidified with HCl, and extracted with 3x200 mL Et_2O. The pooled extracts were washed with 2x200 mL saturated $NaHCO_3$, and then the Et_2O was removed under vacuum. The residual black oil, 41.3 g, was distilled at 1.0 mm/Hg to give a fraction boiling at 140-145 °C as a pale amber oil that set up as crystals. The weight of the isolated 4-ethoxy-3-methoxyphenol was 29.1 g. An analytical sample had a mp of 45.5-46 °C. This product can be used either for the synthesis of MME (see below) or for the synthesis of EME (see separate recipe). A solution of 0.5 g of this phenol, and 0.5 g methyl



isocyanate in 10 mL hexane containing 1 mL CH_2Cl_2 was treated with three drops of triethylamine. In about 1 h, there was the spontaneous formation of white crystals of 4-ethoxy-3-methoxyphenyl N-methyl carbamate, with a mp of 104-105 °C.

A solution of 14 g of the distilled, solid 4-ethoxy-3-methoxyphenol in 20 mL MeOH was treated with a solution of 5.3 g KOH in 100 mL hot MeOH. There was then added 11.9 g methyl iodide, and the mixture was held at reflux temperature for 2 h. The reaction was quenched with 3 volumes H_2O, made strongly basic by the addition of 1 volume of 5% NaOH, and extracted with 2x150 mL Et_2O. Pooling the extracts and removal of the solvent under vacuum gave 9.7 g of 2,4-dimethoxy-1-ethoxybenzene as a clear, off-white oil that showed a single peak by GC. An acceptable alternate synthesis of this ether is the ethylation of 2,4-dimethoxyphenol, which is described in the recipe for TMA-4. The index of refraction was $n_D^{25} = 1.5210$.

A mixture of 17.3 g N-methylformanilide and 19.6 g $POCl_3$ was allowed to stand at room temperature until a strong red color had been generated (about 0.5 h). There was then added 9.2 g 2,4-dimethoxy-1-ethoxybenzene and the mixture was heated on the steam bath for 2 h. The black, viscous product was poured onto 800 mL cracked ice, and mechanically stirred. The deep color gradually faded to a yellow solution, and then yellow crystals began to form. After standing overnight, these were removed by filtration and sucked as dry as possible, yielding 16 g of a wet, crude product. This was dissolved in 100 mL boiling MeOH which, on cooling, deposited fluffy, white crystals of 2,4-dimethoxy-5-ethoxybenzaldehyde. The dry weight was 8.8 g and the mp was 107-108 °C. The mother liquor showed no isomeric aldehydes by GC, but there were small suggestions of isomers seen in the CH_2Cl_2 extracts of the original water filtration. A sample of 0.7 g of the aldehyde obtained as a second crop from the methanolic mother liquors was dissolved, along with 0.5 g malononitrile, in 20 mL hot EtOH. The addition of 3 drops of triethylamine generated the almost immediate formation of brilliant yellow crystals, 1.4 g after filtration and EtOH washing, with a mp of 134-135.5 °C. Recrystallization from toluene gave an analytical sample of 2,4-dimethoxy-5-ethoxybenzalmalononitrile with a mp of 135-136 °C.

A solution of 6.7 g 2,4-dimethoxy-5-ethoxybenzaldehyde in 23 g glacial acetic acid was treated with 3.3 g nitroethane and 2.05 g anhydrous ammonium acetate. The mixture was heated on the steam bath for 2.5 h. The addition of a little water to the cooled solution produced a gel which was a mixture of starting aldehyde and product nitrostyrene. The solvent was decanted from it, and it was triturated under MeOH, to provide a yellow solid with a mp of 76-84 °C. Recrystallization from 30 mL boiling MeOH gave, after filtering and air drying, 4.3 g of a yellow solid with a mp of 90-92 °C. There was still appreciable aldehyde present, and this was finally removed by yet another recrystallization from toluene. The product, 1-(2,4-dimethoxy-5-ethoxyphenyl)-2-nitropropene, was obtained as bright yellow crystals with a mp of 96-97 °C. The analytical sample was dried in vacuum for 24 h to completely dispel the tenacious residual traces of toluene. Anal. ($C_{13}H_{17}NO_5$) C,H.

To a gently refluxing suspension of 1.6 g LAH in 120 mL anhydrous Et_2O

under a He atmosphere, there was added 2.1 g 1-(2,4-dimethoxy-5-ethoxyphenyl)-2-nitropropene by allowing the condensing ether to drip into a shunted Soxhlet thimble containing the nitrostyrene. This effectively added, dropwise, a warm saturated solution of the nitrostyrene to the reaction mixture. Refluxing was continued for 6 h, and after cooling the reaction flask to 0 °C the excess hydride was destroyed by the cautious addition of 1.5 N H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated, and 40 g of potassium sodium tartrate was dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was >9, and this was then extracted with 3x200 mL CH_2Cl_2. Evaporation of the solvent under vacuum produced 1.6 g of an amber oil that was dissolved in 300 mL anhydrous Et_2O and saturated with anhydrous HCl gas. There was an immediate white blush, then there was the generation of an oily solid that upon further administration of HCl became a fine, loose white powder. This was removed by filtration, Et_2O washed, and air dried to give 1.6 g 2,4-dimethoxy-5-ethoxyamphetamine hydrochloride (MME) with a mp of 171-172 °C. Anal. ($C_{13}H_{22}ClNO_3$) C,H,N.

DOSAGE: 40 mg and above.

DURATION : probably 6 - 10 h.

QUALITATIVE COMMENTS: (with 40 mg) "At the one hour point there was a real threshold, and at the second hour, while I was walking down 24th Street, there was an honest 1+. By the third hour it was at, or just under a ++, with the earmarks of a possibly interesting collection of effects, were it just a bit more intense. I had unexpected diarrhea at hour #5, and by #6 I was mending, and by #8 I was largely down. The day was very encouraging, and this must be re-tried at 50 or 60 milligrams."

EXTENSIONS AND COMMENTARY: This is one of the very few compounds with which I actually risked (and took) the lives of experimental animals. I was still impressed by the scientific myth that pharmacological research wasn't really acceptable without animal support data. And I had access to an experimental mouse colony at the University. I injected one mouse with a dose of 300 mg/Kg., i.p. That sounds pretty scientific. But what it really means is that I picked up a mouse by the scruff of the back with my left hand, then turned my hand over so that the mouse was belly-up. I put the ring finger over a hind leg to keep things relatively immobile. Usually at this point there is a little urine evident where there had been none before. And I took a syringe equipped with a very fine needle and containing about 8 milligrams of MME in a fraction of a mL of a water solution and pushed that needle into the mouse at about where the navel would be if one could see the mouse's navel, and then I pulled the needle back just a little so that there should be nothing at the business end but the loose folds of the peritoneum. Then I pushed the syringe

plunger home, effectively squirting the water solution into the area that surrounds the intestines. I dropped the mouse back into his cage, and watched. In this case, the mouse went into a twitching series of convulsions (known as clonic in the trade) and in five minutes he was dead.

Fired with the lust for killing, I grabbed another mouse, and nailed him with 175 mg/Kg. Dead in 6 minutes. Another one at 107 mg/Kg. Dead in 5 minutes. Another at 75 mg/Kg. Well, he looked pretty sick there for a while, and had some shakes, and then he seemed to be pretty much OK. One final orgy of murder. I injected 5 mice at 100 mg/Kg i.p., and watched four of them die within 20 minutes. I took in my hands the sole survivor, and I went outside the laboratory and let him loose on the hillside. He scampered away and I never saw him again.

And what did I learn, at the cost of seven precious lives which I can never replace? Not a damned thing. Maybe there is an LD-50 somewhere around 60 or 80 mg/Kg. This is for mice, not for men. I was intending to take an initial trial dose of 300 micrograms of this completely untested compound, and it would have made no difference to me if the LD-50 had been 600 mg/Kg or 6 mg/Kg. I still took my trial dose, and had absolutely no effects, and I never killed another mouse again. No, that is simply out-and-out dishonest. I had an invasion of field mice last winter coming up through a hole in the floor behind the garbage holder under the kitchen sink, and I blocked the hole, but I also set some mouse traps. And I caught a couple. But never again for the simple and stupid reasons of being able to say that "This compound has an LD-50 in the mouse of 70 mg/Kg." Who cares? Why kill?

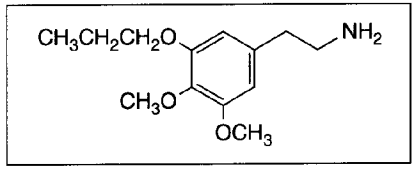
But there are two very valuable things that have come out of this simple study with MME. One is, of course, that it is an active compound and as such warrants additional attention. And the other, and even more important, is that as one of the three possible ethoxy homologues of TMA-2, it is less active than MEM. The third possible ethoxy compound is EMM and, as will be found elsewhere in this book, it is even less active. Thus it is MEM, only, that maintains the potency of TMA-2, and this was the initial observation that really focused my attention on the importance of the 4-position.

#137 MP; METAPROSCALINE; 3,4-DIMETHOXY-5-(n)-PROPOXYPHENETHYLAMINE

SYNTHESIS: There was mixed 96 g of 5-bromovanillin and 90 mL 25% NaOH. The solution was almost complete, when there was a sudden deposition of a heavy precipitate. This was diluted with 200 mL water. There was then added 300 mL methylene chloride, 85 g methyl iodide, and 3 g decyltriethylammonium chloride. The heterogenous mixture was vigorously stirred for 2 days. The organic phase was separated, and the aqueous phase extracted once with 100 mL CH_2Cl_2. The organic phase and extract were pooled, washed with water and the solvent removed under

vacuum The residue weighed 46.3 g and spontaneously crystallized. It was recrystallized from 40 mL of MeOH to yield 34 g of 3-bromo-4,5-dimethoxybenzaldehyde as white crystals with a mp of 60.5-61 °C. An additional 4 g product was obtained from the mother liquor. Acidification of the aqueous phase above produced, after recrystalization from IPA/acetone, 13.2 g of recovered 5-bromovanillin, with a mp of 166-169 °C.

A mixture of 38.7 g 3-bromo-4,5-dimethoxybenzaldehyde and 17.2 g cyclohexylamine was heated with an open flame at about 120 °C until it appeared to be free of H_2O. The residue was put under a vacuum (0.2 mm/Hg) and distilled at 146-160 °C yielding 44.6 g 3-bromo-N-cyclohexyl-4,5-dimethoxybenzylidenimine as a clear oil which did not crystallize. The imine stretch in the infra-red was at 1640 cm^{-1}. Anal. ($C_{15}H_{20}BrNO_2$) C,H.



A solution of 31.6 g 3-bromo-N-cyclohexyl-4,5-dimethoxybenzylidenimine in 300 mL anhydrous Et_2O was placed in an atmosphere of He, stirred magnetically, and cooled with an dry ice/acetone bath. Then 71 mL of a 1.55 M solution of butyllithium in hexane was added over a 2 min period. The reaction mixture turned cloudy and a light precipitate formed which seemed heaviest at the half-way point. Stirring remained easy and was continued for 10 min. There was then added 35 mL of butyl borate at one time. The precipitate dissolved, and the stirred solution allowed to return to room temperature. There was then added 200 mL of an aqueous solution containing 20 g ammonium sulfate. The Et_2O layer was separated, washed with saturated ammonium sulfate solution, and the organic solvents removed under vacuum. The residue was dissolved in 250 mL of 70% MeOH and 14 mL of 30% hydrogen peroxide added in small portions. This reaction was very exothermic, and stirring was continued for 1 h. The reaction mixture was then added to 500 mL H_2O, which knocked out white solids. A small sample of this intermediate, N-cyclohexyl-3,4-dimethoxy-5-hydroxybenzylidineimine was recrystallized from MeOH to a white crystal with a mp of 148-149 °C and which showed the C=N bond as a doublet at 1635 and 1645 cm^{-1} in the infra-red. These wet solids were suspended in 200 mL 5% HCl and heated on the steam bath for 1 h. Stirring was continued until the reaction was again at room temperature and then it was extracted with 2x100 mL CH_2Cl_2. These extracts were pooled and in turn extracted with 2x75 mL dilute NaOH. The aqueous extracts were reacidified with HCl, and reextracted with 2x100 mL CH_2Cl_2. These extracts were pooled, and the solvent removed under vacuum to yield a brown viscous oil as a residue. This was distilled at 105-120 °C at 0.2 mm/Hg to yield 8.8 g of 3,4-dimethoxy-5-hydroxybenzaldehyde as a distillate that set to white crystals. Recrystallization from toluene/hexane gave a sample with the mp 64-65 °C. The literature mps are several, ranging from at about 60 °C to about 70 °C.

A solution of 4.7 g of 3,4-dimethoxy-5-hydroxybenzaldehyde in 75 mL

acetone was treated with 6.0 g powdered KI, 16 mL (21 g) propyl bromide, and 7.0 g finely powdered anhydrous K_2CO_3, and this mixture was held at reflux on a steam bath for 15 h. The reaction mixture was added to 1 L H_2O, made strongly basic, and extracted with 3x100 mL CH_2Cl_2. The extracts were pooled, washed with 5% NaOH, and the solvent removed under vacuum yielding 8.8 g of a yellow oil, undoubtedly containing propyl iodide. This residue was distilled at 133-145 °C at 0.15 mm/Hg to yield 4.5 g of 3,4-dimethoxy-5-(n)-propoxybenzaldehyde as a white oil which did not crystallize. There was an appreciable pot residue. This product was clearly impure, having a minor, slower moving component not the starting phenol, as seen by TLC (on silica gel, with CH_2Cl_2 as a developing solvent). Fusion of a small amount of impure aldehyde with p-anisidine produced a crystalline anil which, on hydrolysis with dilute acid, produced an aldehyde sample free of this impurity. But as this sample also remained as an oil, the above crude product was used in the following preparation.

To a solution of 3.8 g 3,4-dimethoxy-5-(n)-propoxybenzaldehyde in 50 mL nitromethane, there was added 0.5 g anhydrous ammonium acetate. This was held at reflux for 50 min. The excess nitromethane was removed under vacuum and 2 volumes of boiling MeOH were added to the residue. The hot solution was decanted from some residual insolubles, and on cooling spontaneously crystallized. These solids were removed by filtration, washed sparingly with MeOH and air dried yielding 3.3 g yellow crystals of 3,4-dimethoxy-ß-nitro-5-(n)-propoxynitrostyrene as yellow crystals melting at 79-81 °C. Recrystallization from MeOH or cyclohexane neither improved the mp nor freed the product from a residual opalescenceseen in the melt. Anal. ($C_{13}H_{17}NO_5$) C,H.

A solution of 1.5 g LAH in 30 mL anhydrous THF under He was cooled to 0 °C and vigorously stirred. There was added, dropwise, 1.0 mL of 100% H_2SO_4, followed by the dropwise addition of a solution of 2.3 g 3,4-dimethoxy-ß-nitro-5-(n)-propoxynitrostyrene in 10 mL anhydrous THF, over the course of 5 min. The mixture was stirred at 0 °C for a while, and then brought to a reflux on the steam bath. After cooling again, the excess hydride was destroyed with IPA added dropwise, followed by the addition of about 10 mL of 10% NaOH which was sufficient to covert the solids to a white, granular form. These were removed by filtration, the filter cake washed with IPA, the mother liquor and filtrates were combined, and the solvents were removed under vacuum to yield an amber oil. This residue was added to 75 mL dilute H_2SO_4 which produced a gummy insoluble phase which was physically removed with a spatula. The aqueous phase was washed with 3x50 mL CH_2Cl_2. It was then made basic with 25% NaOH, and extracted with 2x75 mL CH_2Cl_2. The solvent was removed from these pooled extracts and the residue distilled at 106-116 °C at 0.2 mm/Hg to provide 1.3 g of the product as a colorless liquid. This was dissolved in 4 mL IPA, neutralized with about 20 drops of concentrated HCl, and diluted with 4 volumes of anhydrous Et_2O added slowly with continuous stirring. A white crystalline salt crystallized out spontaneously and was isolated by filtration, washed first with IPA, then with Et_2O, and air dried giving 1.3

g 3,4-dimethoxy-5-(n)-propoxyphenethylamine hydrochloride (MP) with a mp of 170-171 °C. Anal. ($C_{13}H_{22}ClNO_3$) C,H.

DOSAGE: greater than 240 mg.

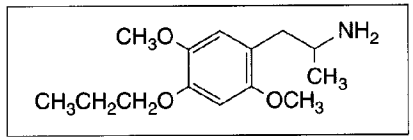
DURATION: unknown.

QUALITATIVE COMMENTS: (with 160 mg) "There might have been some disturbance at the three to four hour point, but it was extremely light if at all."
(with 240 mg) "No effects whatsoever."

EXTENSIONS AND EXTRAPOLATIONS: The loss of activity on lengthening the carbon chain on the meta-oxygen from two to three (from metaescaline to metaproscaline) discouraged any further exploration at this specific point of the molecule. The isopropyl analog (3,4-dimethoxy-5-(i)-propoxyphenethylamine, metaisoproscaline, MIP) was started and carried along as far as the aldehyde, and abandoned with the discovery that metaproscaline was without activity. There were other fish to fry.

#138 MPM; 2,5-DIMETHOXY-4-(n)-PROPOXYAMPHETAMINE

SYNTHESIS: To a solution of 68 g 2,5-dimethoxybenzaldehyde in 250 mL glacial acetic acid that had been warmed to 25 °C and well stirred, there was added, dropwise, 86 g of a 40% peracetic acid solution (in acetic acid). The reaction was exothermic, and the rate of addition was dictated by the need to maintain the internal temperature within a few degrees of 28 °C. External cooling was used as needed. The addition took 1 h, and when the reaction had clearly been completed (there was no further temperature rise) the entire reaction mixture was added to 3 volumes of H_2O. The excess acid was neutralized with solid K_2CO_3. The dark solution was extracted with 3x100 mL Et_2O, the extracts pooled, and stripped of solvent under vacuum to give 59 g of crude 2,4-dimethoxyphenyl formate. This was suspended in 200 mL 10% NaOH, and the mixture heated on the steam bath for 1 h. On cooling, the reaction mixture was washed with 2x200 mL methylene chloride, acidified with HCl, and extracted with 3x200 mL CH_2Cl_2. The extracts were pooled and the solvent removed under vacuum. There remained as residue, 47.4 g 2,5-dimethoxyphenol which was deep amber in color, but clear and fluid. It was homogenous by GC and completely correct by NMR. It was used without further purification.



To a solution of 3.08 g 2,5-dimethoxyphenol in 20 g MeOH, there was added a solution of 1.26 g flaked KOH in 20 g hot MeOH. There was then added 2.46 g n-propyl bromide, and the mixture held at reflux for 2 h on the steam bath. This was quenched in 5 volumes H_2O, made strongly basic with 10% NaOH, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent from the pooled extracts left 2.0 g of 1,4-dimethoxy-2-(n)-propoxybenzene as a clear, amber oil. The IR spectrum was appropriate, no phenol was present, and this residue was used in the following reaction without further purification or characterization.

A mixture of 3.5 g N-methylformanilide and 4.0 g $POCl_3$ was held at room temperature for 0.5 h producing a deep red color. To this there was added 2.0 g 1,4-dimethoxy-2-(n)-propoxybenzene, and the mixture was held on the steam bath for 1.75 h. It was then poured over 400 mL shaved ice, and vigorous stirring was maintained until the dark complex had completely broken up. This aqueous mixture was allowed to stand overnight, and the crude aldehyde solids that had formed were removed by filtration, water washed, and sucked as dry as possible. This 2.0 g damp material was crystallized from 20 mL boiling MeOH giving, after filtering and drying to constant weight, 1.4 g 2,5-dimethoxy-4-(n)-propoxybenzaldehyde as reddish-tan solids, with a mp of 97-98 °C. To the methanolic mother liquors of this crystallization there was added a gram of malononitrile and a few drops of triethylamine. The eventual addition of a little H_2O encouraged the separation of crystals which were removed, and had a mp of 150-152 °C. Recrystallization from toluene gave gold-colored crystals of the benzalmalononitrile with a mp of 153.5-155 °C, but the melt remained slightly cloudy.

To a solution of 1.4 g 2,5-dimethoxy-4-(n)-propoxybenzaldehyde and 0.65 g nitroethane in 4.4 g glacial acetic acid there was added 0.4 g anhydrous ammonium acetate, and the mixture was heated on the steam bath for 5 h. The addition of a modest amount of H_2O and scratching with a glass rod produced crystal seed. The reaction was diluted with about 5 mL H_2O, seeded, and allowed to stand at room temperature overnight. There was generated a crystalline product which was removed by filtration and air dried. There was thus obtained 0.6 g 1-(2,5-dimethoxy-4-(n)-propoxyphenyl)-2-nitropropene as yellow-orange crystals, with a mp of 83-84 °C. The addition of H_2O to the mother liquors provided an additional 0.3 g of an orange solid which proved to be largely unreacted starting aldehyde.

To a stirred, warm suspension of 0.5 g LAH in 20 mL anhydrous Et_2O under a He atmosphere, there was added 0.6 g 1-(2,5-dimethoxy-4-(n)-propoxyphenyl)-2-nitropropene dissolved in a little anhydrous Et_2O. The mixture was heated and stirred for a few h, and the excess hydride decomposed with 30 mL 1.5 N H_2SO_4. The two layers were separated, and 15 g potassium sodium tartrate was dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was >9, and this was then extracted with 3x50 mL CH_2Cl_2. Removal of the solvent under vacuum gave 0.7 g of an amber oil that was dissolved in anhydrous Et_2O and saturated with anhydrous HCl gas. No crystals formed, and so the ether was removed under vacuum, leaving a residue that set up to crystals that were then no longer soluble in ether. They were, however, very soluble in chloroform. These were ground under

dry Et_2O, removed by filtration, and air dried giving 0.35 g 2,5-dimethoxy-4-(n)-propoxyamphetamine hydrochloride (MPM) with a mp of 123 - 125 °C.

DOSAGE: 30 mg or more.

DURATION: probably short.

QUALITATIVE COMMENTS: (with 15 mg) "This is just barely threshold. A marginal intoxication at best. This level is producing less response that the 11 mg. trial of MEM, so the propoxy is off in potency. At four and a half hours I am out of whatever little there was."

(with 30 mg) "By the mid-second hour, I am at a valid plus one. I cannot identify the nature — with eyes closed it would be lost, as it would also be if I were watching a play or movie. It would have been interesting to see where it could have gone. Seventh hour, completely clear."

EXTENSIONS AND COMMENTARY: The 4-propoxy homologue of TMA-2 and MEM is clearly less active, and this has discouraged me from putting too much more effort in this direction. Three additional materials of this pattern were prepared and either shown to be even less active, or simply were not assayed at all. These are the 4-isopropoxy isomer (MIPM), the (n)-butoxy homologue (MBM), and the (n)-amyl homologue (MAM). They scarcely warrant separate recipes as they were all made in a manner similar to this one describing MPM.

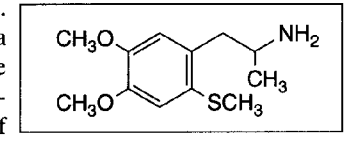
For the preparation of MIPM, the above phenol, 2,5-dimethoxyphenol was isopropylated with isopropyl bromide in methanolic KOH giving 2,5-dimethoxy-1-(i)-propoxybenzene as an oil. This formed the benzaldehyde with the standard Vilsmeier conditions, which melted at 77-78 °C from hexane and which gave a yellow malononitrile derivative melting at 171.5-173 °C. The nitrostyrene, from nitroethane in acetic acid was orange colored and melted at 100-101 °C from either methanol or hexane. This was reduced with lithium aluminum hydride in ether to give 2,5-dimethoxy-4-(i)-propoxyamphetamine hydrochloride (MIPM). The properties of the isolated salt were strange (soluble in acetone but not in water) and the microanalysis was low in the carbon value. The molecular structure had a pleasant appeal to it, with a complete reflection symmetry shown by the atoms of the amphetamine side chain and the isopropoxy side chain. But the nature of the actual product in hand had no appeal at all, and no assay was ever started.

For the preparation of MBM, the starting phenol was alkylated to 2-(n)-butoxy-1,4-dimethoxybenzene in methanolic KOH with n-butyl bromide. The benzaldehyde melted at 79.5-81 °C from methanol, and formed a malononitrile derivative that had a melting point of 134.5-135 C. The nitrostyrene from the aldehyde and nitroethane in acetic acid crystallized from methanol with a mp of 71-72 °C. Lithium aluminum hydride reduction in ether gave the ether-insoluble chloroform-soluble product 4-(n)-butoxy-2,5-dimethoxyamphetamine hydrochloride (MBM) with a melting point of 128-130 °C. This product met all tests for structural integrity, and assays were started. At levels of up to 12.0 milligrams, there were no effects noted.

As to the preparation of MAM, the exact same sequence was used, except for the employment of n-amyl bromide. The benzaldehyde crystallized from methanol with a mp of 79-80 °C, and formed a malononitrile derivative which was bright yellow and melted at 103-104 °C. The nitrostyrene, when pure, melted at 57-58.5 °C but proved very difficult to separate from the aldehyde. The final product, 4-(n)-amyloxy-2,5-dimethoxyamphetamine hydrochloride (MAM) was obtained by lithium aluminum hydride reduction in ether and melted at 125-127 °C. It was assayed at up to 16 milligrams, at which level there was noted a heaviness in the chest and head at the 2-hour point, but no cardiovascular disturbance and no mydriasis. This was called an inactive level, and no higher one has yet been tried.

#139 ORTHO-DOT; 4,5-DIMETHOXY-2-METHYLTHIO-AMPHETAMINE

SYNTHESIS: To 26.4 g veratrol that was being magnetically stirred without any solvent, there was added 50 g chlorosulfonic acid a bit at a time over the course of 20 min. The reaction was exothermic, and evolved considerable HCl. The deeply colored mixture that resulted was poured over 400 mL crushed ice and when all had thawed, it was extracted with 2x150 mL CH_2Cl_2. Removal of the solvent under vacuum gave a residue that set up as a crystalline mass. The weight of the crude 3,4-dimethoxybenzene-sulfonyl chloride was 37.1 g and it had a mp of 63-66 °C. Recrystallization raised this to 72-73 °C. Reaction with ammonium hydroxide gave the sulfonamide as colorless needles from EtOH, with a mp of 132-133 °C.



The finely pulverized 3,4-dimethoxybenzenesulfonyl chloride (33 g) was added to 900 mL of crushed ice in a 2 L round-bottomed flask equipped with a heating mantle and reflux condenser. There was then added 55 mL concentrated H_2SO_4 and, with vigorous mechanical stirring, there was added 50 g of zinc dust in small portions. This mixture was heated until a vigorous reaction ensued and refluxing was continued for 1.5 h. After cooling to room temperature and decantation from unreacted metallic zinc, the aqueous phase was extracted with 3x150 mL Et_2O. The pooled extracts were washed once with saturated brine and the solvent was removed under vacuum. The residue was distilled to give 20.8 g of 3,4-dimethoxythiophenol boiling at 86-88 °C at 0.4 mm/Hg.

A solution of 10 g 3,4-dimethoxythiophenol in 50 mL absolute EtOH was protected from the air by an atmosphere of N_2. There was added a solution of 5 g

85% KOH in 80 mL EtOH. This was followed by the addition of 6 mL methyl iodide, and the mixture was held at reflux for 30 min. This was poured into 200 mL H_2O and extracted with 3x50 mL Et_2O. The pooled extracts were washed once with aqueous sodium hydrosulfite, then the organic solvent was removed under vacuum. The residue was distilled to give 10.3 g of 3,4-dimethoxythioanisole with a bp of 94-95 °C at 0.4 mm/Hg. The product was a colorless oil that crystallized on standing. Its mp was 31-32 °C.

To a mixture of 15 g $POCl_3$ and 14 g N-methylformanilide that had been warmed briefly on the steam bath there was added 8.2 g of 3,4-dimethoxythioanisole, the exothermic reaction was heated on the steam bath for an additional 20 min, and then poured into 200 mL H_2O. Stirring was continued until the insolubles had become completely loose and granular. These were removed by filtration, washed with H_2O, sucked as dry as possible, and then recrystallized from 100 mL boiling EtOH. The product, 4,5-dimethoxy-2-(methylthio)benzaldehyde, was an off-white solid, weighing 8.05 g and having a mp of 112-113 °C. Anal. ($C_{10}H_{12}O_3S$) C,H.

A solution of 2.0 g 4,5-dimethoxy-2-(methylthio)benzaldehyde in 8 mL nitroethane was treated with 0.45 g anhydrous ammonium acetate and heated on the steam bath for 4.5 h. Removal of the excess solvent under vacuum gave a red residue which was dissolved in 5 mL boiling MeOH. There was the spontaneous formation of a crystalline product which was recrystallized from 25 mL boiling MeOH to give, after cooling, filtering and air drying, 1.85 g of 1-(4,5-dimethoxy-2-methylthio-phenyl)-2-nitropropene as bright orange crystals with a mp of 104-105 °C. Anal. ($C_{12}H_{15}NO_4S$) C,H,N.

A suspension of 1.3 g LAH in 50 mL anhydrous THF was placed under an inert atmosphere and stirred magnetically. When this had been brought to reflux conditions, there was added, dropwise, 1.65 g of 1-(4,5-dimethoxy-2-methylthio-phenyl)-2-nitropropene in 20 mL THF. The reaction mixture was maintained at reflux for 18 h. After being brought back to room temperature, the excess hydride was destroyed by the addition of 1.3 mL H_2O in 10 mL THF. There was then added 1.3 mL of 3N NaOH followed by an additional 3.9 mL H_2O. The loose, inorganic salts were removed by filtration, and the filter cake washed with additional 20 mL THF. The combined filtrate and washes were stripped of solvent under vacuum yielding a light yellow oil as a residue. This was dissolved in 20 mL IPA, neutralized with 0.9 mL concentrated HCl, and diluted with 200 mL anhydrous Et_2O. There was thus formed 1.20 g of 4,5-dimethoxy-2-methylthioamphetamine hydrochloride (ORTHO-DOT) as a pale yellow crystalline product. This melted at 218-219.5 °C, and recrystallization from EtOH yielded a white product and increased the mp to 222-223 °C with decomposition Anal. ($C_{12}H_{20}ClNO_2S$) C,H,N.

DOSAGE: greater than 25 mg.

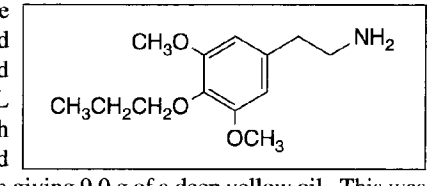
DURATION: unknown.

QUALITATIVE COMMENTS: (with 25 mg) "Vague awareness, with the feeling of an impending something. Light food sat uncomfortably. By the late afternoon there was absolutely nothing. Threshold at best."

EXTENSIONS AND COMMENTARY: This material, ORTHO-DOT, can be looked at as the sulfur homologue of TMA-2 with the sulfur atom located in place of the oxygen at the 2-position of the molecule. At what level this compound might show activity is completely unknown, but wherever that might be, it is at a dosage greater than that for the PARA-DOT isomer, ALEPH-1 (or ALEPH), which was fully active at 10 milligrams (ALEPH can be looked at as TMA-2 with the sulfur atom located in place of the oxygen at the 4-position of the molecule). A lot of variations are easily makable based on this structure, but why bother? ALEPH is the much more appealing candidate for structural manipulation.

#140 P; PROSCALINE; 3,5-DIMETHOXY-4-(n)-PROPOXY-PHENETHYLAMINE

SYNTHESIS: A solution of 5.8 g of homosyringonitrile (see under E for its synthesis), 100 mg decyltriethylammonium iodide, and 10 g n-propyl bromide in 50 mL anhydrous acetone was treated with 6.9 g finely powdered anhydrous K_2CO_3 and held at reflux for 10 h. An additional 5 g of n-propyl bromide was added to the mixture, and the refluxing continued for another 48 h. The mixture was filtered, the solids washed with acetone, and the combined filtrate and washes stripped of solvent under vacuum. The residue was suspended in acidified H_2O, and extracted 3x175 mL CH_2Cl_2. The pooled extracts were washed with 2x50 mL 5% NaOH, once with dilute HCl (which lightened the color of the extract) and then stripped of solvent under vacuum giving 9.0 g of a deep yellow oil. This was distilled at 132-142 °C at 0.3 mm/Hg to yield 4.8 g of 3,5-dimethoxy-4-(n)-propoxyphenylacetonitrile as a clear yellow oil. Anal. ($C_{13}H_{17}NO_3$) C H N.



A solution of 4.7 g 3,5-dimethoxy-4-(n)-propoxyphenylacetonitrile in 20 mL THF was treated with 2.4 g powdered sodium borohydride. To this well-stirred suspension there was added, dropwise, 1.5 mL trifluoroacetic acid. There was a vigorous gas evolution from the exothermic reaction. Stirring was continued for 1 h, then all was poured into 300 mL H_2O. This was acidified cautiously with dilute H_2SO_4, and washed with 2x75 mL CH_2Cl_2. The aqueous phase was made basic with dilute NaOH, extracted with 2x75 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. The residue was distilled at 115-125 °C at 0.3 mm/Hg to give 1.5 mL of a colorless oil which upon dissolving in 5 mL IPA, neutralizing with

27 drops concentrated HCl, and dilution with 25 mL anhydrous Et_2O yielded 1.5 g 3,5-dimethoxy-4-(n)-propoxyphenethylamine hydrochloride (P) as spectacular white crystals. The catalytic hydrogenation process for reducing the nitrile (see under E) also succeeded with this material. The mp was 170-172 °C. Anal. ($C_{13}H_{22}ClNO_3$) C,H,N.

DOSAGE: 30 - 60 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 30 mg) "Proscaline dulled my sense of pain and made the other senses really sharp. Everything felt really soft, and clean and clear. I could feel every hair my hand was touching. I felt so relaxed and at ease. I know that under the appropriate circumstances, this material would lead to uninhibited eroticism."

(with 35 mg) "The whole experiment was very quiet. There was no nystagmus, no anorexia, and insignificant visuals with the eyes closed. I was restless with a bit of tremor for the first couple of hours, and then became drowsy. Would I do this again? Probably not. It doesn't seem to offer anything except speculation about the nature of the high. The high was pleasant, but quite uneventful."

(with 40 mg) "For me there was a deep feeling of peace and contentment. The euphoria grows in intensity for several hours and remains for the rest of the day making this one of the most enjoyable experiences I have ever had. It was marvelous talking and joking with the others. However, I was a little disappointed that there was no enhanced clarity and no deep realizations. There was not a problem to be found. There were no motivations to discuss anything serious. If I had any objection, it would be with the name, not the pharmacology."

(with 60 mg) "The development of the intoxication was complete in a couple of hours. I feel that there is more physical effect than mental, in that there is considerable irritability. This should probably be the maximum dose. Despite feeling quite drunk, my thinking seems straight. The effects were already waning by the fifth hour, but sleep was not possible until after the twelth hour. There was no hangover the next day."

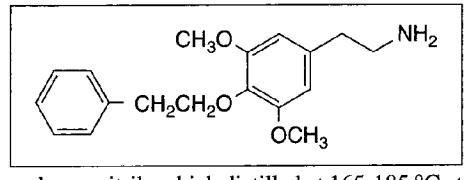
EXTENSIONS AND COMMENTARY: There is a very early report describing the human use of proscaline tucked away in the Czechoslovakian literature that describes experiments at up to 80 milligrams. At these dosages, there were reported some difficulty with dreams, and the residual effects were still apparent even after 12 hours.

The amphetamine homologue of proscaline, 3,5-dimethoxy-4-(n)-propoxyamphetamine is an unexplored compound. Its synthesis could not be achieved in parallel to the description given for P. Rather, the propylation of syringaldehyde to

give 3,5-dimethoxy-4-(n)-propoxybenzaldehyde, followed by coupling with nitroethane and the reduction of the formed nitrostyrene with lithium aluminum hydride would be the logical process. Following the reasoning given under E, the initials for this base would be 3C-P, and I would guess it would be active, and a psychedelic, in the 20 to 40 milligram range.

#141 PE; PHENESCALINE; 3,5-DIMETHOXY-4-PHENETHYLOXYPHENETHYLAMINE

SYNTHESIS: To a solution of 5.8 g homosyringonitrile (see under E for its preparation) in 50 mL of acetone containing 100 mg decyltriethylammonium iodide, there was added 14.8 g ß-phenethylbromide and 6.9 g of finely powdered anhydrous K_2CO_3. The greenish mixture was refluxed for 3 days, with two additional 4 g batches of anhydrous K_2CO_3 being added at 24 h intervals. After addition to aqueous base, the product was extracted with CH_2Cl_2, the pooled extracts were washed with dilute base (the organic phase remained a deep purple color) and then finally with dilute HCl (the organic phase became a pale yellow). The solvent was removed giving 15.6 g crude 3,5-dimethoxy-4-phenethyloxyphenylacetonitrile which distilled at 165-185 °C at 0.3 mm/Hg to yield 3,5-dimethoxy-4-phenethyloxyphenylacetonitrile as a reddish viscous oil weighing 8.1 g. Anal. ($C_{18}H_{19}NO_3$) C,H.



A solution of 7.9 g of distilled 3,5-dimethoxy-4-phenethyloxyphenylacetonitrile in 15 mL dry THF was added to a 0 °C solution of AH prepared from a vigorously stirred solution of 4.6 g LAH in 160 ml THF which had been treated, at 0 °C with 3.6 mL 100% H_2SO_4 under an atmosphere of He. The gelatinaceous reaction mixture was brought to a brief reflux on the steam bath, then cooled again. It was treated with 5 mL IPA which destroyed the unreacted hydride, followed by sufficient 15% NaOH to give loose, white filterable solids. These were removed by filtration and washed with THF. The filtrate and the washes were combined and, after removal of the solvent under vacuum, there remained 7.8 g of the product as a crude base which crystallized spontaneously. Distillation of this product at 170-180 °C at 0.35 mm/Hg gave 5.1 g white solids, with a mp of 85-86 °C from hexane. This base was dissolved in 20 mL warm IPA and treated with 1.6 mL concentrated HCl. To the resulting clear solution, there was added 75 mL anhydrous Et_2O which gave, after a few moments of stirring, a spontaneous crystallization of 3,5-dimethoxy-4-phenethyloxyphenethylamine hydrochloride (PE) as beautiful white crystals. The weight was 5.4 g after air drying, and the mp was 151-152 °C. Anal. ($C_{18}H_{24}ClNO_3$) C,H.

DOSAGE: greater than 150 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 150 mg) "At most, there was a bare threshold over the course of the afternoon. A vague unreal feeling, as if I had not had quite enough sleep last night. By late afternoon, even this had disappeared and I was left with an uncertainty that anything at all had occurred."

EXTENSIONS AND COMMENTARY: There is not much there, so there is not much to make commentary on. This response is called a "threshhold" effect, and cannot be used to predict with any confidence just what level (if any) would produce psychological effects.

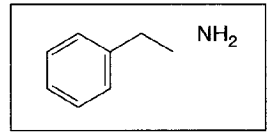
A similar chain on the 4-position, but with one less carbon atom, deserves special comment. Rather than a phenethyloxy group, this would be benzyloxy group (which in this day and age of Chemical Abstracts purity should probably be called a phenylmethoxy group). If one were to follow the naming philosophy of "proscaline equals P and buscaline equals B" convention, one would call it 4-benzescaline, and give it the code name BZ. The nomenclature purist would probably call the compound PM (for phenylmescaline or, more likely phenylmethoxydimethoxyphenethylamine), since the term BZ is awkward and misleading. It is a code name that has been given to a potent CNS agent known as quinuclidin-3-yl benzilate, which is a chemical and biological warfare (CBW) incapacitating agent currently being stored by the military to the extent of 20,000 pounds. And, BZ has also recently become the jargon name given to benzodiazepine receptors. They have been called the BZ-receptors.

However, let's be awkward and misleading, and call this benzyloxy-base BZ. For one thing, the three-carbon analogue 3C-BZ has already been described in its own recipe using this code. And the 4-fluoroanalogue of it, 3C-FBZ, is also mentioned there. And BZ has already been described synthetically, having been made in exactly the procedure given for escaline, except that the reduction of the nitrile was not done by catalytic hydrogenation but rather by sodium borohydride in the presence of cobalt chloride. It has been shown to be a effective serotonin agonist, and may warrant human experimentation. The serotonin activity suggests that it might be active at the same levels found for proscaline.

All of this says very little about PE. But then, there is very little to say about PE except that it may be active at very high levels, and I am not sure just how to get there safely.

#142 PEA; PHENETHYLAMINE

SYNTHESIS: This compound has been made industrially by a number of routes, with the reduction of benzyl cyanide and the decarboxylation of phenylanaline being the more important. It is offered in the catalogs of all the major chemical supply houses for a few pennies per gram. It is a very strong base with a fishy smell, and rapidly forms a solid carbonate salt upon exposure to the air. It is a natural biochemical in both plants and animals.



DOSAGE: greater than 1600 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 200, 400, 800 and 1600 mg) "No effects."
(with 500 mg) "No effects."
(with 800 and 1600 mg) "No effects."
(with 25 and 50 mg i.v.) "No effects."

EXTENSIONS AND COMMENTARY: Here is the chemical that is central to this entire book. This is the structural point of departure for every compound that is discussed here. It is the "P" in PIHKAL. It is without activity in man! Certainly not for the lack of trying, as some of the dosage trials that are tucked away in the literature (as abstracted in the "Qualitative Comments" given above) are pretty heavy duty. Actually, I truly doubt that all of the experimenters used exactly that phrase, "No effects," but it is patently obvious that no effects were found. It happened to be the phrase I had used in my own notes.

This, the simplest of all phenethylamines, has always been the darling of the psychopharmacologists in that it is structurally clean, it is naturally present in various human fluids and tissues, and because of its close chemical relationship to amphetamine and to the neurotransmitters. These facts continuously encourage theories that involve PEA in mental illness. Its levels in urine may be decreased in people diagnosed as being depressed. Its levels may be increased in people diagnosed as being paranoid schizophrenics. Maybe it is also increased in people under extreme stress. The human trials were initially an attempt to provoke some psychological change, and indeed some clinicians have reported intense headaches generated in depressives following PEA administration. But then, others have seen nothing. The studies evolved into searches for metabolic difference that might be of some diagnostic value. And even here, the jury is still out.

Phenethylamine is found throughout nature, in both plants and animals. It is the end product of phenylalanine in the putrefaction of tissue. One of its most popularized occurrences has been as a major component of chocolate, and it has hit

psychedelic. As possible mis-synthesized products, they may appear quite unintentionally and must be evaluated as totally new materials. The gamma-amine analogue of MDA, a methylenedioxy substituted three carbon side-chain with the amine-nitrogen on the gamma carbon, has indeed been made and evaluated, and is discussed under MDA. The extension of the chain of mescaline to three atoms, by the inclusion of an oxygen atom, has produced two compounds that have also been assayed. They are mentioned in the recipe for mescaline.

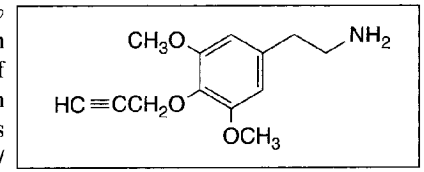
The chain that reaches out to the amine group can be tied back in again to the ring, with a second chain. There are 2-aminobenzoindanes which are phenethylamines with a one-carbon link tying the alpha-position of the chain back to the aromatic ring. And there are 2-aminotetralines which are phenethylamines which have a two-carbon link tying the alpha-position of the chain back to the aromatic ring. Both unsubstituted ring systems are known and both are fair stimulants. Both systems have been modified with the DOM substituent patterns (called DOM-AI and DOM-AT respectively), but neither of these has been tried in man. And the analogues with the MDA substitution pattern are discussed elsewhere in this book.

And there is one more obvious remaining methylation pattern. What about phenethylamine or amphetamine compounds with two methyl groups on the nitrogen? The parent amphetamine example, N,N-dimethylamphetamine, has received much notoriety lately in that it has become a scheduled drug in the United States. Ephedrine is a major precursor in the illicit synthesis of methamphetamine, and with the increased law-enforcement attention being paid to this process, there has been increasing promotion of the unrestricted homologue, N-methylephedrine, to the methamphetamine chemist. This starting material gives rise to N,N-dimethylamphetamine which is a material of dubious stimulant properties. A number of N,N-dimethylamphetamine derivatives, with "psychedelic" ring substituents, have been explored as iodinated brain-flow indicators, and they are explicitly named within the appropriate recipes. But none of them have shown any psychedelic action.

This is as good a place as any to discuss two or three simple compounds, phenethylamines, with only one substituent on the benzene ring. The 2-carbon analog of 4-MA, is 4-methoxyphenethylamine, or MPEA. This is a kissing cousin to DMPEA, of such fame in the search for a urine factor that could be related to schizophrenia. And the end results of the search for this compound in the urine of mentally ill patients are as controversial as they were for DMPEA. There has been no confirmed relationship to the diagnosis. And efforts to see if it is centrally active were failures — at dosages of up to 400 milligrams in man, there was no activity. The 4-chloro-analogue is 4-chlorophenethylamine (4-Cl-PEA) and it has actually been pushed up to even higher levels (to 500 milligrams dosage, orally) and it is also without activity. A passing bit of charming trivia. A positional isomer of MPEA is 3-methoxyphenethylamine (3-MPEA) and, although there are no reported human trials with this, it has been graced with an Edgewood Arsenal code number, vis., EA-1302.

#143 PROPYNYL; 3,5-DIMETHOXY-4-(2-PROPYNYLOXY)-PHENETHYLAMINE

SYNTHESIS: To a solution of 5.8 g homosyringonitrile (see under E for its preparation) in 50 mL acetone containing 100 mg decyltriethylammonium iodide, there was added 12 g of an 80% solution of propargyl bromide in toluene and 6.9 g of finely powdered anhydrous K_2CO_3. This mixture was held at reflux on the steam bath for 12 h, after which the solvent was removed under vacuum. The residues were added to 0.5 L H_2O, acidified, and extracted with 3x75 mL CH_2Cl_2. The extracts were pooled, washed with 5% NaOH, and then with dilute HCl which discharged the deep color. Removal of the organic solvent under vacuum yielded 6.6 g of crude product. This was distilled at 138-148 °C at 0.25 mm/Hg, yielding 4.3 g 3,5-dimethoxy-4-(2-propynyloxy)phenylacetonitrile which spontaneously crystallized. A small sample from MeOH had a mp of 94-95 °C. Anal. ($C_{13}H_{13}NO_3$) C,H.



A suspension of 2.8 g LAH in 70 mL anhydrous THF was cooled to 0 °C with good stirring under He, and treated with 2.0 g 100% H_2SO_4. To this, a solution of 4.2 g 3,5-dimethoxy-4-(2-propynyloxy)phenylacetonitrile in 30 mL anhydrous THF was added very slowly. After the addition had been completed, the reaction mixture was held at reflux on the steam bath for 0.5 h, cooled to room temperature, treated with IPA to decompose the excess hydride, and finally with 15% NaOH to convert the solids to a white filterable mass. The solids were separated by filtration, the filter cake was washed with THF, and the filtrate and washes were pooled. After removal of the solvent, the residue was added to 100 mL dilute H_2SO_4, and washed with 3x75 mL CH_2Cl_2. The aqueous phase was made basic with dilute NaOH, and the product extracted with 2x75 mL CH_2Cl_2. After removal of the solvent under vacuum, the residue was distilled at 125-155 °C at 0.3 mm/Hg to provide 2.4 g of a light amber viscous liquid. This was dissolved in 10 mL IPA, acidified with concentrated HCl until a droplet produced a red color on dampened, external universal pH paper, and then diluted with 40 mL anhydrous Et_2O with good stirring. After a short delay, 3,5-dimethoxy-4-(2-propynyloxy)phenethylamine hydrochloride (PROPYNYL) spontaneously crystallized. The product was removed by filtration, washed first with an IPA/Et_2O mixture, and finally with Et_2O. The yield was 3.0 g of white needles.

DOSAGE: 80 mg or more.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 55 mg) "I have cold feet — literally — I

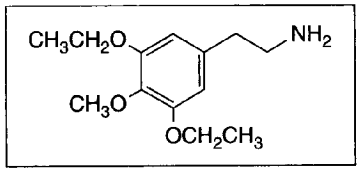
don't mean that in the spiritual or adventurous sense. But also I am somewhat physically fuzzy. I feel that if I were in public my behavior would be such that someone would notice me. Everything was OK without any question at the ninth hour. I could walk abroad again."

(with 80 mg) "There is a body load. The flow of people around me all day has demanded my attention, and when I had purposefully retreated to be by myself, there was no particular reward as to visuals or anything with eyes closed, either. Sleep was easy at midnight (the twelth hour of the experiment) but the morning was sluggish, and on recalling the day, I am not sure of the events that had taken place. Higher might be all right, but watch the status of the body. There certainly wasn't that much mental stuff."

EXTENSIONS AND COMMENTARY: No experiments have been performed that describe the action of this drug at full level. This compound does not seem to have the magic that would encourage exploration at higher levels.

#144 SB; SYMBESCALINE; 3,5-DIETHOXY-4-METHOXY-PHENETHYLAMINE

SYNTHESIS: A solution of 15 g 1,3-diethoxybenzene and 15 mL of N,N,N',N'-tetramethylethylenediamine in 200 mL anhydrous Et_2O was placed in a He atmosphere, magnetically stirred, and cooled to 0 °C with an ice bath. Over the course of 10 min there was added 63 mL of a 1.6 M solution of butyllithium in hexane, which produced a fine white precipitate. After an additional 15 min stirring, 20 mL of tributyl borate was added which dissolved the precipitate. The stirring was continued for an additional 15 min. The reaction was quenched by the addition of 50 mL of a concentrated aqueous solution of ammonium sulfate. The resulting "cottage cheese" mass was transferred to a beaker, treated with an additional 300 mL of the ammonium sulfate solution, and allowed to stir until the solids had dispersed to a fine texture. The organic phase was separated and the aqueous phase extracted with 2x100 mL Et_2O. The organic phases were combined, evaporated under vacuum, and the off-white residue dissolved in 100 mL MeOH. This cloudy solution was cooled (ice bath) and, with stirring, 20 mL of 35% hydrogen peroxide was added portionwise, . The reaction was allowed to continue stirring for 15 min, and then with the addition of 600 mL H_2O, crystalline solids were formed. These were removed, washed with H_2O, and upon drying yielded 15.4 g of 2,6-diethoxyphenol with a mp of 79.5-81.5 °C. Efforts to diethylate pyrogallol produced mixtures of 2,6-diethoxyphenol and the isomer, 2,3-diethoxyphenol, and these proved difficult



to separate. The pure 2,3-isomer was synthesized from ortho-diethoxybenzene by the process used above, and the product was an oil. Both phenols yielded crystalline 3,5-dinitrobenzoates. This derivative of 2,6-diethoxyphenol, upon recrystallization from CH_3CN had a mp of 161-162 °C. The derivative from 2,3-diethoxyphenol, also upon recrystallization from CH_3CN, melted at 167-168 °C. The mixed mp was appropriately depressed (mp 137-140 °C.).

A solution of 7.6 g 2,6-diethoxyphenol in 40 mL MeOH was treated with 4.9 g of a 40% aqueous solution of dimethylamine followed by 3.6 g of a 40% aqueous solution of formaldehyde. The mixture was heated 1 h on the steam bath, and all volatiles were removed under vacuum. The residual dark oil was dissolved in 36 mL IPA and 10.3 g of methyl iodide was added. There was spontaneous heating, and the deposition of fine white solids. After standing for 10 min, these were removed by filtration, and the filter cake washed with more IPA. The crude product was freed from solvent (air dried weight, 1.7 g) and dissolved in 7 mL hot H_2O. To this hot solution there was added 1.7 g sodium cyanide which slowly discharged the color and again deposited flocculant white solids. After cooling, these were removed by filtration, washed with H_2O, and after thorough drying the isolated 3,5-diethoxy-4-hydroxyphenylacetonitrile weighed 0.5 g and had a mp of 107.5-108.5 °C. Anal. ($C_{12}H_{15}NO_3$) C,H.

To a solution of 2.1 g 3,5-diethoxy-4-hydroxyphenylacetonitrile in 20 mL anhydrous acetone, there was added 30 mg triethyldecylammonium iodide, 4.6 g methyl iodide, and finally 2.3 g powdered anhydrous K_2CO_3. This mixture was held at reflux for 5 h. The reaction mixture was quenched with 200 mL acidified H_2O and extracted with 3x75 mL CH_2Cl_2. The extracts were pooled, washed with 2x75 mL 5% NaOH, and finally once with dilute HCl. The solvent was removed under vacuum, and the residue distilled at 110-115 °C at 0.3 mm/Hg to provide 3,5-diethoxy-4-methoxyphenylacetonitrile as a solid. This weighed 1.3 g and had a mp of 58-59 °C. Anal. ($C_{13}H_{17}NO_3$) C,H.

To 30 mL of a 1 M solution LAH in THF that had been cooled to 0 °C with vigorous stirring, under a He atmosphere, there was added dropwise 0.78 mL of 100% H_2SO_4. When the addition was complete, there was added dropwise a solution of 1.3 g of 3,5-diethoxy-4-methoxyphenylacetonitrile in 10 mL anhydrous THF. The reaction mixture was brought to room temperature and stirred an additional 10 min, then refluxed on a steam bath for 1.5 h. After cooling to room temperature the excess hydride was destroyed by the addition of about 2 mL IPA, followed by sufficient 15% NaOH to make the reaction basic to external pH paper and to render the aluminum oxides white and filterable. These were removed by filtration, the filter cake was washed with IPA, then the filtrate and washes were combined. The solvents were removed under vacuum and the residue dissolved in dilute H_2SO_4. This was washed with 2x75 mL CH_2Cl_2, the aqueous phase made basic with 5% NaOH, and extracted with 3x75 mL CH_2Cl_2. The extracts were pooled, the solvent removed under vacuum, and the residue distilled at 120-140 °C at 0.3 mm/Hg to yield 0.9 g of a white oil. This was dissolved in 4 mL of IPA and neutralized with concentrated

HCl to an end-point determined by damp external pH paper. There was the immediate formation of solids which were removed by filtration and washed first with IPA and then with Et_2O. This provided 1.0 g of 3,5-diethoxy-4-methoxyphenethylamine hydrochloride (SB) as white crystals, with a mp of 186-187 °C. Anal. ($C_{13}H_{22}ClNO_3$) C,H.

DOSAGE: above 240 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 120 mg) "There were no effects. Sleep that evening was strange, however, and I was fully awake at 4:00 AM, alert, and mentally restless. And there was a strange outburst of anger in the mid-morning. Might these be related to the material the previous day?"

(with 240 mg) "There was a slight chill that reminded me that I had taken symbescaline a half hour earlier. There was what might be called a vague threshold for about three hours, then nothing more. This material had a God-awful taste that lingers in the mouth far too long. If ever again, it will be in a gelatin capsule."

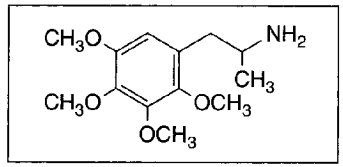
EXTENSIONS AND COMMENTARY: It must be concluded that SB is "probably" not active. There was no convincing evidence for much effect at levels that would clearly be active for mescaline. This is the kind of result that puts some potentially ambiguous numbers in the literature. One cannot say that it is inactive, for there might well be something at 400 or 800 or 1200 milligrams. But since it has been tried only up to 240 milligrams, I have used the phrase that the activity is greater than 240 milligrams. This will be interpreted by some people as saying that it *is* active, but only at dosages higher than 240 milligrams. What is meant, is that there was no activity observed at the highest level tried, and so if it *is* active, the active dose will be greater than 240 milligrams, and so the potency will be less than that of mescaline. However you phrase it, someone will misinterpret it.

#145 TA; 2,3,4,5-TETRAMETHOXYAMPHETAMINE

SYNTHESIS: To a solution of 50 g 2,3,4-trimethoxybenzaldehyde in 157 mL glacial acetic acid which was well stirred and preheated to 25 °C there was added 55.6 g 40% peracetic acid in acetic acid. The rate of addition was adjusted to allow the evolved heat of the exothermic reaction to be removed by an external ice bath at a rate that kept the internal temperature within a degree of 25 °C. When the addition was complete and there was no more heat being evolved, the reaction mixture was diluted with 3 volumes of H_2O, and neutralized with solid K_2CO_3. All was extracted with 3x250 mL Et_2O, and the removal of the solvent from the pooled

extracts under vacuum gave 42 g of residue that appeared to be mainly phenol, with a little formate and aldehyde. This was dissolved in 200 mL of 10% NaOH, allowed to stand for 2 h at ambient temperature, washed with 2x75 mL CH_2Cl_2, acidified with HCl, and extracted with 3x100 mL Et_2O. The pooled extracts were washed with saturated $NaHCO_3$, and the solvent removed to give 34.7 g of 2,3,4-trimethoxyphenol as an amber oil which was used without further purification. The infra-red spectrum showed no carbonyl group, of either the formate or the starting aldehyde.

A solution of 11.4 g flaked KOH in 100 g EtOH was treated with 33.3 g 2,3,4-trimethoxyphenol and 21.9 g allyl bromide. The mixture was held at reflux for 1.5 h, then poured into 5 volumes of H_2O, made basic with the addition of 25% NaOH, and extracted with 3x200 mL CH_2Cl_2. Removal of the solvent from the pooled extracts gave about 40 g of a crude 2,3,4-trimethoxy-1-allyloxybenzene that clearly had unreacted allyl bromide as a contaminant.



A 39 g sample of crude 2,3,4-trimethoxy-1-allyloxybenzene in a round-bottomed flask with an immersion thermometer was heated with a soft flame. At 225 °C there was a light effervescence and at 240 °C an exothermic reaction set in that raised the temperature immediately to 265 °C. It was held there for 5 min, and then the reaction was allowed to cool to room temperature. GC and IR analysis showed the starting ether to be gone, and that the product was largely 2,3,4-trimethoxy-6-allylphenol. It weighed 34.4 g.

To a solution of 9.4 g KOH in 100 mL MeOH, there was added 33.3 g of 2,3,4-trimethoxy-6-allylphenol and 21.2 g methyl iodide and the mixture was held on the steam bath for 2 h. This was poured into aqueous base, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent from the pooled extracts gave 30 g of an amber oil residue that was distilled at 100-125 °C at 0.5 mm/Hg to provide 23.3 g of nearly colorless 2,3,4,5-tetramethoxyallylbenzene.

The total distillation fraction, 23.3 g 2,3,4,5-tetramethoxyallylbenzene, was dissolved in a solution of 25 g flaked KOH in 25 mL EtOH and heated at 100 °C for 24 h. The reaction mixture was poured into 500 mL H_2O, and extracted with 2x100 mL CH_2Cl_2. The aqueous phase was saved. The pooled organic extracts were stripped of solvent under vacuum to give 13.8 g of a fluid oil that was surprising pure 2,3,4,5-tetramethoxypropenylbenzene by both GC and NMR analysis. The basic aqueous phase was acidified, extracted with 2x100 mL CH_2Cl_2, and the solvent stripped to give 7.5 g of an oil that was phenolic, totally propenyl (as opposed to allyl), and by infra-red the phenolic hydroxyl group was adjacent to the olefin chain. This crude 2-hydroxy-3,4,5-trimethoxypropenylbenzene was methylated with methyl iodide in alcoholic KOH to give an additional 5.6 g of the target 2,3,4,5-tetramethoxypropenylbenzene. This was identical to the original isolate above. The distilled material had an index of refraction, $n_D^{24} = 1.5409$.

A well stirred solution of 17.9 g 2,3,4,5-tetramethoxypropenylbenzene in 80 mL distilled acetone was treated with 6.9 g pyridine, and cooled to 0 °C with an

external ice bath. There was then added 14 g tetranitromethane over the course of a 0.5 min, and the reaction was quenched by the addition of a solution of 4.6 g KOH in 80 mL H_2O. As the reaction mixture stood, there was a slow deposition of yellow crystals, but beware, this is not the product. This solid weighed 4.0 g and was the potassium salt of trinitromethane. This isolate was dried and sealed in a small vial. After a few days standing, it detonated spontaneously. The filtrate was extracted with 3x75 mL CH_2Cl_2, and the removal of the solvent from these extracts gave a residue of 20.8 g of crude 2-nitro-1-(2,3,4,5-tetramethoxyphenyl)propene which did not crystallize.

A solution was made of 20.3 g of the crude 2-nitro-1-(2,3,4,5-tetramethoxyphenyl)propene in 200 mL anhydrous Et_2O, and this was filtered to remove some 2.7 g of insoluble material which appeared to be the potassium salt of trinitromethane by infra-red analysis. A suspension of 14 g LAH in 1 L anhydrous Et_2O was stirred, placed under an inert atmosphere, and brought up to a gentle reflux. The above clarified ether solution of the propene was added over the course of 1 h, and the mixture was held at reflux for 24 h. After cooling, the excess hydride was destroyed by the cautious addition of 1 L 1.5 N H_2SO_4 (initially a drop or two at a time) and when the two phases were complete clear, they were separated. The aqueous phase was treated with 350 g potassium sodium tartrate, and brought to a pH >9 with base. This was extracted with 3x150 mL CH_2Cl_2, and the removal of the solvent from the pooled extracts gave a residue that was dissolved in 200 mL anhydrous Et_2O, and saturated with anhydrous HCl gas. An Et_2O-insoluble oil was deposited and, after repeated scratching with fresh Et_2O, finally gave a granular white solid. This product was recrystallized from acetic anhydride, giving white crystals that were removed by filtration, Et_2O washed, and air dried. The yield of 2,3,4,5-tetramethoxyamphetamine hydrochloride (TA) was 1.9 g and had a mp of 135.5-136.5 °C.

DOSAGE: probably above 50 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 30 mg) "Definite threshold. There was eye dilation, and some unusual humor — a completely wild day with chi-square calculations on the PDP-7 that were on the edge of bad taste. But I was definitely baseline in the afternoon during the Motor Vehicle Department interactions."

(with 35 mg) "I had some gastric upset, but nonetheless there was a distinct intoxication. The next morning I had a foul headache."

EXTENSIONS AND COMMENTARY: This is pretty thin stuff from which to go out into a world that is populated by pharmacological sharks and stake out claims as to psychedelic potency. The structure of this molecule has everything going for it. It is an overlay of TMA (active) and TMA-2 (even more active) so it is completely

reasonable that it should be doing something at a rational dosage. But that dosage might well be in the many tens of milligrams.

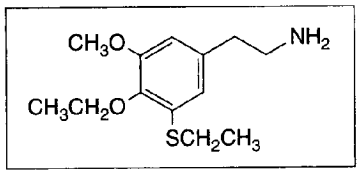
Tens of milligrams. Now there is a truly wishy-washy phrase. There is an art to the assignment of an exact number or, as is sometimes desperately needed, a fuzzy number, to a collection of things. In my youth (somewhere way back yonder in the early part of the century) I had been taught rules of grammer that were unquestionably expected of any well-educated person. If you used a Latin stem, you used a Latin prefix. And if you used a Greek stem, you used a Greek prefix. Consider a collection of things with simple geometric sides (a side is a *latus* in Latin). One would speak of a one-sided object as being unilateral, and a bilateral object has two sides. A trilateral, and quadrilateral, and way up there to multilateral objects, are referred to as having three or four or a lot of sides, respectively. Just the opposite occurs with geometric objects with faces. A face is a *hedra* in Greek, so one really should use the Greek structure. If one has just one face, one has a monohedron, a dihedron has two faces, and there are trihedron, tetrahedron, and polyhedron for things that have three, four, or a lot of faces. Actually, the prefix "poly" swings both ways. It was initially a Greek term, but as was the fate of many Greek words, it wandered its way from East to West, and ended up as a Latin term as well.

But back to the problem of how to refer to something that is more than one or two, but not as much as a lot? If you know exactly how many, you should use the proper prefix. But what if you don't know how many? There are terms such as "some." And there is "several." There is a "few" and a "number of" and "numerous" and "a hand full." One desperately looks for a term that is a collective, but which carries the meaning of an undefined number. There are English gems such as a pride of lions and a host of daffodils. But without a specific animal or plant of reference, one must have a target collective that is appropriate, to let the term "many" or "few" imply the proper size. There were many hundreds of persons (a few thousands of persons) at the rally. Several dozen hunters (a few score hunters) were gathered at the lake. A wonderful prefix is "oligo" which means a few, not a lot, and it means that I am not sure just how many are meant. Say, for example, that you have synthesized something in a biochemical mixture that contains three or four peptides. Di-and tri- and tetrapeptides are exact terms, but they do not describe what you have done. Polypeptide is way too big. However, an oligopeptide means that there are a few peptide units, I'm not sure how many. This may well be the most accurate description of just what you have.

I love the British modesty that is shown by hiding a person's physical weight by referring to it with the dimension known as the stone. This is, as I remember, something like 14 pounds. So, if stones were the weight equivalent of 10 milligrams, the activity of TA would be several stone. And since the synthetic intermediate 1-allyl-2,3,4,5-tetramethoxybenzene is one of the ten essential oils, the amination step from our hypothetical reaction in the human liver would make TA one of the so-called Ten Essential Amphetamines.

#146 3-TASB; 3-THIOASYMBESCALINE; 4-ETHOXY-3-ETHYLTHIO-5-METHOXYPHENETHYLAMINE

SYNTHESIS: Without any solvent, there was combined 21.7 g of solid 5-bromovanillin and 11.4 mL cyclohexylamine. There was the immediate generation of a yellow color and the evolution of heat. The largely solid mass was ground up under 50 mL of boiling IPA to an apparently homogeneous yellow solid which was removed by filtration and washed with IPA. There was thus obtained about 27 g of 3-bromo-N-cyclohexyl-4-hydroxy-5-methoxybenzylidenimine with a mp of 229-231 °C and which proved to be insoluble in most solvents (EtOH, CH_2Cl_2, acetone). A solution in dilute NaOH was unstable with the immediate deposition of opalescent white solids of the phenol sodium salt. A small scale recrystallization from boiling cyclohexanone yielded a fine yellow solid with a lowered mp (210-215 °C). Anal. ($C_{14}H_{18}BrNO_2$) C,H.



A solution of 32.5 g 3-bromo-N-cyclohexyl-4-hydroxy-5-methoxybenzylidenimine in 60 mL of hot DMF was cooled to near room temperature, treated with 24.5 g ethyl iodide and followed by 14.0 g of flake KOH. This mixture was held at reflux for 1 h, cooled, and added to 1 L H_2O. Additional base was added and the product was extracted with 3x150 mL CH_2Cl_2. These pooled extracts were washed with dilute NaOH, then with H_2O, and finally the solvent was removed under vacuum. The crude amber-colored residue was distilled. The fraction coming over at 118-135 °C at 0.4 mm/Hg weighed 8.7 g, spontaneously crystallized, and proved to be 3-bromo-4-ethoxy-5-methoxybenzaldehyde, melting at 59-60 °C after recrystallization from MeOH. Anal. ($C_{10}H_{11}BrO_3$) C,H. The fraction that came over at 135-155 °C at 0.2 mm/Hg weighed 10.5 g and also solidified in the receiver. This product was 3-bromo-N-cyclohexyl-4-ethoxy-5-methoxybenzylidenimine which, upon recrystallization from two volumes MeOH, was a white crystalline material with a mp of 60-61 °C. Anal. ($C_{16}H_{22}BrNO_2$) C,H. The two materials have identical mps, but can be easily distinguished by their infra-red spectra. The aldehyde has a carbonyl stretch at 1692 cm^{-1}, and the Schiff base a C=N stretch at 1641 cm^{-1}.

A solution of 20.5 g 3-bromo-N-cyclohexyl-4-ethoxy-5-methoxybenzylidenimine in about 300 mL anhydrous Et_2O was placed in a He atmosphere, well stirred, and cooled in an external dry ice acetone bath to -80 °C. There was then added 50 mL of 1.6 N butyllithium in hexane. The mixture became yellow and very viscous with the generation of solids. These loosened up with continuing stirring. This was followed by the addition of 10.7 g diethyldisulfide. The reaction became extremely viscous again, and stirring was continued while the reaction was allowed to warm to room temperature. After an additional 0.5 h stirring, the reaction mixture was added to 800 mL of dilute HCl. The Et_2O phase was separated and the solvent removed under vacuum. The residue was returned to the original aqueous phase, and the entire mixture heated on the steam bath for 2 h. The bright yellow color faded and there was the formation of a yellowish phase on the surface of the H_2O. The aqueous solution was cooled to room temperature, extracted with 3x100 mL CH_2Cl_2, the extracts pooled, washed first with dilute HCl, then with saturated brine, and the solvent removed under vacuum. The residue was an amber oil weighing 20.4 g, and was distilled at 130-140 °C at 0.3 mm/Hg to yield 12.9 g of 4-ethoxy-3-ethylthio-5-methoxybenzaldehyde as a straw colored oil that did not crystallize. Anal. ($C_{12}H_{16}O_3S$) C,H.

A solution of 1.0 g 4-ethoxy-3-ethylthio-5-methoxybenzaldehyde in 20 g nitromethane was treated with about 0.2 g of anhydrous ammonium acetate and heated on the steam bath. TLC analysis showed that the aldehyde was substantially gone within 20 min and that, in addition to the expected nitrostyrene, there were four scrudge products (see the discussion of scrudge in the extensions and commentary section under 3-TSB). Removal of the excess nitromethane under vacuum gave an orange oil which was diluted with 5 mL cold MeOH but which could not be induced to crystallize. A seed was obtained by using a preparative TLC plate (20x20 cm) and removing the fastest moving spot (development was with CH_2Cl_2). Placing this in the above MeOH solution of the crude nitrostyrene allowed crystallization to occur. After filtering and washing with MeOH, 0.20 g of fine yellow crystals were obtained which melted at 75-77 °C. Recrystallization from MeOH gave a bad recovery of yellow crystals of 4-ethoxy-3-ethylthio-5-methoxy-ß-nitrostyrene that now melted at 78.5-79 °C. Anal. ($C_{13}H_{17}NO_4S$) C,H. This route was discarded in favor of the Wittig reaction described below.

A mixture of 27 g methyltriphenylphosphonium bromide in 150 mL anhydrous THF was placed under a He atmosphere, well stirred, and cooled to 0 °C with an external ice water bath. There was then slowly added 50 mL of 1.6 N butyllithium in hexane which resulted in the initial generation of solids that largely redissolved by the completion of the addition of the butyllithium and after allowing the mixture to return to room temperature. There was then added 11.7 g of 4-ethoxy-3-ethylthio-5-methoxybenzaldehyde without any solvent. There was the immediate formation of an unstirrable solid, which partially broke up into a gum that still wouldn't stir. This was moved about, as well as possible, with a glass rod, and then all was added to 400 mL H_2O. The two phases were separated and the lower, aqueous, phase extracted with 2x75 mL of petroleum ether. The organic fractions were combined and the solvents removed under vacuum to give the crude 4-ethoxy-3-ethylthio-5-methoxystyrene as a pale yellow fluid liquid.

A solution of 10 mL of borane-methyl sulfide complex (10 M BH_3 in methyl sulfide) in 75 mL THF was placed in a He atmosphere, cooled to 0 °C, treated with 21 mL of 2-methylbutene, and stirred for 1 h while returning to room temperature. This was added directly to the crude 4-ethoxy-3-ethylthio-5-methoxystyrene. The slightly exothermic reaction was allowed to stir for 1 h, and then the excess borane was destroyed with a few mL of MeOH (in the absence of air to avoid the formation of the dialkylboric acid). There was then added 19 g of elemental iodine followed,

over the course of about 10 min, by a solution of 4 g NaOH in 50 mL hot MeOH. The color did not fade. Addition of another 4 mL 25% NaOH lightened the color a bit, but it remained pretty ugly. This was added to 500 mL H_2O containing 5 g sodium thiosulfate and extracted with 3x100 mL petroleum ether. The extracts were pooled, and the solvent removed under vacuum to provide crude 1-(4-ethoxy-3-ethylthio-5-methoxyphenyl)-2-iodoethane as a residue.

To this crude 1-(4-ethoxy-3-ethylthio-5-methoxyphenyl)-2-iodoethane there was added a solution of 20 g potassium phthalimide in 150 mL anhydrous DMF, and all was held at reflux overnight. After adding to 500 mL of dilute NaOH, some 1.4 g of a white solid was generated and removed by filtration. The aqueous filtrate was extracted with 2x75 mL Et_2O. These extracts were combined, washed with dilute HCl, and the solvent removed under vacuum providing 23.6 g of a terpene-smelling amber oil. This was stripped of all volatiles by heating to 170 °C at 0.4 mm/Hg providing 5.4 g of a sticky brown residue. This consisted largely of the desired phthalimide. The solids proved to be a purer form of 1-(4-ethoxy-3-ethylthio-5-methoxy)-2-phthalimidoethane and was recrystallized from a very small amount of MeOH to give fine white crystals with a mp of 107.5-108.5 °C. Anal. ($C_{21}H_{23}NO_4S$) C,H. The white solids and the brown impure phthalimide were separately converted to the final product, 3-TASB.

A solution of 1.2 g of the crystalline 1-(4-ethoxy-3-ethylthio-5-methoxyphenyl)-2-phthalimidoethane in 40 mL of warm n-butanol was treated with 3 mL of 66% hydrazine, and the mixture was heated on the steam bath for 40 min. The reaction mixture was added to 800 mL dilute H_2SO_4. The solids were removed by filtration, and the filtrate was washed with 2x75 mL CH_2Cl_2. The aqueous phase was made basic with 25% NaOH, extracted with 3x75 mL CH_2Cl_2, and the solvent from these pooled extracts removed under vacuum yielding 6.2 g of a residue that was obviously rich in butanol. This residue was distilled at 138-144 C. at 0.3 mm/Hg to give 0.6 g of a colorless oil. This was dissolved in 2.4 mL IPA, neutralized with concentrated HCl, and diluted with 25 mL anhydrous Et_2O. The solution remained clear for about 10 seconds, and then deposited white crystals. These were removed by filtration, washed with additional Et_2O, and air dried to give 0.4 g 4-ethoxy-3-ethylthio-5-methoxyphenethylamine hydrochloride (3-TASB) with a mp of 140-141 °C. Anal. ($C_{13}H_{22}ClNO_2S$) C,H. The amber-colored impure phthalimide, following the same procedure, provided another 0.9 g of the hydrochloride salt with a mp of 138-139 °C.

DOSAGE: about 160 mg.

DURATION: 10 - 18 h.

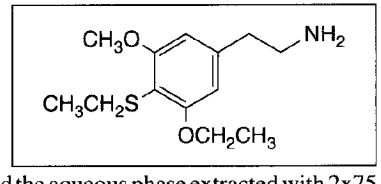
QUALITATIVE COMMENTS: (with 120 mg) "This is no more than a plus one, and it didn't really get there until about the third hour. By a couple of hours later, I feel that the mental effects are pretty much dissipated, but there is some real physical residue. Up with some caution."

(with 160 mg) "The taste is completely foul. During the first couple of hours, there was a conscious effort to avoid nausea. Then I noticed that people's faces looked like marvelous parodies of themselves and that there was considerable time slowing. There was no desire to eat at all. Between the eighth and twelth hour, the mental things drifted away, but the body was still wound up. Sleep was impossible until about 3:00 AM (the 18th hour of the experiment) and even the next day I was extremely active, anorexic, alert, excited, and plagued with occasional diarrhea. This is certainly a potent stimulant. The next night I felt the tensions drop, and finally got an honest and easy sleep. There is a lot of adrenergic push to this material."

EXTENSIONS AND COMMENTARY: No pharmacological agent has an action that is pure this or pure that. Some pain-killing narcotics can produce reverie and some sedatives can produce paranoia. And just as surely, some psychedelics can produce stimulation. With 3-TASB we may be seeing the shift from sensory effects over to out-and-out stimulation. It would be an interesting challenge to take these polyethylated phenethylamines and assay them strictly for their amphetamine-like action. Sadly, the potencies are by and large so low, that the human animal can't be used, and any sub-human experimental animal would not enable the psychedelic part of the equation to be acknowledged. If an order of magnitude of increased potency could be bought by some minor structural change, this question could be addressed. Maybe as the three-carbon amphetamine homologs, or as the 2,4,5- or 2,4,6- substitution patterns, rather than the 3,4,5-pattern used in this set.

#147 4-TASB; 4-THIOASYMBESCALINE; 3-ETHOXY-4-ETHYLTHIO-5-METHOXYPHENETHYLAMINE

SYNTHESIS: A solution of 20.5 g N,N,N',N'-tetramethylethylenediamine and 22.3 g of 3-ethoxyanisole was made in 100 mL hexane under a He atmosphere with good stirring. There was added 125 mL 1.6 M butyllithium in hexane, which formed a white granular precipitate. This was cooled in an ice bath, and there was added 24.4 g of diethyldisulfide which produced an exothermic reaction and changed the precipitate to a creamy phase. After being held for a few min at reflux temperature, the reaction mixture was added to 500 mL dilute H_2SO_4 which produced two clear phases. The hexane phase was separated, and the aqueous phase extracted with 2x75 mL methylcyclopentane. The organics were combined, and the solvents removed under vacuum. There was obtained a residue which was distilled under a vacuum.



At 0.3 mm/Hg the fraction boiling at 95-105 °C was a yellow liquid weighing 28.5 g which was largely 3-ethoxy-2-(ethylthio)anisole which seemed to be reasonably pure chromatographically. It was used as such in the bromination step below.

To a stirred solution of 15.0 g of 3-ethoxy-2-(ethylthio)anisole in 100 mL CH_2Cl_2 there was added 12 g elemental bromine dissolved in 25 mL CH_2Cl_2. There was the copious evolution of HBr. After stirring at ambient temperature for 3 h, the dark solution was added to 300 mL H_2O containing sodium dithionite. Shaking immediately discharged the residual bromine color, and the organic phase was separated, The aqueous phase was extracted once with 100 mL CH_2Cl_2, the pooled extracts washed with dilute base, and then the solvent was removed under vacuum to give a light brown oil. This wet product was distilled at 112-122 °C at 0.3 mm/Hg to yield 4-bromo (and/or 6-bromo)-3-ethoxy-2-(ethylthio)anisole as a light orange oil. This was used in the following benzyne step without separation into its components.

To a solution of 36 mL diisopropylamine in 150 mL anhydrous THF under a He atmosphere, and which had been cooled to -10 °C with an external ice/MeOH bath, there was added 105 mL of a 1.6 M solution of butylithium in hexane. There was then added 5.1 mL of dry CH_3CN followed by the dropwise addition of 15.0 g 4-bromo-(and/or 6-bromo)-3-ethoxy-2-(ethylthio)anisole diluted with a little anhydrous THF. There was an immediate development of a dark red-brown color. The reaction was warmed to room temperature and stirred for 0.5 h. This was then poured into 600 mL of dilute H_2SO_4. The organic phase was separated, and the aqueous fraction extracted with 2x50 mL CH_2Cl_2. These extracts were pooled and the solvent removed under vacuum. The residue was a dark oil and quite complex as seen by thin layer chromatography. This material was distilled at 0.3 mm/Hg yielding two fractions The first boiled at 112-125 °C and weighed 3.9 g. It was largely starting bromo compound with a little nitrile, and was discarded. The second fraction distilled at 130-175 °C and also weighed 3.9 g. This fraction was rich in the product 3-ethoxy-4-ethylthio-5-methoxyphenylacetonitrile, but it also contained several additional components as seen by thin layer chromatographic analysis. On standing for two months, a small amount of solid was laid down which weighed 0.5 g after cleanup with hexane. But even it consisted of three components by TLC, none of them the desired nitrile. The crude fraction was used for the final step without further purification or microanalysis.

A solution of LAH in anhydrous THF under N_2 (15 mL of a 1.0 M solution) was cooled to 0 °C and vigorously stirred. There was added, dropwise, 0.40 mL 100% H_2SO_4, followed by about 3 g of the crude 3-ethoxy-4-ethylthio-5-methoxyphenylacetonitrile diluted with a little anhydrous THF. The reaction mixture was stirred until it came to room temperature, and then held at reflux on the steam bath for 2 h. After cooling to room temperature, there was added IPA to destroy the excess hydride (there was quite a bit of it) and then 15% NaOH to bring the reaction to a basic pH and convert the aluminum oxide to a loose, white, filterable consistency. This was removed by filtration, and washed first with THF followed

by IPA. The filtrate and washes were stripped of solvent under vacuum, the residue added to 100 mL dilute H_2SO_4. This was washed with 2x75 mL CH_2Cl_2, made basic with 25% NaOH, and extracted with 2x50 mL CH_2Cl_2. After combining, the solvent was removed under vacuum providing a residue that was distilled. A fraction boiling at 122-140 °C at 0.3 mm/Hg weighed 1.0 g and was a colorless oil. This was dissolved in 10 mL of IPA, and neutralized with 20 drops of concentrated HCl and diluted, with stirring, with 40 mL anhydrous Et_2O. There was the slow formation of a fine white crystalline salt, which was removed by filtration, washed with Et_2O, and air dried. The product 3-ethoxy-4-ethylthio-5-methoxyphenethylamine hydrochloride (4-TASB), weighed 0.5 g, and had a mp 139-140 °C. Gas chromatographic analysis by capillary column chromatography of the free base (in butyl acetate solution on silica SE-54) showed a single peak at a reasonable retention time, verifying isomeric purity of the product. Anal. ($C_{13}H_{22}ClNO_2S$) C,H.

DOSAGE: 60 - 100 mg.

DURATION: 10 - 15 h.

QUALITATIVE COMMENTS: (with 60 mg) "The compound has a petroleum-refinery type taste. There was a looseness of the bowels as I got into it. Here we have another of these 'What is it' or 'What isn't it' compounds. Somehow I seemed to have to push the erotic, the visual, the whole psychedelic shmeer, to document that this was indeed effective. I am not impressed."

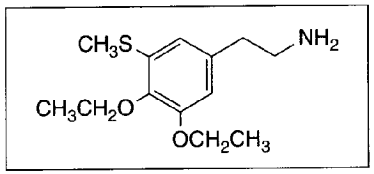
(with 100 mg) "There were some trivial physical problems during the early stages of this experiment. But there was fantasy stuff to music, and some jumpy stuff to music. Is there a neurological hyperreflexia? I was able to sleep at the 12 hour point but I felt quite irritable. I am agitated. I am twitchy. This has been very intense, and I am not completely comfortable yet. Let's wait for a while."

(with 100 mg) "Music was lovely during the experiment, but pictures were not particularly exciting. I had feelings that my nerve-endings were raw and active. There was water retention. There was heartbeat wrongness, and respiration wrongness. During my attempts to sleep, my eyes-closed fantasies became extremely negative. I could actually feel the continuous electrical impulses travelling between my nerve endings. Disturbing. There was continuous erotic arousability, and this seemed to be part of the same over-sensitivity of the nervous system; orgasm didn't soothe or smooth out the feeling of vulnerability. This is a very threatening material. DO NOT REPEAT."

EXTENSIONS AND COMMENTARY: Again, another drug with more physical problems than psychic virtue, but with no obvious structural feature to hang it all onto. Some day this will all make sense!

#148 5-TASB; 5-THIOASYMBESCALINE; 3,4-DIETHOXY-5-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution of 11.5 g 3-bromo-N-cyclohexyl-4,5-diethoxybenzylidinimine (see under ASB for its preparation) in 150 mL anhydrous Et_2O was placed in a He atmosphere, well stirred, and cooled in an external dry ice/acetone bath to -80 °C. There was light formation of fine crystals. There was then added 25 mL of 1.6 N butyllithium in hexane and the mixture stirred for 15 min. This was followed by the addition of 4.3 mL dimethyldisulfide over the course of 20 min, during which time the solution became increasingly cloudy and then thinned out again. The mixture was allowed to come to room temperature over the course of an additional h, and then added to 400 mL of dilute HCl. There was the generation of a lot of yellow solids, and the Et_2O phase was almost colorless. This was separated, the solvent removed under vacuum, and the residue combined with the original aqueous phase. This phase was then heated on the steam bath for 2 h. The aqueous solution was cooled to room temperature, extracted with 3x100 mL CH_2Cl_2, the extracts pooled, washed with H_2O, and the solvent removed under vacuum to yield 9.4 g of an amber oil which spontaneously crystallized. This was distilled at 125-132 °C at 0.2 mm/Hg to yield 7.1 g of 3,4-diethoxy-5-(methylthio)benzaldehyde as a white oil that spontaneously crystallized. The crude product had a mp of 73-74 °C that actually decreased to 72-73 °C after recrystallization from MeOH. Anal. ($C_{12}H_{16}O_3S$) C,H.



A solution of 16.2 g methyltriphenylphosphonium bromide in 200 mL anhydrous THF was placed under a He atmosphere, well stirred, and cooled to 0 °C with an external ice water bath. There was then added 30 mL of 1.6 N butyllithium in hexane which resulted in the generation of a clear yellow solution. The reaction mixture was brought up to room temperature, and 7.0 g 3,4-diethoxy-5-(methylthio)benzaldehyde in 50 mL THF was added dropwise, dispelling the color, and the mixture was held at reflux on the steam bath for 1 h. The reaction was quenched in 800 mL H_2O, the top hexane layer separated, and the aqueous phase extracted with 2x75 mL of petroleum ether. The organic fractions were combined and the solvents removed under vacuum to give 12.0 g of the crude 3,4-diethoxy-5-methylthiostyrene as a pale amber-colored oil.

A solution of 6.0 mL of borane-methyl sulfide complex (10 M BH_3 in methyl sulfide) in 45 mL THF was placed in a He atmosphere, cooled to 0 °C, treated with 12.6 g of 2-methylbutene, and stirred for 1 h while returning to room temperature. To this there was added a solution of the impure 3,4-diethoxy-5-methylthiostyrene in 25 mL THF. This was stirred for 1 h during which time the color deepened to a dark yellow. The excess borane was destroyed with about 2 mL MeOH (all this still in the absence of air). There was then added 11.4 g elemental iodine followed by a solution of 2.4 g NaOH in 30 mL of boiling MeOH, added over the course of 10 min. This was followed by sufficient 25% NaOH to discharge the residual iodine color (about 4 mL was required). The reaction mixture was added to 500 mL water, and sodium hydrosulfite was added to discharge the remaining iodine color (about 4 g). This was extracted with 3x100 mL petroleum ether, the extracts pooled, and the solvent removed under vacuum to provide 25.9 g of crude 1-(3,4-diethoxy-5-methylthiophenyl)-2-iodoethane as a pale yellow fluid oil. Thin layer chromatographic analysis of this material on silica gel plates (using a 90:10 mixture of CH_2Cl_2/methylcyclopentane as solvent) showed largely the iodo-product (Rf 0.9) with no visible starting aldehyde (Rf 0.7).

To this crude 1-(3,4-diethoxy-5-methylthiophenyl)-2-iodoethane there was added a solution of 12 g potassium phthalimide in 90 mL anhydrous DMF, and all was held at reflux in a heating mantle. The reaction progress was followed by TLC, and at 1.5 h it was substantially complete. After adding to 500 mL 5% NaOH, the organic phase was separated, and the aqueous phase was extracted with 2x75 mL Et_2O. The organic fractions were combined, and the solvent removed under vacuum providing 19.3 g of an amber oil. The residual volatiles were removed by distillation up to 170 °C at 0.2 mm/Hg. The distillate weighed 7.0 g and contained little if any phthalimide by TLC. The pot residue was a viscous amber oil, and also weighed 7.0 g. About half of this was employed in the following hydrolysis step, and the rest was rubbed under an equal volume of MeOH providing 1-(3,4-diethoxy-5-methylthiophenyl)-2-phthalimidoethane as a white solid. A small sample was recrystallized from an equal volume of MeOH to give white crystals with a mp of 79.5-81 °C. Re-recrystallization from MeOH produced an analytical sample with a mp of 83-84 °C. Anal. ($C_{21}H_{23}NO_4S$) C,H.

A solution of 3.2 g of the impure 1-(3,4-diethoxy-5-methylthiophenyl)-2-phthalimidoethane in 150 mL of n-butanol there was added 20 mL of 66% hydrazine, and the mixture was heated on the steam bath for 2 h. This was added to 600 mL of dilute H_2SO_4, and the two layers were separated. The butanol layer was extracted with 2x100 mL dilute H_2SO_4. These extracts were added to the original aqueous phase, and this was washed with 3x75 mL CH_2Cl_2. This was then made basic with 5% NaOH, extracted with 3x75 mL CH_2Cl_2, and the solvent from these pooled extracts removed under vacuum. The residue (which weighed 9.7 g and contained much butanol) was distilled at 140-145 °C at 0.3 mm/Hg to give 0.7 g of a colorless oil. This was dissolved in 3.0 mL IPA, neutralized with concentrated HCl, and diluted with 12 mL anhydrous Et_2O to give a solution that immediately crystallized to provide white crystals of 3,4-diethoxy-5-methylthiophenethylamine hydrochloride (5-TASB). These weighed 0.7 g after washing with Et_2O and drying to constant weight. The mp was 182-183 °C, and an analytical sample was dried at 100 °C for 24 h. Anal. ($C_{13}H_{22}ClNO_2S$) C,H.

DOSAGE: about 160 mg.

DURATION: about 8 h.

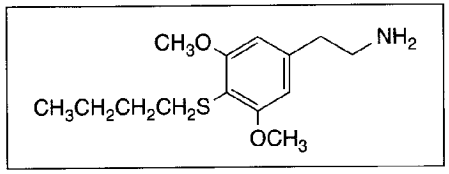
QUALITATIVE COMMENTS: (with 120 mg) "Maybe there is something at about hour 5. My talking with innocent people had hints of strangeness. And there was the slightest suggestion of some physical effect. Call it an overall (+)."

(with 160 mg) "I am immediately warm at the extremities. An awareness grows upon me for a couple of hours. I am a little light-headed, and I feel that there is more physical than there is mental, and it is not all entirely nice. I am slightly hyperreflexive, and there is a touch of diarrhea. I am happy that I held this at 160 milligrams. I am mentally flat at the eighth hour, although there are some physical residues. The effects are real, but I don't want to go higher. Some trace physical memory seems to stay with me as a constant companion."

EXTENSIONS AND COMMENTARY: There is a ponderousness about adding a couple of ethyl groups and a sulfur that seems to say, "no fun." 5-TASB has something going for it (but not much) and 3-TASB is quite a bit more peppy and, actually, 4-TASB has quite a bit of life. But there is a sense of "why bother?" There were a couple of bouts of light-headedness, but there was no unexpected excitement discovered in this methodical study. No surprises. Keep the chain lengths down.

#149 TB; 4-THIOBUSCALINE; 3,5-DIMETHOXY-4-(n)-BUTYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution was made of 12.1 g N,N,N',N'-tetramethylethylenediamine and 13.8 g of 1,3-dimethoxybenzene in 200 mL 30-60 °C petroleum ether. This was stirred vigorously under a He atmosphere and cooled to 0 °C with an external ice bath. There was added 66 mL of 1.6 M butyl lithium in hexane which produced a white granular precipitate. The reaction mixture was brought up to room temperature for a few minutes, and then cooled again to 0 °C. There was then added 18.7 g of di-(n)-butyl disulfide (this reagent was quite yellow, but was used without any purification) which changed the granular precipitate to a strange salmon color. Stirring was continued while the reaction mixture was brought up to room temperature and finally up to reflux. The reaction mixture was then added to 600 mL of dilute H_2SO_4. The two phases were separated, and the aqueous phase extracted with 2x75 mL Et_2O. The organic phases were combined and the solvent removed under vacuum. The residue weighed 33.0 g and was a dark yellow oil. Efforts to remove this color by reductive extraction of a CH_2Cl_2 solution with aqueous sodium hydrosulfite were futile. The residue was distilled at 0.3 mm/Hg to give two fractions. The first boiled at 95-115 °C, weighed 4.1 g and was largely recovered dibutyl disulfide. The product 2-(n)-butylthio-1,3-dimethoxybenzene boiled at 115-135 °C and weighed 19.5 g. It was a pale amber oil that could not be induced to crystallize. Anal. ($C_{12}H_{18}O_2S$) C,H.



To a stirred solution of 19.5 g of 2-(n)-butylthio-1,3-dimethoxybenzene in 75 mL CH_2Cl_2 there was added 14.5 g elemental bromine dissolved in 75 mL CH_2Cl_2. The evolution of HBr was evident, but the reaction was not exothermic. The reaction was allowed to stir for 1 h and then heated briefly to a reflux on the steam bath. It was then washed with H_2O containing sodium hydrosulfite which discharged the residual color. After washing with saturated brine, the solvent was removed under vacuum leaving 26.0 g of a pale amber oil. This was distilled at 120-140 °C at 0.4 mm/Hg yielding 4-bromo-2-(n)-butylthio-1,3-dimethoxybenzene as a yellow-orange oil. It could not be crystallized. Anal. ($C_{12}H_{17}BrO_2S$) C,H.

To a solution of 11.5 mL diisopropylamine in 50 mL hexane that was stirred under N_2 there was added 50 mL of 1.6 M butyllithium. After 15 min stirring, the reaction mixture became very viscous, and it was diluted with 150 mL anhydrous THF. After cooling in an ice bath there was added 2.0 mL CH_3CN followed in 1 min with 6.0 g of 4-bromo-2-(n)-butylthio-1,3-dimethoxyanisole a bit at a time over the course of 1 min. There was the immediate formation of a deep red color. After stirring for 0.5 h, the mixture was poured into dilute H_2SO_4. The organic layer was separated, and the aqueous layer extracted with 3x75 mL CH_2Cl_2. These extracts were pooled, dried with anhydrous K_2CO_3, and the solvent was removed under vacuum. The residue was distilled at 0.25 mm/Hg and yielded two fractions. The first fraction boiled at 125-145 °C, weighed 0.8 g and was discarded. The second fraction came over at 145-175 °C as a light yellow oil and weighed 2.2 g. This product, 4-(n)-butylthio-3,5-dimethoxyphenylacetonitrile, was reduced as such without further purification or analysis.

A solution of LAH under N_2 (20 mL of a 1 M solution in anhydrous THF) was cooled to 0 °C and vigorously stirred. There was added, dropwise, 0.53 mL 100% H_2SO_4, followed by 2.0 g 4-(n)-butylthio-3,5-dimethoxyphenylacetonitrile in 10 mL anhydrous THF. The reaction mixture was stirred at 0 °C for a few min, then brought to room temperature for 1 h, and finally to a reflux for 1 h on the steam bath. After cooling back to room temperature, there was added IPA (to destroy the excess hydride) followed by 10% NaOH which brought the reaction to a basic pH and converted the aluminum oxides to a loose, white, filterable consistency. These were removed by filtration, and washed with THF and IPA. The filtrate and washes were stripped of solvent under vacuum, the residue was suspended in 150 mL of dilute NaOH and extracted with 3x100 CH_2Cl_2. These extracts were pooled and extracted with 2x75 mL diluteH_2SO_4. Emulsions required that a considerable additional quantity of H_2O be added. The aqueous phase was made basic, and extracted with 2x100 mL CH_2Cl_2. After combining these extracts, the solvent was removed under vacuum providing a residue that was distilled. The product distilled at 138-168 °C at 0.4 mm/Hg as a white oil weighing 0.7 g. This was dissolved in a small amount of IPA, neutralized with concentrated HCl and, with continuous stirring, diluted with several volumes of anhydrous Et_2O. After filtering, Et_2O

washing, and air drying, 4-(n)-butylthio-3,5-dimethoxyphenethylamine hydrochloride (TB) was obtained, weighed 0.6 g, and had a mp of 154-155 °C. Anal. ($C_{14}H_{24}ClNO_2S$) C,H.

DOSAGE: 60 - 120 mg.

DURATION: about 8 h.

QUALITATIVE COMMENTS: (with 35 mg) "I was aware of something at about an hour, and it developed into a benign and beautiful experience which never quite popped into anything psychedelic. At the fifth hour there was a distinct drop, and I made what might be thought of as a foolish effort to rekindle the state with an additional 20 milligrams but it was too little and too late. There was no regeneration of anything additional."

(with 60 mg) "A very subtle threshold, probably, and six hours into it there seems to have been little if any effect. My memory of it is not that certain and now I am not sure that there had been anything at all."

(with 80 mg) "I am vaguely aware of something. The body discomfort may reflect the use of sardines in tomato sauce for lunch, but still things are not quite right. Five hours into it I am still in a wonderful place spiritually, but there seem to be some dark edges. I might be neurologically sensitive to this."

(with 120 mg) "The course of the action of this is extremely clear. The development was from 5 PM to 7 PM [the experiment started at 4 PM] and by 10 PM I was dropping and by midnight I went to bed and slept well. Food was not too interesting, and a glass of wine before sleeping produced no noticeable effect. This was an uneventful experience that never really made it off the ground. It was pleasant, but certainly not psychedelic."

EXTENSIONS AND COMMENTARY: There is a term "dose-dependent" in pharmacology. When there is a complex action produced by a drug, then each of the components of this mixture of effects should be expected to become more intense following a bigger dose of the drug. This is certainly true with most of the actions of psychoactive drugs.

As to the psychedelic aspects of some drugs, there can be visual effects, eyes-open (edge-ripples or colors or retinal games) or eyes-closed (images of the elaborately decorated doors of the mosque, or of an orchestra floating suspended by its music) or fantasy (you are moving beyond the confines of your body and invading someone else's space). The same applies to tactile enhancement, to the anaesthetic component, to the depth of insight realized from a drug. The more the drug, as a rule, the more the effect, up to the point that new and disruptive effects are realized. This latter is called toxicity.

As to the stimulant component, the same is true. The person gets wired up, and there is no sleep because there is no hiding from a cascade of images and

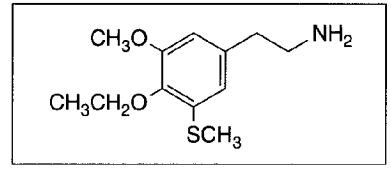
meanings, and the body lies there unwilling to yield guard since both the pounding heart and the interpretive psyche are demanding attention. These aspects also intensify with increasingly higher doses.

But an exception to this is the euphoria-producing aspect of a drug. One sees with increasing doses a continuing "threshold" that makes you aware, that fluffs the senses, but which seems not, at any level, to take over or to command the ship. It is truly a catalytic on or off. You are or you are not. In the "Tomso" effect, this action is produced by alcohol. There is disinhibition with alcohol which allows a central intoxication from the drug TOMSO regardless of the amount of drug used (see under TOMSO). One sees again, here with TB, the case of a perpetual series of "thresholds." Never the psychedelic or the stimulant action that increases with increased dose. Always the simple and ephemeral catalyst of euphoria without substance and without body. It is a compound that can never be pinned and labeled in the butterfly collection since it defies an accepted classification.

This action was seen first with the compound called ARIADNE and when it was called an anti-depressant, it proved to be commercially interesting. It is fully possible that TB would be of value to certain depressed people in exactly the same way.

#150 3-TE; 3-THIOESCALINE; 4-ETHOXY-5-METHOXY-3-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution of 10.4 g of 3-bromo-N-cyclohexyl-4-ethoxy-5-methoxybenzylidenimine (see under 3-TASB for its preparation) in 125 mL anhydrous Et_2O, in a He atmosphere, was cooled with an external dry ice acetone bath to -80 °C with good stirring. To this clear pale yellow solution there was added 25 mL 1.6 M butyllithium in hexane (about a 25% excess) which produced a fine white precipitate over the following 15 min. There was then added 4.2 g dimethyl disulfide. At the half-addition point, the generated solids became so heavy that stirring became difficult, but towards the end of the addition the reaction thinned out again and became quite loose. The dry ice bath was removed and the reaction allowed to come to room temperature, which again allowed the formation of a heavy solid phase while warming and, again, a loose and easily stirred mixture when finally at room temperature. All was added to 400 mL H_2O which had been strongly acidified with HCl. The two phases were separated, and the aqueous phase (which contained a small amount of yellow oily matter insoluble in either phase) was heated on the steam bath for 0.75 h. On cooling, the oily component set to a yellow solid, which was removed by filtration and washed with H_2O. This crude product, 5.9 g of yellow solid, was distilled 115-125 °C at 0.3 mm/Hg to give 4.9 g of 4-ethoxy-



3-methoxy-5-(methylthio)benzaldehyde as a pale yellow solid that had a mp of 43-45 °C. Recrystallization from MeOH gave a mp of 47-48 °C. Anal. ($C_{11}H_{14}O_3S$) C,H. This product can also be prepared from the anion of 3-thiosyringaldehyde (mp 141-143 °C as crystals from MeOH) by reaction with ethyl iodide in the presence of phase-transfer catalyst, but the yield is quite poor.

To a solution of 4.4 g 4-ethoxy-5-methoxy-3-(methylthio)benzaldehyde in 75 mL nitromethane, there was added 0.5 g anhydrous ammonium acetate and the mixture was heated on the steam bath for 80 min. Care must be taken in the length of time, and there must be frequent TLC montoring, as there is a rapid scrudge buildup (see under 3-TSB for a discussion of scrudge). The reaction mixture was stripped of nitromethane under vacuum, and the residual deep-yellow oil was dissolved in 20 mL of boiling MeOH. This was decanted from a small amount of insoluble matter and, upon cooling, deposited bright yellow crystals of 4-ethoxy-5-methoxy-3-methylthio-ß-nitrostyrene. This was removed by filtration and, after washing with cold MeOH and air drying, weighed 2.4 g. The mp was ambiguous. The above crude material melted at 92-93 °C, which is probably too high! Earlier samples which melted in the low 80's appeared to have a mp, after repeated recrystallization from MeOH, of 87-88 °C. This latter was the property of the analytical sample. Anal. ($C_{12}H_{15}NO_4S$) C,H. The mp of the TLC low-moving component is always quite high, and might have been a factor in the assignment of this physical property.

AH was prepared in the usual manner from a suspension of 2.0 g LAH in 75 mL anhydrous THF, cooled to 0 °C, well stirred in an inert atmosphere of He, and treated with 1.33 mL of 100% H_2SO_4 added dropwise. There was added, dropwise and over the course of 10 min, a solution of 2.4 g 4-ethoxy-5-methoxy-3-methylthio-ß-nitrostyrene in 15 mL anhydrous THF. The reaction was exothermic, and was heated on the steam bath at reflux for an additional 10 min. After cooling again, there was added enough IPA to decompose the excess hydride and sufficient 10% NaOH to convert the aluminum oxide solids to a white, easily filterable mass. This was filtered, the filter cake washed with additional IPA, the filtrate and washes combined, and the solvent removed under vacuum. This was dissolved in 100 mL of dilute H_2SO_4 which was washed with 2x50 mL CH_2Cl_2. The aqueous phase was made basic with NaOH, extracted with 2x50 mL CH_2Cl_2, and the extracts pooled and the solvent removed under vacuum to yield a residue of a colorless oil. This distilled at 118-122 °C at 0.4 mm/Hg producing 1.9 g of a colorless oil. This was dissolved in 10 mL IPA, neutralized with 30 drops of concentrated HCl and, with good stirring, diluted with 20 mL anhydrous Et_2O. The product 4-ethoxy-5-methoxy-3-methylthiophenethylamine hydrochloride (3-TE) was removed by filtration, washed with Et_2O, and air dried to provide a white solid that weighed 1.0 g and melted at about 180 °C. Anal. ($C_{12}H_{20}ClNO_2S$) C,H.

DOSAGE: 60 - 80 mg.

DURATION: 8 - 12 h.

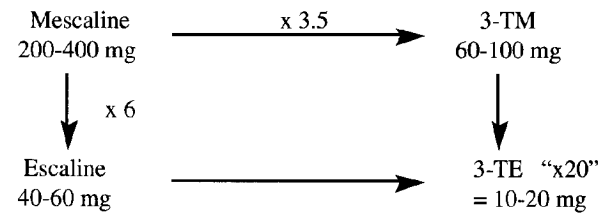
QUALITATIVE COMMENTS: (with 60 mg) "There may well be time slowing. I noticed that the voices on the radio seemed to be of a deeper pitch. And with music there is a most easy flight of fantasy. I tried to keep a logical conversation going on the telephone, but I am pretty sure there were problems. I found myself down sooner than I would have liked."

(with 70 mg) "I found myself in a good, rich place, and thoroughly enjoyed my introspection. I didn't want to talk and interact, and that seemed just fine with everyone else. Several of the others seemed restless, but I lay back and let them do their thing. My appetite was fine towards the end, and I might have actually overeaten. I was able to drive home that evening, but there seemed to be some slight residual something after waking in the morning. I would certainly repeat without hesitation."

(with 80 mg) "Art interpretation and imagery with music are remarkable. This material touches on the psychedelic — rather than just being stoned. The body is higher than the mind, but where the mind is makes it all OK. It's worth the cost. My getting to sleep was easy that evening, but sleep was not too restful and there was something strange about it."

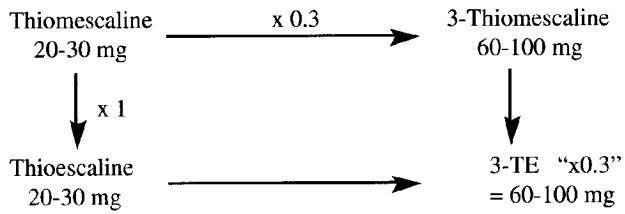
EXTENSIONS AND COMMENTARY: There is a good lesson to be learned in the attempts to predict the potency of 3-TE before it was actually explored. All pharmacological prediction follows pretty much a single mechanism. Find things that are close in some way, and arrange them in a manner that allows comparison. A relates to B in this way, and A relates to C in that way, and since D incorporates both this and that of each, it will probably be such-and-such. The Roman square.

Here is the square with the horizontal arrow adding a sulfur in the 3-position and the vertical arrow adding an ethyl group in place of a methyl group at the 4-position:



and one would predict a potency of some 20x that of mescaline, or something in the range of 15 mg.

Here is an equally likely square, based on the horizontal arrow relocating a sulfur from the 4-position to the 3-position, and the vertical arrow again adding an ethyl group in place of a methyl group in the 4-position:



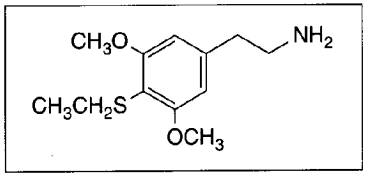
and one would predict a potency of some one third of that of thiomescaline, or something in the range of 80 milligrams.

This latter square gave a prediction that was very close to the observed potency, but it would be careless, and probably wrong, to assume that the latter relationships had any more significance than the former ones. As one accumulates the potencies of many compounds it is tempting to draw complex relationships such as these, and to be seduced into believing that they must explain things. And, especially, beware the multivariable power of the computer which can explore monstrous numbers of variables at breakneck speeds, and spew forth fantastic correlations with marvelous ease.

But nothing can ever substitute for the simple art of tasting something new.

#151 TE; 4-TE; 4-THIOESCALINE; 3,5-DIMETHOXY-4-ETHYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution was made of 45.2 g N,N,N',N'-tetramethylethylenediamine and 41.4 g of 1,3-dimethoxybenzene in 300 mL hexane. This was stirred vigorously under a He atmosphere and cooled to 0 °C with an external ice bath. There was added 225 mL of 1.6 M butyllithium in hexane which produced a white granular precipitate. The reaction mixture was stirred for 15 min. There was then added 38 mL of diethyl disulfide which changed the granular precipitate to a creamy character. Stirring was continued for an additional 5 min, then the reaction mixture was poured into 1 L of dilute H_2SO_4. The two phases were separated, and the aqueous phase extracted with 2x150 mL Et_2O. The organic phases were combined, and the solvent removed under vacuum to provide 60 g of 2-ethylthio-1,3-dimethoxybenzene as an off-white oil that spontaneously crystallized. It was distilled nonetheless, boiling at 85-96 °C at 0.4 mm/Hg. This distillate can be recrystallized from hexane to form long needles with a mp of 45-46 °C. Anal. ($C_{10}H_{14}O_2S$) C,H.



To a stirred solution of 60 g of 2-ethylthio-1,3-dimethoxybenzene in 300 mL CH_2Cl_2 there was added 49 g elemental bromine dissolved in 100 mL CH_2Cl_2.

The reaction was not exothermic, and it was allowed to stir for 2 h. The reaction mixture was washed with H_2O, then with aqueous NaOH, and finally with H_2O that contained sodium hydrosulfite. The solvent was removed under vacuum leaving 84 g of an amber oil as residue. This was distilled at 105-115 °C at 0.15 mm/Hg yielding 73.3 g of 4-bromo-2-ethylthio-1,3-dimethoxybenzene as a light yellow oil. Anal. ($C_{11}H_{15}BrO_2S$) C,H.

To a solution of 27 mL diisopropylamine in 150 mL anhydrous THF that was stirred under a N_2 atmosphere and cooled to -10 °C with an external ice/MeOH bath, there was added in sequence 83 mL of 1.6 M butyllithium in hexane, 4.4 mL of dry CH_3CN over the course of 5 min, and finally 12.1 g of 4-bromo-2-ethylthio-1,3-dimethoxybenzene which had been dissolved in 20 mL THF (also added over the course of 5 min). The color progressed from yellow to orange to deep red-brown. Stirring was continued for 10 min, and then the reaction mixture was poured into 300 mL dilute H_2SO_4. The organic layer was separated, and was washed with more dilute H_2SO_4. The aqueous phases were combined, and extracted with 2x100 mL CH_2Cl_2. These extracts were pooled with the original organic phase, and the solvents removed under vacuum. The residue was distilled into two fractions at 0.3 mm/Hg. The first fraction boiled at 95-115 °C and weighed 4.9 g. It was made up of several components, but it contained little nitrile material and was discarded. The second fraction came over at 145->200 °C and weighed 2.9 g. By thin layer chromatography this fraction was largely 3,5-dimethoxy-4-ethylthiophenylacetonitrile, and was used as such in the following reduction.

A suspension of 1.25 g LAH in 50 mL anhydrous THF under N_2 was cooled to 0 °C and vigorously stirred. There was added, dropwise, 0.8 mL 100% H_2SO_4, followed by 2.7 g 3,5-dimethoxy-4-ethylthiophenylacetonitrile, neat, over the course of 5 min. The reaction mixture was stirred at 0 °C for a few min, then brought to a reflux for 15 min on the steam bath. After cooling back to room temperature, there was added 15 mL IPA to destroy the excess hydride and 10% NaOH to bring the reaction to a basic pH and convert the aluminum oxide to a loose, white, filterable consistency. This was removed by filtration, and washed with 50 mL portions of IPA. The filtrate and washes were stripped of solvent under vacuum, and the residue suspended between 50 mL CH_2Cl_2 and 50 mL dil. H_2SO_4. The organic phase was separated, and extracted with 2x50 mL dilute H_2SO_4. The original aqueous phase and these two extracts were combined, made basic with aqueous NaOH, and extracted with 3x50 mL CH_2Cl_2. These extracts were stripped of solvent under vacuum. The residue was distilled at 112-135 °C at 0.2 mm/Hg to give 1.1 g of a slightly yellow viscous liquid. This was dissolved in 4 mL IPA, neutralized with 14 drops of concentrated HCl and, with continuous stirring, diluted with 10 mL anhydrous Et_2O. The product was removed by filtration, washed with Et_2O, and air dried to give 1.0 g of 3,5-dimethoxy-4-ethylthiophenethylamine hydrochloride (TE) as white crystals with some solvent of crystallization. The crude mp of 101-106 °C was only slightly improved by recrystallization from CH_3CN (mp 106-109 °C). But upon fusion and resolidification, the melting point was 167-168 °C and this

sample was further dried by heating at 100 °C for 24 h before analysis. Anal. ($C_{12}H_{20}ClNO_2S$) C,H.

DOSAGE: 20 - 30 mg.

DURATION: 9 - 12 h.

QUALITATIVE COMMENTS: (with 20 mg) "I feel it in my ovaries. It is very sensuous. This is total energy, and I am aware of my every membrane. This has been a marvelous experience, very beautiful, joyous, and sensuous. But maybe the dose is a little too high as there is too much body tingling. I am jangly."

(with 20 mg) "The predominant characteristic was the feeling of clean burning, pure energy, a long-lasting clear-headedness and clarity of thought, and an ease of talking and sharing. I did not have a strong feeling of Presence, but more a wonderful feeling of converting energy into action. I found that my initial look inwards was always a look of fear, and I wondered if this might not be the same feeling that others express as excitement. They were certainly of the same nature, they arose at the same point on the fringe of the unknown, and they point to a basic difference in attitude. The excitement is for the new, and is based on trust. The fear is a return to the past, and is defensive, with reluctance to reexperience past pain. The aftermath of this experience was the most profound of any that I have had in a long time. For the following week, I found myself on a new level of functioning, very energetic and very much in the flow of life and free of mental distractions. I have become a great deal more aware of the traps of meditation, and how you can build walls around yourself and around certain concepts, if you are not careful."

(with 22 mg) "Totally developed at 2 hours, to a +++. No clearing of the sinuses, so it is not a decongestant. There is a lot of visual activity. In the group there is good communication, and a lot of laughter."

(with 25 mg) "There is a disconnection, there is complex depth without definition. Without music, this is almost negative, as I can find no definition. But talking gives me some structure. And I got into some pretty extraordinary conversations. About President Hoover, Omni magazine, the colors of spices, and a couple of personal relatives. This is extra-good for ideas and talking. It is indeed a clean experience, and superb for communication."

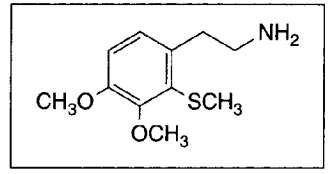
(with 30 mg) "I was at a plus three for certainly three hours. There were some visuals, some eyes-closed fantasy, but little imagery. Somehow I could at no time interlock with music. It seemed always to get in the way. Sexual activity is an excellent way to relieve the muscular tension and the body's heaviness. There was little hunger and I ate lightly, and I felt somehow depleted. Sleep OK at the twelth hour. The AM was fine, but on retrospect the experience was overall strangely cloudy, not negative, but there was not enough mental to balance the physical."

(with 30 mg) "My alert was in 40 minutes, and I was completely developed by 2 hours. There was a large measure of erotic fantasy, but the body load was also quite heavy. I had a slight cloak effect, where I was over-energized but somehow under a blanket of quietness. I would certainly repeat this, but at maybe 25 milligrams."

EXTENSIONS AND COMMENTARY: Although the ethyl group (of the ethylthio on the 4-position) is just one carbon atom longer than the methyl group (of TM) that small change already produces hints and indicators of some physical toxicity. The propyl compound (see TP) is still of similar potency, but appears to be yet more difficult, physically. The butyl homolog never made it off the ground at all as a psychedelic, but the physical difficulties seem less as well. All that was left to come through was the euphoria. If this 4-position sulfur analogue series of mescaline is ever to be more carefully explored, it must almost certainly be with the shortest possible chain (TM, as a psychedelic) or with long, long chains (the four-carbon chain of the butyl group in TB), as a feel-good compound.

#152 2-TIM; 2-THIOISOMESCALINE; 3,4-DIMETHOXY-2-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: A short foreword to the synthetic portion is needed. First, although the required thioanisole, 2,3-dimethoxythioanisole, is now commercially available, it is of the utmost importance that it be free of the impurity, veratrole. I know that the material presently available from Aldrich Chemical Company is satisfactory, as I have had a hand in making it. But, if veratrole is present, there are very difficult separations encountered during these preparations. And secondly, the synthesis of 2-TIM and 4-TIM requires a separation of isomers. The first intermediates are common to both. They will be presented here, under this recipe for 2-TIM.



A solution of 150 mL of 1.6 M butyllithium in hexane under N_2 was vigorously stirred and diluted with 150 mL petroleum ether (30-60 °C) and then cooled with an external ice bath to 0 °C. The addition of 26.7 g of veratrole produced a flocculant white precipitate. Next, there was added a solution of 23.2 g of N,N,N',N'-tetramethylethylenediamine in 100 mL anhydrous Et_2O and the stirred reaction mixture was allowed to come to room temperature. The subsequent addition of 20.7 g of dimethyl disulfide over the course of several min produced an exothermic response, and this was allowed to stir for an additional 30 min. There was then added 10 mL EtOH followed by 250 mL of 5% NaOH. The organic phase was washed first with 150 mL 5% NaOH, followed by 2x100 mL portions of 5% dilute HCl. The removal of solvent and bulb-to-bulb distillation of the residue provided 2,3-

dimethoxythioanisole boiling at 72-80 °C at 0.4 mm/Hg as a white oil. This product contained some 20% unreacted veratrole as a contaminant and the isolation of subsequent products from this impure material was extraordinarily difficult. The effort needed for careful purification at this point was completely justified. The product could be obtained in a pure state by distillation at 0.1 mm/Hg through a 6 cm Vigreaux column with collection of several fractions. Those that distilled at 84-87 °C were pure 2,3-dimethoxythioanisole. An analytical sample can be obtained by cooling a concentrated MeOH solution in dry ice, filtering the generated crystals, and washing with cold MeOH. This product melts at 36.5-37 °C. Anal. ($C_9H_{12}O_2S$) C,H,S. The picrate can be formed by treatment with a saturated EtOH solution of picric acid. It formed orange crystals with a mp of 73-78 °C. Anal. ($C_{15}H_{15}N_3O_9S$) N.

To 18 mL of $POCl_3$ there was added 25 mL N-methylformanilide and the solution allowed to stand at room temperature for 0.5 h, until the color had developed to a rich claret. There was then added 25.0 g of 2,3-dimethoxythioanisole and the mixture heated on the steam bath for 2.5 h. This was added to 500 mL H_2O and stirred at ambient temperature for 2 h. The product was extracted with 4x150 mL CH_2Cl_2, the extracts combined, and the solvent removed under vacuum. The residue was distilled through a Vigreaux column under vacuum (0.1 mm/Hg) with the fraction boiling at 125-135 °C being richest in aldehydes, as determined by GC analysis. If the starting 2,3-dimethoxythioanisole contains appreciable veratrole as a contaminant, then this aldehyde fraction contains three components. There is present both 2,3-dimethoxy-4-(methylthio)benzaldehyde and 3,4-dimethoxy-2-(methylthio)benzaldehyde (the two desired precursors to 4-TIM and 2-TIM, respectively), but also present is 3,4-dimethoxybenzaldehyde from the veratrole contamination. The weight of this fraction was 11.9 g and was a white oil free of starting thioether.

Although efforts to separate this mixture were not effective, one of the aldehydes could be isolat small yield by derivative formation. This was too wasteful to be of preparat lue, but it did allow the generation of seed that was of great value in the later separation of the mixed nitrostyrenes that were prepared. If a 1 g portion of this mixture was fused with 0.6 g p-anisidiine over an open flame and then cooled, the melt set up as a solid. Triturating under MeOH gave a yellow solid (0.45 g, mp 77-80 °C) which on recrystallization from hexane appeared to be a single one of the three possible Schiff's bases that could theoretically be prepared. It had a mp of 80-81 °C. Anal. ($C_{17}H_{19}NO_3S$) C,H. Hydrolysis with hot 3 N HCl freed the benzaldehyde which was isolated by quenching in H_2O and extraction with CH_2Cl_2. The extracts were stripped of solvent under vacuum and the residue distilled bulb-to-bulb under vacuum to give white crystals of 3,4-dimethoxy-2-(methylthio)-benzaldehyde (the 2-TIM aldehyde) with a mp of 23-24 °C. A micro-scale conversion of this to the corresponding nitrostyrene provided the seed that was effectively used in the large scale preparation described below.

A solution of 9.0 g of a mixture of 3,4-dimethoxy-2-(methylthio)-benzaldehyde and 2,3-dimethoxy-4-(methylthio)benzaldehyde in 50 mL of nitromethane was treated with 1.5 g anhydrous ammonium acetate and held at reflux for 5 h. The excess nitromethane was removed under vacuum to yield 10.4 g of a dark orange oil which, upon dissolving in 40 mL hot MeOH and being allowed to cool and slowly evaporate at ambient temperatures, provided dark colored crystals. Filtration (save the mother liquors!) and recrystallization from 40 mL MeOH provided 6.3 g of a yellow crystalline solid. A second recrystallization from 50 mL MeOH gave 5.0 g of lemon yellow plates 3,4-dimethoxy-2-methylthio-ß-nitrostyrene with a mp of 102-103.5 °C. An analytical sample, from IPA, had a mp of 103-104 °C and a single spot on TLC with $CHCl_3$, with an Rf of 0.54. Anal. ($C_{11}H_{13}NO_4S$) C,H. When there had been veratrole left as a contaminant in the original 2,3-dimethoxythioanisole, the nitrostyrene that was isolated by this method had, after recrystallization, a mp of 93-95 °C. This substance acted as a single compound through a number of recrystallization trials, but on TLC analysis always gave two components (silica gel, chloroform) with Rf's of 0.54 and 0.47. It proved to be a mixture of 3,4-dimethoxy-2-methylthio-ß-nitrostyrene and 3,4-dimethoxy-ß-nitrostyrene in an exact molecular ratio of 2:1. This latter nitrostyrene is the precursor to DMPEA, q.v. Anal. ($C_{32}H_{37}N_3O_{12}S_2$) C,H. The mother liquor above is the source of the 4-TIM nitrostyrene, and its isolation is described in the recipe for 4-TIM.

A solution of 4.2 g LAH in 70 mL anhydrous THF was cooled to 0 °C under He and with stirring. There was added, dropwise, 2.8 mL of 100% H_2SO_4, followed by 4.4 g of 3,4-dimethoxy-2-(methylthio)-ß-nitrostyrene dissolved in 25 mL THF. Stirring was continued for a few min as the reaction returned to room temperature, and then it was heated to a reflux for 10 min on the steam bath. The reaction was cooled again, and 25% NaOH was added dropwise until a white granular precipitate was obtained. This was removed by filtration, and the filter cake was washed with 2x50 mL Et_2O. The filtrate was extracted into 100 mL dilute H_2SO_4 which was, in turn, made basic again and extracted with 2x100 mL CH_2Cl_2. The extracts were pooled, and the solvent removed under vacuum to give a residue of crude product. This was distilled from 100-115 °C at 0.3 mm/Hg yielding 3.2 g of a clear white oil. This was dissolved in 25 mL IPA, neutralized with 23 drops of concentrated HCl, and diluted with 75 mL anhydrous Et_2O. There was a deposition of beautiful white platelets of 3,4-dimethoxy-2-methylthiophenethylamine hydrochloride (2-TIM) which were removed by filtration, washed with ether, and air dried. This hydrochloride salt contained a quarter mole of H_2O of crystallization. The mp was 183-184 °C. Anal. ($C_{11}H_{18}ClNO_2S{\cdot}1/4\ H_2O$) C,H,N.

DOSAGE: greater than 240 mg.

DURATION: unknown.

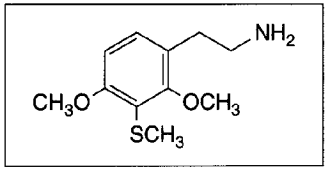
QUALITATIVE COMMENTS: (with 160 mg) "There was perhaps some awareness in an hour or so, but in another hour there was absolutely nothing. A small

amount of wine in the evening was quite intoxicating."
(with 240 mg) "No effects of any kind."

EXTENSIONS AND COMMENTARY: The problems that might be associated with the making of the three amphetamines that correspond to 2-TIM, 3-TIM and 4-TIM might very well prove quite exciting. These would be the three thio analogues of TMA-3; vis, 3,4-dimethoxy-2-methylthioamphetamine, 2,4-dimethoxy-3-methylthioamphetamine, and 2,3-dimethoxy-4-thioamphetamine. The first challenge would be to name them. Using the 2C-3C convention, they would be the 3C analogs of trivially named 2-carbon compounds, namely 3C-2-TIM, 3C-3-TIM and 3C-4-TIM. Using the thio convention (the number before the T is the position of the sulfur atom), they would be 2-T-TMA-3, 3-T-TMA-3 and 4-T-TMA-3. The second challenge would be their actual synthesis. The information gained from the separation of the 2-carbon nitrostyrenes and that most remarkable mixed-nitrostyrene thing that acted as a single pure material, would not be usable. But it is intriguing to speculate if there might be some parallel problems in the 3-carbon world. It seems almost certain that none of the compounds would be pharmacologically active, so the incentive would be the challenge of the chemistry. Some day, maybe.

#153 3-TIM; 3-THIOISOMESCALINE; 2,4-DIMETHOXY-3-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: A mixture of 3.1 g $POCl_3$ 2.8 g N-methylformanilide was heated on a steam bath until it was a deep claret color (about 5 min). To this there was then added 3.0 g of 2,6-dimethoxythioanisole (see under 4-TM for its preparation), and heating was continued for 30 min. The reaction mixture was then added to 75 mL H_2O and stirred overnight. The dark oily mixture was extracted with 3x75 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. The residue was extracted with 3x20 mL boiling hexane, each extract being poured off from the insoluble residue. Pooling and cooling these extracts yielded 1.5 g of 2,4-dimethoxy-3-(methylthio)-benzaldehyde as an off-white crystalline solid with a mp of 67-69 °C. Recrystallization from either MeOH or cyclohexane tightened the mp, but lowered it to 67-68 °C and 66-67 °C, resp. Anal. ($C_{10}H_{12}O_3S$) C,H.



To a solution of 1.3 g 2,4-dimethoxy-3-(methylthio)benzaldehyde in 60 mL nitromethane there was added 0.3 g anhydrous ammonium acetate and the mixture was heated at reflux for 3 h. The hot solution was decanted from a little insoluble material, and the excess nitromethane was removed under vacuum. The residue dissolved in 10 mL hot MeOH. On cooling, yellow crystals of 2,4-dimethoxy-3-methylthio-ß-nitrostyrene were obtained which were removed by filtration and air-dried, and weighed 0.9 g. The mp was 130-133 °C and could be improved to 136-137 °C following recrystallization from MeOH (10 g/g). Anal. ($C_{11}H_{13}NO_4S$) C,H.

A well-stirred solution of 0.6 g LAH in 10 mL anhydrous THF was cooled to 0 °C under He. There was added, dropwise, 0.4 mL of 100% H_2SO_4, followed by 0.6 g of 2,4-dimethoxy-3-methylthio-ß-nitrostyrene dissolved in a little THF. Stirring was continued for a few min as the reaction returned to room temperature, and then it was heated to a reflux for 5 min on the steam bath. The reaction was cooled again, and 25% NaOH was added dropwise until a white granular precipitate was obtained. This was removed by filtration, and the filter cake was washed with 2x25 mL Et_2O. The filtrate was extracted into 25 mL dilute H_2SO_4 which was, in turn, made basic again and extracted with 2x25 mL CH_2Cl_2. The extracts were pooled, and the solvent removed under vacuum to give a residue of crude product. This was distilled from 120-140 °C at 0.3 mm/Hg yielding 0.25 g of a clear white oil. This was dissolved in 5 mL IPA, neutralized with about 3 drops of concentrated HCl, and diluted with 15 mL anhydrous Et_2O. Scratching with a glass rod instigated crystallization of bright white solids which were filtered, washed with Et_2O, and air dried. The weight of 2,4-dimethoxy-3-methylthiophenethylamine hydrochloride (3-TIM) was 0.2 g and the mp was 204-206 °C with decomposition. This hydrochloride appeared to be a hemihydrate. Anal. ($C_{11}H_{18}ClNO_2S \cdot 1/2\,H_2O$) C,H,N.

DOSAGE: greater than 240 mg.

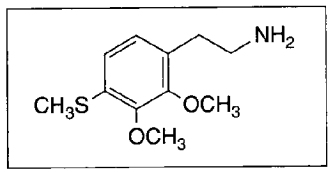
DURATION: unknown.

QUALITATIVE COMMENTS: (with 240 mg) "Briefly I thought that there might have been an alert at the 2 to 3 hour point, but I now think it was nothing. During the following day I had a mild stomach upset off and on, but I can't believe that it was connected with 3-TIM."

EXTENSIONS AND COMMENTARY: Isomescaline itself is not active, but there is no way of knowing just how "non-active" it really is. If it were to be active just beyond the levels assayed, then the introduction of a sulfur into the molecule in place of an oxygen could have increased the potency to where it might have some effect. The absence of any activity from this TIM, and the other two TIMs, might well suggest that isomescaline is really very "non-active," if that makes sense!

#154 4-TIM; 4-THIOISOMESCALINE; 2,3-DIMETHOXY-4-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: The mother liquors from the initial crystallization of the 2-TIM nitrostyrene (see under 2-TIM) was the source and raw material for all 4-TIM chemistry. Once the bulk of the 2-TIM nitrostyrene has been removed, these mother liquors could be processed to give the 4-TIM nitrostyrene. The easier procedure was to evaporate these mother liquors to a residue under vacuum, and hope for a spontaneous crystallization. If this failed, flash chromatography could be used. For reference purposes, the three nitrostyrenes involved in the 2-TIM/4-TIM problem movedon silica gel TLC with $CHCl_3$ solvent in the following manner: 2,3-dimethoxy-4-methylthio-ß-nitrostyrene (leading to 4-TIM), Rf = 0.61; 3,4-dimethoxy-2-methylthio-ß-nitrostyrene (leading to 2-TIM), Rf = 0.54; and 3,4-dimethoxy-ß-nitrostyrene (leading to DMPEA), Rf = 0.47. For flash chromatography, a small portion of the residue from the mother liquor was dissolved in $CHCl_3$, and placed on a silica gel column. $CHCl_3$ was used as the eluding solvent. The first material breaking through from the column was the 4-TIM nitrostyrene and on evaporation of this fraction, seed was obtained as gold-colored crystals that had a mp of 71-73 °C. This, when added to the residues from the described 2-TIM synthesis nitrostyrenes, started the crystallization process. The gummy solid that was produced was triturated under MeOH, and the crystals so revealed were removed by filtration. Recrystallization from 10 mL MeOH gave 1.9 g of solids. A second recrystallization from 5 mL MeOH provided 0.7 g of pumpkin-colored crystals of 2,3-dimethoxy-4-methylthio-ß-nitrostyrene with a mp of 70-71 °C.



A solution of 1.2 g LAH in 20 mL anhydrous THF was cooled to 0 °C under He and stirred. There was added, dropwise, 0.8 mL of 100% H_2SO_4, followed by 0.9 g of 2,3-dimethoxy-4-methylthio-ß-nitrostyrene dissolved in 20 mL THF. Stirring was continued for a few min as the reaction returned to room temperature, and then it was heated to a reflux for 5 min on the steam bath. The reaction was cooled again, EtOAc was added to destroy the excess hydride, followed by 25% NaOH added dropwise until a white granular precipitate was obtained. This was removed by filtration, and the filter cake was washed with 2x35 mL Et_2O. The filtrate was extracted into 50 mL dilute H_2SO_4 which was washed with Et_2O and, in turn, made basic again and extracted with 2x50 mL CH_2Cl_2. The extracts were pooled, and the solvent removed under vacuum to give a residue of crude product. This distilled cleanly from 100-115 °C at 0.3 mm/Hg yielding 0.45 g of a clear white oil. This was dissolved in 6 mL IPA, neutralized with 5 drops of concentrated HCl, and diluted with 25 mL anhydrous Et_2O. There was a deposition of white solids which were removed by filtration, washed with Et_2O, and air dried. The 2,3-dimethoxy-4-methylthiophenethylamine hydrochloride so obtained (4-TIM) weighed 0.3 g and contained a molecule of H_2O of crystallization. The mp was 212-213 °C. Anal. ($C_{11}H_{18}ClNO_2S{\cdot}H_2O$) C,H,N.

DOSAGE: greater than 160 mg.

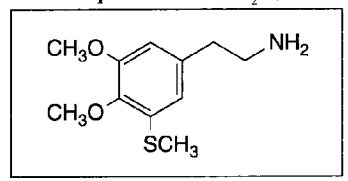
DURATION: unknown.

QUALITATIVE COMMENTS: (with 160 mg) "Everything seemed normal. Pulse was under 80, there was nothing with eyes-closed, my appetite was normal. The compound was completely inactive."

EXTENSIONS AND COMMENTARY: There has been much noise made about the effectiveness of an unusual substitution group at the 4-position of the phenethylamine molecule. Here is a methylthio group at this position, and it is an inactive compound. I was just a little bit surprised.

#155 3-TM; 3-THIOMESCALINE; 3,4-DIMETHOXY-5-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: To an ice cold and well stirred solution of 15 g vanillin and 20 g sodium thiocyanate in 150 mL acetic acid there was added, dropwise over the course of 15 min, a solution of 16 g elemental bromine in 40 mL acetic acid. This was followed by the addition of 30 mL of 5% HCl and 300 mL EtOH, and stirring was continued for an additional 30 min. The mixture was heated to its boiling point, and filtered while hot. The mother liquor was diluted with an equal volume of H_2O, which initiated the crystallization of crude 5-formyl-7-methoxy-2-oxo-1,3-benzoxathiole as a flocculant yellow solid. On filtration and air-drying, this weighed 12.5 g. After recrystallization from EtOH, the product was white and had a mp of 164 °C sharp.



A suspension of 12.5 g of crude 5-formyl-7-methoxy-2-oxo-1,3-benzoxathiole in 100 mL MeOH containing 28.4 g methyl iodide was treated with a solution of 12 g NaOH in 100 mL warm MeOH. The mixture was held at reflux for 1 h and then the solvents were removed under vacuum. A solution of 14.2 g methyl iodide in 100 mL DMSO was added and the mixture stirred for 1 h. An additional 2.4 g of NaOH and 16 g methyl iodide were added, and the stirring was continued for another 2 h. The reaction mixture was poured into 800 mL H_2O, acidified with HCl, and extracted with 3x75 mL CH_2Cl_2. The pooled extracts were washed with 5% NaOH, then water, and the solvent removed under vacuum. Distillation at 110-130 °C at 0.4 mm/Hg gave 0.9 g 3,4-dimethoxy-5-(methylthio)benzaldehyde

which had a mp of 57-58 °C after crystallization from EtOH. Anal. ($C_{10}H_{12}O_3S$) C,H.

A solution of 0.9 g 3,4-dimethoxy-5-(methylthio)benzaldehyde in 100 mL nitromethane containing 0.5 g anhydrous ammonium acetate was held at reflux for 4 h. The excess nitromethane was removed under vacuum, and the deep brown residue was dissolved in 4 mL hot MeOH. On cooling, the yellow crystals were removed by filtration, washed with cold MeOH and air dried yielding 0.4 g yellow crystals of 3,4-dimethoxy-5-methoxy-ß-nitrostyrene, with a mp of 119.5-120.5 °C after recrystallization from EtOH. Anal. ($C_{11}H_{13}NO_4S$) C,H.

To a solution of 1.0 g LAH in 25 mL anhydrous THF under He, cooled to 0 °C and vigorously stirred, there was added, dropwise, 0.7 mL of 100% H_2SO_4, followed by a solution of 0.7 g 3,4-dimethoxy-5-methylthio-ß-nitrostyrene in 10 mL anhydrous THF. The mixture was brought briefly to a reflux, cooled again, and the excess hydride destroyed with H_2O in THF, followed by the dropwise addition of 15% NaOH until the solids became white and granular. The solids were removed by filtration, the filter cake washed with THF, the mother liquor and filtrates combined, diluted with an equal volume of Et_2O, and extracted with 2x40 mL dilute H_2SO_4. The aqueous extracts were combined, washed with Et_2O, made basic with aqueous NaOH, and extracted with 2x50 mL CH_2Cl_2. The solvent was removed from these extracts and the residue distilled to provide 0.4 g of a white oil boiling at 124-130 °C at 0.2 mm/Hg. This oil was dissolved in 8 mL IPA, neutralized with concentrated HCl, and diluted with 30 mL anhydrous Et_2O. The white crystalline product was the monohydrate of 3,4-dimethoxy-5-methylthiophenethylamine hydrochloride (3-TM) which melted at 167-168 °C and weighed 0.29 g. Anal. ($C_{11}H_{18}ClNO_2S{\cdot}H_2O$) C,H,N.

DOSAGE: 60 - 100 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 80 mg) "I went into the experience with the question of whether it (3-TM) might be a writing aid. I found a considerable color enhancement (this was at the one hour point) and there seems to be no problem in writing physical words. But there is no urge to, as there are no new things. This is progressing into something more complex and there is an interesting shielding effect. I still have the desire to write and I sense that many things are going on underneath, but my conscious control suppresses their availability. It is now the third hour. Music. I would like to try this material at 100 milligrams. Now awareness seems much more pointed. I have need to build a writing table. This material is physically relaxing, insisting repose, but with conflicting energy. Seated in a chair, but I seem unable to find a comfortable position in order to write.

"Pine trees seem a good place
To start. Notwithstanding this table

Of pine, unfinished, unruled,
The pulp upon which we reveal
The unnerved thoughts.
How casual we are at discarding
Our feelings, a rubble we
Leave behind for the living.
Who among us can absorb
The spiritual load we see as
What others carry.

"This material is not poetic, I should say, does not enhance poetry, prose is much more comfortable. I think I should let the experience develop further. It is now the fifth hour. There is something of a violence (emotional) suppressed in all of us, a socially repressed vision of oneself in a direct conflict with oneself. The music has a lot to do with this material. And it changes with time. In the first part there is sublimity, peacefulness, mild intoxication. And a lot more tension in the part that followed the four hour point. There the territories seem much better defined, with the benign shielding of the first half largely dissipated. I have developed a slightly irritated view of myself, probably wanting once again to regain the serenity."

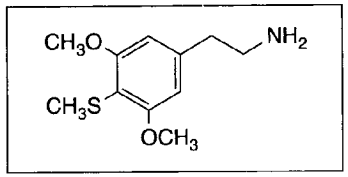
(with 80 mg) "Delightful day. Not insight depth but persistent feeling of pleasant good humor. It is good-natured and very verbal. Everyone talked and the instinct was to express and comment on everything. There were no visuals during the first three to four hours — with the eyes open one could barely detect the intoxication. Eyes closed — quiet lovely window, no images. About +2. And then someone brought in a radio with music on, into the room. There was a tremendous eruption of closed-eyes visual images and fantasy. Bright colors, funny, rich and elaborate. Marvelous. I was suddenly at +3. Next day, no hangover. Pleasant feeling persisted."

(with 100 mg) "I found the day had two halves. The first few hours were characterized by occasional defensiveness (paranoia) and irritability. In interpersonal interactions there was a guardedness, due to a feeling of vulnerability. I went off by myself, and with eyes closed, there was rich imagery and color synthesis to musical imput. And then things smoothed out, and I could express an easy flow of ideas and concepts without always watching my step. And then all too soon, the intensity of the experience began fading away."

EXTENSIONS AND COMMENTARY: The amphetamine which would correspond with this base would be 3,4-dimethoxy-5-methylthioamphetamine (3-T-TMA) and should be an active compound. Its synthesis should be straightforward from the benzaldehyde described above, employing nitroethane rather than nitromethane. It is apparently an unknown compound.

#156 TM; 4-TM; 4-THIOMESCALINE; 3,5-DIMETHOXY-4-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution of 24.2 g N,N,N',N'-tetramethylethylenediamine and 27.6 g of 1,3-dimethoxybenzene was dissolved in 400 mL anhydrous hexane. This was stirred vigorously under a N_2 atmosphere and cooled to 0 °C with an external ice bath. There was added 125 mL of 2.0 M butyllithium in hexane. The stirred reaction mixture became yellow and sludgy, and was briefly warmed back to room temperature to allow easy stirring. After cooling again to 0 °C, there was added 18.8 g of dimethyl disulfide which converted the viscous yellow phase to a loose white solid. Stirring was continued while the reaction mixture was brought up to room temperature, and then all was added to 2 L of dilute H_2SO_4. There was the immediate formation of a white cystalline solid which was removed by filtration, sucked relatively free of water, and recrystallized from 50 mL of boiling MeOH. There was thus obtained 18.9 g of 2,6-dimethoxythioanisole as white crystals with a mp of 81-82 °C. Extraction of the aqueous filtrate with 2x50 mL CH_2Cl_2 and removal of the solvent under vacuum gave a residue which, when combined with the mother liquors from the MeOH crystallization, afforded an additional 3.3 g product with a mp 77-79 °C.



To a stirred solution of 18.9 g of 2,6-dimethoxythioanisole in 200 mL CH_2Cl_2 there was added 16 g elemental bromine dissolved in 75 mL CH_2Cl_2. The initial dark red color gradually faded to a pale yellow color and there was a copious evolution of HBr. The solvent was removed under vacuum leaving 27.5 g of a pale yellow residual oil. This was distilled at 118-121 °C at 0.25 mm/Hg to yield 3-bromo-2,6-dimethoxythioanisole as a white oil weighing 25.3 g. Crystallization from hexane provided white crystals with a mp of 30-30.5 °C. Anal. ($C_9H_{11}BrO_2S$) C,H.

To a solution of 19.3 g diisopropylamine in 150 mL anhydrous THF that was stirred under a N_2 atmosphere and cooled to -10 °C with an external ice/MeOH bath, there was added in sequence 83 mL of 1.6 M butyllithium in hexane, 4.4 mL of dry CH_3CN, and 11.6 g of 3-bromo-2,6-dimethoxythioanisole (which had been dissolved in a little anhydrous THF). The turbid reaction mixture gradually developed color, initially yellow and progressively becoming orange and finally a deep red brown. Stirring was maintained for a total of 20 min, and then the reaction mixture was poured into 1 L H_2O that containing 10 mL concentrated H_2SO_4. This was extracted with 3x75 mL CH_2Cl_2, these extracts pooled, washed with dilute H_2SO_4 followed by saturated brine, and the solvent was removed under vacuum yielding 8.7 g of a viscous oil as a residue. This was distilled at 0.11 mm/Hg yielded two fractions. The first boiled at 115-125 °C and weighed 3.8 g. This material set to an oily crystalline mass which was filtered, washed with cold MeOH and then recrystallized from MeOH. The white solids had a mp of 60-63 °C and were not the desired product. This material has not yet been identified. The second fraction came over at 150-180 °C, weighed 1.8 g and spontaneously crystallized. It was triturated under cold MeOH and filtered yielding, after air drying, 1.1 g 3,5-dimethoxy-4-methylthiophenylacetonitrile, which had a mp of 95-96.5 °C. Anal. ($C_{11}H_{13}NO_2S$) C,H.

A suspension of 1.0 g LAH in 40 mL anhydrous THF under N_2 was cooled to 0 °C and vigorously stirred. There was added, dropwise, 0.7 mL 100% H_2SO_4, followed by 1.2 g 3,5-dimethoxy-4-methylthiophenylacetonitrile in 10 mL anhydrous THF. The reaction mixture was stirred at 0 °C for a few min, then brought to room temperature for 1 h, and finally to a reflux for 30 min on the steam bath. After cooling to room temperature, there was added 1 mL H_2O in 5 mL THF to destroy the excess hydride, followed by 3 mL of 15% NaOH to bring the reaction to a basic pH, and finally 2 mL H_2O which converted the aluminum oxide to a loose, white, filterable consistency. This was removed by filtration, and washed with THF. The filtrate and washes were stripped of solvent under vacuum, the residue was dissolved in 200 mL CH_2Cl_2, and this was extracted with 3x100 mL diute H_2SO_4. These extracts were pooled, washed with CH_2Cl_2, made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. After combining, the solvent was removed under vacuum providing 1.2 g of a colorless oil as a residue. This was distilled at 122-132 °C at 0.05 mm/Hg to give a colorless oil. This was dissolved in 8 mL of IPA, neutralized with concentrated HCl and, with continuous stirring, diluted with 100 mL anhydrous Et_2O. The product was removed by filtration, washed with Et_2O, and air dried to give 0.95 g. 3,5-dimethoxy-4-methylthiophenethylamine hydrochloride (4-TM) as spectacular white crystals with a mp of 193-194 °C. Anal. ($C_{11}H_{18}ClNO_2S$) C,H.

DOSAGE: 20 - 40 mg.

DURATION: 10 - 15 h.

QUANTITATIVE COMMENTS: (with 25 mg) "I was first aware of any effects as I was sitting in back of the house on a big fluffy pillow. The sun was warm and the grass tall and green, but I felt strange inside. There was distinct uterine cramping, and I could not find a comfortable position for sitting. The others had gone out to the garden leaving me here. It seemed that walking might relieve the physical discomfort, so I went to find them. Walking was easy, but I was a little light-headed and I had to watch my steps with care. They were not there (we had passed on opposite sides of the house) and I returned in some haste to my warm nest behind the house to find my pillow gone. A strange detail, but it perhaps gave me the flavor for my day. The pillow was for me. It was gone. My place was gone. Therefore I am gone. I am dead and yet I can see and think. The small touch of panic at finding myself dead dispelled any internal concerns and I ran inside to find the others; they had brought my pillow in. I was alive again, but the entire day balanced

between the alive unreality and the illusion that I was something removed and merely watching the surrounding alive unreality. Everything that happened was completely unlikely.

"Like the soup scene. We decided that some hot soup would be welcome, and so R. brought out three cans of Campbell soup for the three of us. But one was cream mushroom, one asparagus, and one tomato. The discussion as to how to use two cans only, which two, without mixing, and even how to decide to decide was totally beyond any of us. The situation was hopelessly unresolvable, hilariously funny, and distinctly schizophrenic.

"Or like the kite scene. We were returning from a short walk to the back of the property, and I spotted a red thing in the parking area. It had not been there before. None of us could identify it from this distance, and we speculated wildly as to what it was, as we came closer. And at the last approach, we found that there was loose string everywhere about the driveway, all part of a downed kite. The red object had apparently fallen from the sky, right here in front of the garage. There had been no sounds of voices of kite-flyers, and there was no one to be seen in any direction. And then one of us spotted a sheet of paper, torn to the center where there was a small hole, and it was flattened up against the kite. There was a message. Apparently whoever had been flying it had put a message on the string, and let the wind take it up to the kite itself. I reached for the sheet of paper, and removed it. Nothing on either side. The message was that there was no message. Exactly out of Marshall McLuhan. Completely appropriate for this particular day.

"That evening we were to be picked up by my friends for dinner. Choosing what to wear, how to dress myself, how to adjust my persona to fit other people, all this was chaotic. Somehow the dinner succeeded, but I was able to flip in and out of the immediate company easily, but not completely voluntarily. Sleep was comfortable that night, and I feel that the entire day had been very intense, not too much fun, but somehow quite rewarding."

(with 30 mg) "At the one and a half hour point, I was reminded more than anything of LSD, with a distinct feeling of standing just a few feet to the right of ordinary reality. There has been a mild tremor ever since the first effects were evident, but it doesn't bother me except to make my handwriting uncertain. I would not want to double this level. Suddenly the concept of my 5:30's swept over me. I had a penetrating view of myself as a person who had become invested in a pattern of behavior that I had succumbed to, to come home and complete my day with a transition from the work-world to the home-world, by changing the inside clock at 5:30. My wife had been my 5:30 for nearly 30 years and this had been my tacit agreement with her. Never questioned, never challenged, and certainly never violated. And with her death, I have found myself imposing this same 5:30-ness on myself, as some form of an emasculating pattern that is comfortable and stable. No, it is not comfortable, it is simply the course of the least thought and the least disruption. If I were to meet someone else, would I have such a negative image of myself that I would expect her to become my 5:30 so as not to have to disrupt these

tired and comfortable patterns? That would be completely unfair to this other person. And I can see where it is completely destructive to me. No new person should ever have to play my wife's old role. I need never again play my old role. And I won't."

(with 30 mg) "At 2:20 PM I ingested 30 mg of TM. It had a mildly alkaloid taste. Since the afternoon was warm, I took a two mile walk with the dog, and with my two companions K.T. and T.T., both also with 30 mg. We talked without any difficulty even after the onset of the first signs of effect. The major emotional and physical effects came on very gradually and quite pleasantly as we sat in the patio. But soon we all grew chilled, and put on more clothing. Nothing really helped the inward chill, and we were to discover that it stayed with us throughout the experience. At 3:30 we went inside where the room temperature was set at 70 degrees, and we all lay down. I launched into an engrossing, somewhat chaotic and erotic reverie, that followed no linear progression, but which lasted perhaps an hour. The ease of talking surprised me; the content was cogent and I felt myself to be articulate. It dawned on me after about two hours had gone by, that the height of the experiment had already passed without any real exhilaration on my part. But my companions suggested that my expectations from the past had been misleading me and, as time went on, they proved to be correct. The clarity and the continued ability to talk, especially with K.T. on a personally difficult topic, were for me the particular genius of this material. When I went inward, which I could do without effort, the sensations were neutral in affect but restful in some way. But coming out was entirely lucid and pleasant. I soon found that I preferred this. I enjoyed a light supper at 8:30 and found the dropoff gentle, and the conversation most amiable until we separated at 1:00 AM. Sleep did not come until 3:00 AM and then only after 10 mg Librium to quell the active mental processes. The next day I awoke around 8:30 AM feeling languid but cheerful."

(with 40 mg) "For quite a while there was some physical concern. Not actual nausea but a generalized uneasiness, with a distinct body tremor. There was little urine produced (500 mL in 18 hours), and I felt the need to search out fluids. There was mild intestinal cramping. I found that my thoughts were able to go in several directions at once, but since they stayed nowhere long enough to structure anything, this was more annoying than constructive. I saw this as a reality shell about me like a Möbius strip, continuous, yet with no consistent side being presented. I was reminded of a similar place with DOB, some few years ago. While lying down with eyes closed, I found the imagery to be very impressive, but my thought processes were quite convoluted and disjointed. Some were most interesting, and some were ugly. I cannot see this as a party drug."

EXTENSIONS AND COMMENTARY: The dosage range has been broadened to include the 20 milligram level, in that several subjects found that even with that small amount there was difficulty in walking and in keeping one's equilibrium. Walking was described as a floating procedure, and one could tilt to one side or the

other if care was not taken. Anorexia was occasionally noted, and most people commented on some degree of anesthesia to touch.

All in all, this drug evoked a mixed bag of responses. The most startling and unexpected property was the dramatic increase in potency over the parent prototype, mescaline. The substitution of a sulfur atom for an oxygen atom increased the power of the drug some ten-fold, without any apparent decrease in complexity of action. As there were many materials that were outgrowths of mescaline with the studies of ethyl this and diethyl that, each and all of these would be interesting candidates for synthesis with this or that oxygen atom replaced with sulfur. Most of these have been made, and many of them have proven to be interesting.

What is meaning of the phrase, "sulfur-for-oxygen replacement?" Let me try to explain it for non-chemists.

One of the most exciting bits of architecture in science is the Periodic Table. The principles of electrons and orbitals and different counts of protons in a nucleus gets to be a complex story to try to explain the grid-like structure of the arrangements of atoms. It is easier to simply give the music. And this melody goes: As you look across a row, elements are simple in their binding arrangements on the left, become more complex towards the center where they kind of change polarity, and then get progressively simple again but with the opposite charge as you approach the right-hand side.

And when you look at a column from top to bottom, the bonding complexity stays pretty much the same but the atom gets more and more massive as you go down the column.

The combinations of atoms from the Periodic Table, by and large, is the province of the inorganic chemist. Take one of this, and two of that, and the combination is called a salt, or a complex, or an adduct, and probably has interesting colors, and may even be found in nature as part of a rock somewhere, or coming out of the vent of a volcano.

But if one were to look at just four elements, three in the middle right of the first row, namely carbon, nitrogen and oxygen, and the one up there at the top and the lightest of all, hydrogen, you would find quite a different story. These can be combined in an infinity of ways since there can be dozens of atoms hooked to one-another; this is the territory of the organic chemist, and this is the chemistry of life. With a few exceptions, every molecule within the body, and the food that maintains the body, and the drugs that affect the body, are made up of a bunch of carbons, and an occasional oxygen or two, usually a nitrogen somewhere, and all the remaining loose ends satisfied with hydrogen atoms.

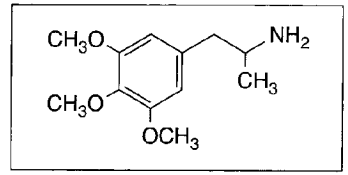
Almost every drug that is to be found in this book is nothing more than a different arrangement of atoms of these four elements.

This compound, thiomescaline, is a byway that takes advantage of one of those vertical columns. Directly below the element oxygen, there is found sulfur, which has much the same binding complexity, but is twice as massive. The

prototype of all the phenethylamine drugs being discussed in this book is mescaline, a very simple compound containing these basic four elements of life and pharmacology; it contains eleven carbon atoms, three oxygen atoms, one nitrogen atom, and there are a total of seventeen hydrogen atoms required to balance the books. One of the oxygen atoms holds a central position, and the other two are reflections of one another and cannot be distinguished chemically. The structure of thiomescaline is generated by plucking out that central oxygen atom of mescaline, and putting a sulfur atom back in its place. The definition of the term "thio" is quite simple — it means a sulfur-in-place-of-an-oxygen, with everything else left alone. It is a little awe-inspiring to think that every oxy anything can have a thio something as a spatially similar analogue. And there are a lot of oxy things in the body and in the medicine cabinet. A number of them are discussed in this book.

#157 TMA; 3,4,5-TRIMETHOXYAMPHETAMINE

SYNTHESIS: To a solution of 39.2 g 3,4,5-trimethoxybenzaldehyde in 30 mL warm EtOH there was added 15.7 g nitroethane followed by 1.5 mL n-butylamine. The reaction mixture was allowed to stand at 40 °C for 7 days. With cooling and scratching, fine yellow needles were obtained which, after removal by filtration and air drying, weighed 48 g. Recrystallization from EtOH gave 2-nitro-1-(3,4,5-trimethoxyphenyl)propene as yellow crystals with a mp of 94-95 °C. Anal. ($C_{12}H_{15}NO_5$) C,H,N. Alternatively, a solution of 20 g of the aldehyde in 75 mL nitroethane was treated with 4 g anhydrous ammonium acetate and heated on the steam bath until a deep red color had been generated. Removal of the excess solvent/reagent under vacuum gave a red oil which was dissolved in an equal volume of boiling MeOH. On cooling, yellow crystals of the nitropropene separated. Recrystallization from MeOH gave, after air drying to constant weight, 13.0 g with the same mp.



Under an inert atmosphere, 38 g LAH was wetted with 100 mL anhydrous Et_2O, and then suspended in 1 L dry THF. This was brought up to a gentle reflux, and there was added, slowly, a solution of 43.7 g 2-nitro-1-(3,4,5-trimethoxyphenyl)propene in 160 mL THF. Refluxing was continued for 36 h, and then the reaction mixture was cooled with an external ice bath. The excess hydride was destroyed by the cautious addition of 38 mL H_2O, and this was followed by 38 mL 15% NaOH, and finally another 114 mL H_2O. The inorganic salts which should have ended up as a loose, granular, easily filterable mass, looked rather like library paste, but they were filtered nonetheless. Washing with THF was attempted, but it was not efficient. The combined filtrate and washes were stripped of solvent under vacuum giving 31.5 g of the crude base as an amber oil. This was dissolved in 140

mL IPA, neutralized with concentrated HCl (15 mL was required), and diluted with 650 mL anhydrous Et_2O. There was an initial oily phase which on continued stirring changed to pale pink solids. These were finely ground under CH_3CN to give 15.2 g of 3,4,5-trimethoxyamphetamine hydrochloride (TMA) as white crystals that melted at 195-211 °C. All aluminum salts from everywhere were dissolved in dilute HCl, and 1 Kg of potassium sodium tartrate was added. There as added 25% NaOH allowed the pH to bring the pH to >9 without the precipitation of basic alumina. Extraction of this phase with CH_2Cl_2 was followed by removal of the solvent and salt formation as described above, allowed the isolation of an additional 6.4 g TMA. The product prepared in this manner contains some 10-15% 3,5-dimethoxy-4-hydroxy-amphetamine as an impurity. A solution of 20 g of the TMA made in this manner in 200 mL 5% NaOH was extracted with 2x200 mL CH_2Cl_2. The pooled extracts were washed with 4x100 mL 5% NaOH, and the aqueous washes were pooled with the original base phase. The organic phase was stripped of its CH_2Cl_2 under vacuum to give an oil that was dissolved in 40 mL IPA, neutralized with concentrated HCl, and diluted with 400 mL anhydrous Et_2O. There was the immediate formation of spectacular white crystals of pure 3,4,5-trimethoxyamphetamine hydrochloride, weighing 15.4 g and having a mp of 220-221 °C. The aqueous phase was brought to neutrality, treated with 10 g potassium di-hydrogen phosphate, brought to pH 9.0 with the careful addition of NaOH, and extracted with 5x100 mL CH_2Cl_2. Evaporation of the solvent under vacuum gave an oil that spontaneously crystallized. This product, 3,5-dimethoxy-4-hydroxyamphetamine could be further purified by sublimation at 130 °C at 0.2 mm/Hg. It was a white crystalline solid that slowly discolored in the air. The literature describes a picrate salt with a mp of 225 °C from EtOH.

DOSAGE: 100 - 250 mg.

DURATION: 6 - 8 h.

QUALITATIVE COMMENTS: (with 135 mg) "I had no nausea, although I always vomit with mescaline. Somehow my personality was divided and exposed, and this allowed me to understand my psychic structure more clearly. But maybe others could look in there, too. The psychiatric use of this drug would be interesting to pursue. It is not completely pleasant, maybe because of this personal intimacy."

(with 140 mg) "There were not the color changes of mescaline there, but certainly a good humor and an over-appreciation of jokes. The images behind the eyes were remarkable and tied in with the music, and I became annoyed at other people's conversations that got in the way. I was out of it in eight hours. I would equate this to 300 or 350 milligrams of mescaline and I rather think that I would prefer the latter."

(with 225 mg) "There was quite a bit of nausea in the first hour. Then I found myself becoming emotionally quite volatile, sometimes gentle and peaceful, sometimes irritable and pugnacious. It was a day to be connected in one way or another with music. I was reading Bernstein's 'Joy of Music' and every phrase was audible to me. On the radio, Rachmaninoff's 2nd piano concerto on the radio put me in an eyes-closed foetal position and I was totally involved with the structure of the music. I was suspended, inverted, held by fine filigreed strands of the music which had been woven from the arpeggios and knotted with the chords. The commercials that followed were irritating, and the next piece, Slaughter on Fifth Avenue, made me quite violent. I was told that I had a, 'Don't cross me if you know what is good for you,' look to me. I easily crushed a rose, although it had been a thing of beauty."

EXTENSIONS AND COMMENTARY: TMA was the very first totally synthetic psychedelic phenethylamine that was found to be active in man, for which there had been any attempt to describe such drug effects in any detail. This was the report of research done in Canada, and it appeared in 1955, six years before my own report on the material. There was an earlier report on TMPEA which is mentioned in the appropriate recipe, but there were few details given. Also there had been interest in reports that adrenalin that had become old and discolored seemed to elicit central effects in man. The oxidation products were identified as the deeply colored indolic compound adrenochrome and the colorless analogue adrenolutin. The controversy that these reports created just sort of died away, and the adrenochrome family has never been accepted as being psychedelic. No one in the scientific community today is looking in and about the area, and at present this is considered as an interesting historical footnote. But, in any case, they are not phenethylamines and so not part of this book.

The Canadian studies with TMA involved the use of a stroboscope as a tool for the induction of visual phenomena. These experiments used levels in the 50-150 milligram range, and generally employed pre-treatment with Dramamine for the successful prevention of nausea. There was reported giddiness and light-headedness, and some remarkable flash-induced visualizations. With higher levels, the visual syntheses are present without external stimulation. But there is a thread of negativity that seems to pervade the experience at these higher levels, and the appearance of a publication that emphasized the possible antisocial nature to TMA seemed to discourage further medical exploration. Military interest was maintained however, apparently, as TMA became a part of the chemical warfare studies where it was referred to with the code name EA-1319. It had been used in human trials with psychiatric patients, but no details of these experiments have been published.

The presence of a potentially active impurity in TMA deserves some comment. In the Canadian work, the material used was described as melting at 219-220 °C, which is the property given for the impurity-free material above. If this was the actual material used in those studies, this impurity (3,5-dimethoxy-4-hydroxy-amphetamine) was probably not present. The Army studies use a material of unreported melting point. In my own studies, the lower melting product was used.

had been broadly used years ago in medicine, called green, or liquid apiol (without the final "e"). It comes from the seeds of parsley by ether extraction, and when the chlorophyll has been removed, it is known as yellow apiol. With the fats removed by saponification and distillation, the old term for the medicine was apiolin. I would assume that any of these would give rise to white, crystalline apiole on careful distillation, but I have never tried to do it. The commercial Oil of Parsley is so readily available.

(9) The 2,3-dimethoxy-4,5-methylenedioxy pattern. The second of the three tetraoxygenated essential oils is 1-allyl-2,3-dimethoxy-4,5-methylenedioxybenzene, commonly called dillapiole and it comes, not surprisingly, from the oils of any of the several dill plants around the world. It is a thick, almost colorless liquid, but its isomerization product, isodillapiole, is a white crystalline product which melts sharply. This, by the theoretical addition of ammonia, gives DMMDA-2.

(10) The tetramethoxy pattern. The third and last of the tetra-oxygenated essential oils, is 1-allyl-2,3,4,5-tetramethoxybenzene. This is present as a minor component in the oil of parsley, but it is much more easily obtained by synthesis. It, and its iso-compound, and the amination product, are discussed under the last of theTen Essential Amphetamines, TA.

One must remember that the term "essential" has nothing to do with the meaning of needed, or required. The word's origin is essence, something with an odor or smell. Thus, the essenti are those oils that have a fragrance, and the Essential Amphetamines are those compounds that can, in principle, be made from them by the addition of ammonia in the body.

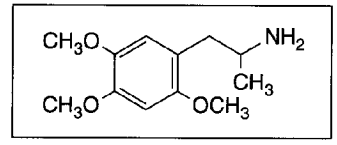
There were a few interesting experimental trials that were based on these natural oils. Methoxyeugenol was assayed up to a 10 milligram level, and asarone at up to a 70 milligram level, and neither had any effects at all. And, in an attempt to challenge the "oil-to-amphetamine" concept, I made up a mixture of 1 part MDA, 2 parts TMA and 5 parts MMDA. A total of 100 milligrams of this combination (which I had named the "Pseunut Cocktail" for pseudo-nutmeg) should be equivalent to the safrole, elemicin and myristicin that would be in 5 grams of nutmeg. And 100 milligrams indeed produced quite a sparkle and considerable eye-dilation. But then, I have never taken 5 grams of nutmeg, so I cannot make any comparisons.

#158 TMA-2; 2,4,5-TRIMETHOXYAMPHETAMINE

SYNTHESIS: To a solution of 50 g 2,4,5-trimethoxybenzaldehyde in 175 mL nitroethane there was added 10 g anhydrous ammonium acetate and the mixture was heated on the steam bath for 2 h. The excess nitroethane was removed under vacuum, and the deep orange oily residue was drained out into a beaker, and the flask washed with 3x60 mL boiling MeOH. On stirring the combined decantation and washings, there was a spontaneous formation of crystals. After cooling, these were

removed by filtration, washed sparing with MeOH, and air dried to constant weight to yield 35.1 g of 2-nitro-1-(2,4,5-trimethoxyphenyl)propene as yellow crystals with a mp of 98-99 °C. Recrystallization from MeOH increased the mp to 101-102 °C.

A suspension of 31.6 g powdered LAH in 1 L anhydrous THF containing a little anhydrous Et_2O was brought to a gentle reflux, and then there was added a solution of 40.0 g of 2-nitro-1-(2,4,5-trimethoxyphenyl)propene in 200 mL anhydrous THF over the course of 4 h. The mixture was held at reflux temperature for 24 h, cooled to 0 °C with external ice, and the excess hydride destroyed by the addition, in sequence, of 32 mL H_2O (which had been diluted with a little THF), 32 mL 15% NaOH, and finally with 96 mL H_2O. The white inorganic solids were removed by filtration, and the filter cake was washed with THF. The combined filtrate and washings were stripped of solvent under vacuum to give 48 g of an impure amber oil. This was dissolved in 180 mL IPA, neutralized with 30 mL concentrated HCl, and the mixture diluted with 1500 mL anhydrous Et_2O. After a short induction period, an oily precipitate separated, which on stirring changed into a loose crystalline phase. This was removed by filtration, washed with Et_2O, and air dried to yield 29.0 g of 2,4,5-trimethoxyamphetamine hydrochloride (TMA-2) as fine white crystals with a mp of 188.5-189.5 °C. Anal. ($C_{12}H_{20}ClNO_3$) C,H,N. A 4.0 g sample of the free base was dissolved in 15 mL pyridine, treated with 2.5 mL acetic anhydride, heated on the steam bath for 20 min, added to 400 mL H_2O, acidified with HCl, and extracted with 3x75 mL CH_2Cl_2. After washing with H_2O the pooled extracts were stripped of solvent under vacuum to give 4.5 g of flakey, off-white solids which, on recrystallization from MeOH, were white, weighed 2.3 g, and had a mp of 132-133 °C. Recrystallization from this acetamide from MEK did not improve its quality. Anal. ($C_{14}H_{21}NO_4$) C,H,N.



DOSAGE: 20 - 40 mg.

DURATION: 8 - 12 h.

QUALITATIVE COMMENTS: (with 20 mg) "I took it in two 10 milligram doses, spaced by two hours. There was a slight movement of surface textures, my hearing was deepened and spatially defined. The body was relaxed and stretching seemed necessary. The further I got into it the more I realized that I was totally lazy. Very lethargic, to the point of laughter. At the sixth hour, I was seeing more life in the woodwork, and the wooden angel hanging on the ceiling was flesh and feathers when I stared at it. Great vision. But by no means overwhelming. Sleep was fine."

(with 20 mg) "The first two hours seemed like an eternity, with time passing slowly. Then it settled into a very calm and enjoyable event (not that it wasn't already). The material seemed somewhat hypnotic. I suspect that I would

believe suggestions, or at least not challenge them too much. I had a little confusion but it was not troublesome. On reflection, the material was quite good. It was benign in the sense that there appeared to be no dark spots. I would try it again, perhaps at 30 milligrams. Almost base-line after 12 hours, but not quite."

(with 24 mg) "I took the dosage in two halves, an hour apart. Initially, I was a little nauseous, with light tremors and modest eye dilation. But after another hour, there was the entire package of mescaline, missing only the intense color enhancement. The world is filled with distorted. moving things. Then my little fingers on both hands got periodically numb. And there was an occasional light-headedness that hinted at fainting. The two phenomena alternated, and never got in each other's ways. Both passed, once I realized that I would recover from this experience. Then the humor and joy of the world returned. The drop-off was quite rapid from the fifth to eighth hour, and no effects remained at all by the twelfth hour."

(with 40 mg) "Very slow coming on. Didn't feel it for an hour, but then at a full +++ in another hour. Beautiful experience. Erotic excellent. Eyes-closed imagery and fantasy to music. No dark corners. Benign and peaceful and lovely. There were brief intestinal cramps early, and a little diarrhea, but no other problems. I was able to sleep after eight hours, but had guarded dreams."

(with 40 mg) "Beautiful plus 3. Some visuals, but not intrusive. Moderate, good-mannered kaleidoscopic imagery against dark. Music superb. Clear thinking. Calmly cosmic. This is a seminal, or archetypal psychoactive material. A very good experience and good for repeats. About 10-12 hrs. Sleep difficult but OK."

EXTENSIONS AND COMMENTARY: There was absolutely no reason to suspect that the simple rearrangement of the methoxy groups of TMA from the classic 3,4,5-positions to this new, 2,4,5-orientation, would dramatically increase potency like this. Mescaline, 3,4,5-trimethoxyphenethylamine, is an extraordinary compound, but it is not particularly potent, requiring hundreds of milligrams for a trip. And going from its 3,4,5-pattern to the 2,4,5-pattern of TMPEA makes the compound even less potent. There was essentially nothing reported in the scientific literature about central activity of 2,4,5-substituted stuff, so there could not have been any logical preparation for the activity of TMA-2. My very first trials were with a rather liberal 400 micrograms, and the levels being explored leaped up in fairly large steps, mostly on separate days. On November 26, 1962, at 6:00 AM, when 12 milligrams proved to be inactive, another 12 milligrams went in and down an hour later. This was the 24 milligram discovery experiment, a fragment of which is given above. The anxiety of being thrust into the unknown certainly played a role in what can now be seen as obvious psychosomatic difficulties.

The unexpected ten-fold increase of effectiveness uncovered by the simple relocation of a single methoxy group of TMA gave the further juggling of methoxy groups a very high priority. There are a total of six arrangements possible for the three groups, namely, 3,4,5- (the original TMA), 2,4,5- (the present TMA-2), and then and in systematic sequence, 2,3,4-, 2,3,5-, 2,3,6-, and 2,4,6. These compounds were totally unknown at that time, and they could and would be assigned the sequential names TMA-3, TMA-4, TMA-5 and TMA-6, respectively. I made them all, and they are all included in this book.

Having found the treasure of 2,4,5-ness, it is instructive to look back at nature, to see what its plant equivalents might be. There are indeed a few essential oils that have their methoxy groups in this arrangement. TMA-2 is thus one of the Essential Amphetamines, and most of the botanical connections are discussed under TMA. The natural skeleton is found in asarone, with alpha-asarone being trans-propenyl, beta-asarone the cis-propenyl and gamma-asarone (also called euasarone) being the allyl-isomer. I had mentioned, in the spice cabinet discussion under TMA, the tasting of asarone at up to 70 milligrams without any effects.

A couple of additional experiments involving TMA-2 had been set up and started, but somehow never had enough fire to get completed. Studies on the optical isomers had gotten up to assays of 6 milligrams on each of the separate isomers, but had never been taken higher. The "R" isomer is much the more potent in rabbit assays, but the human comparisons remain unknown at present. Also, a study of the ^{14}C labeled racemate (5 microcuries in 40 milligrams) was conducted with a view to metabolite analysis, but again, the project was abandoned before any results were obtained. In the rat, the 4-methoxyl carbon appeared as expired carbon dioxide to the extent of about 20%. And this is some four times the amount seen from either of the other two methoxyl carbon atoms.

One final memory in the TMA-2 area. About twenty years ago I co-authored a rather thorough review article in the British journal Nature, that described the structure-activity relationships between the simpler one-ringed psychotomimetics. It also quietly served as a vehicle for mentioning a number of newly-discovered compounds and their human activities. But as a magnificent attestment to youth and brashness, we proposed a complex compound that embraced each and every clue and hint that might tie it to the neurological process. This hybrid monster was 2,ß-dihydroxy-4,5-dimethoxyphenethylamine. It had everything. The 6-hydroxydopamine hydroxy group and the rest of the dopamine molecule intact as represented by the two methoxyl groups. And the beta-hydroxy group gave it the final "norepinephrine" touch. And, with due modesty, we proposed that it might be "an endogenous psychotogen." Why not "*the* endogenous psychotogen?" And then, to compound the picture, what should arrive in the mail a month or two later, and from a most respected scientist, but a sample of just this stuff, synthesized for our investigations. I must have bought a little of my own promotion, as I noted that even after my first four graded dosages with the compound, I was still only up to a 250 microgram dose. And then, as the sample became increasingly brown and was clearly decomposing, the project was finally abandoned.

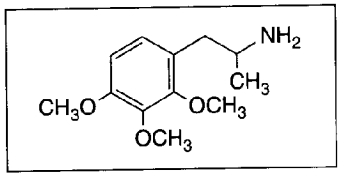
A sad note on how things have changed since that time. I recently queried the editors of Nature, about their thoughts concerning a twenty year retrospective of this area, written by the three authors of the original review. We had each

followed quite divergent paths, but each of us was still keenly the researcher. It would have been a marvelous paper to put together, and it would have delighted the reading audience of Nature, had it been the audience of twenty years ago. But not today. The journal is now dedicated to neutron stars and x-ray sources. The respected old English journal of interdisciplinary interests is not the grand and curious lady she used to be. The Editor's reply was polite, but negative. "Such an article would be unsuitable for publication in Nature at present," they said. And, I am sad to say, they're right.

And I am afraid that the American counterpart journal, Science, has suffered a similar deterioration. It, too, has abandoned multidisciplinary interest, but in a different direction. They are now dedicated to chromosomes, and nucleotide identification, and are totally captivated by the attention paid to, and the apparent importance of, the human genome project. There is where you automatically go to publish, now, if you have unraveled some DNA sequence from the Latvian cockroach.

#159 TMA-3; 2,3,4-TRIMETHOXYAMPHETAMINE

SYNTHESIS: To a solution of 12.4 g 2,3,4-trimethoxybenzaldehyde in 45 mL glacial acetic acid, there was added 7 mL nitroethane and 4.1 g anhydrous ammonium acetate, and all was held at reflux temperature for 1.5 h. To the cooled and well stirred reaction mixture, H_2O was added slowly, dropping out an oily crystalline solid mass. This was separated by filtration, and ground under a quantity of 50% aqueous acetic acid, and re-filtered. The 6.5 g of crude product was recrystallized from boiling MeOH to give, after air drying to constant weight, 5.0 g of 2-nitro-1-(2,3,4-trimethoxyphenyl)propene, with a mp of 56-57 °C. Anal. ($C_{12}H_{15}NO_5$) C,H.



To a gently refluxing suspension of 3.0 g LAH in 300 mL anhydrous Et_2O under a He atmosphere, there was added 3.65 g 2-nitro-1-(2,3,4-trimethoxyphenyl)propene by allowing the condensing Et_2O drip into a shunted Soxhlet thimble containing the nitrostyrene and effectively adding a warm saturated solution of it dropwise. Refluxing was maintained for 5 h following the completion of the addition of the nitrostyrene. The milky reaction mixture was cooled and the excess hydride destroyed by the addition of 200 mL 10% H_2SO_4. When the aqueous and Et_2O layers were finally clear, they were separated, and 75 g of potassium sodium tartrate was dissolved in the aqueous fraction. NaOH (25%) was then added until the pH was >9, and this was then extracted with 3x75 mL CH_2Cl_2. Evaporation of the solvent under vacuum produced 2.5 g of a nearly colorless clear oil that was dissolved in 300 mL anhydrous Et_2O which was saturated with anhydrous HCl gas.

The product, 2,3,4-trimethoxyamphetamine hydrochloride (TMA-3) separated as a fine white solid. This was removed by filtration, Et_2O washed, and air dried to constant weight. The yield was 1.65 g of a product which, after recrystallization from IPA, had a mp of 148-149 °C. Anal. ($C_{12}H_{20}ClNO_3$) C,H.

DOSAGE: greater than 100 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 100 mg) "There were no effects at all. No eye dilation, no believable diversion from complete normalcy. Appetite was normal, as well."

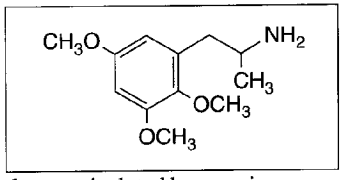
EXTENSIONS AND COMMENTARY: There is a small lesson to be learned from this completely inactive compound. There is no way of saying that it is or is not inactive. All that can be said is that trials were made (in this case using three separate individuals) at an oral level of 100 milligrams. And, at this level, nothing happened. And since a bottom threshold for mescaline would be perhaps 200 milligrams, it can be honestly said that the activity of this compound, if expressed relative to mescaline (using mescaline units) is less than 2 M.U. Had 200 milligrams been inactive, it would have been less than 1.0 M.U. If 2 grams had been inactive, it would have been less than 0.1 M.U. But the actual printed form, activity < 2.0 M.U. was accepted by many readers as indicating that TMA-3 was active, but at dosages greater than 100 milligrams. All that can be said is, *if* there is activity, *then* it will be at oral levels greater than 100 milligrams At the moment, as far as I know, this compound is not active in man, but then I know of no trials in excess of 100 milligrams.

This admonition applies to all the published M.U. values that are preceded by the "less than" sign, the "<."

#160 TMA-4; 2,3,5-TRIMETHOXYAMPHETAMINE

SYNTHESIS: To a solution of 68 g 2,4-dimethoxybenzaldehyde in 250 mL glacial acetic acid that had been warmed to 25 °C and well stirred, there was added, dropwise, 86 g of a 40% peracetic acid solution (in acetic acid). The reaction was exothermic, and the rate of addition was dictated by the need to maintain the internal temperature within a few degrees of 28 °C. External cooling was used as needed. The addition took 1 h, and when the reaction had clearly been completed (no further temperature rise) the entire reaction mixture was added to 3 volumes of H_2O. The excess acid was neutralized with solid K_2CO_3 (283 g were required). This was extracted with 3x100 mL Et_2O, the extracts pooled, and stripped of solvent under vacuum to give 66 g of crude 2,4-dimethoxyphenyl formate. This was suspended

in 125 mL 10% NaOH, and the mixture heated on the steam bath for 1.5 h. On cooling, the reaction mixture set to a heavy black solid. This was removed by filtration, washed with H_2O, and dissolved in 250 mL CH_2Cl_2. The organic phase was washed with dilute HCl, and then with aqueous $NaHCO_3$, which removed much of the color. Removal of the solvent under vacuum gave a deep red goo that was dissolved in 200 mL anhydrous Et_2O and filtered through paper. The resulting clear solution was stripped of solvent, yielding 34.4 g of 2,4-dimethoxyphenol as a red oil that crystallized on cooling. A 1.0 g sample in 4 mL pyridine was treated with 0.9 g benzoyl chloride and heated on the steam bath for a few min. The addition of H_2O gave a pasty solid that was isolated by pressing on a porous plate. The yield of crude 2,4-dimethoxyphenyl benzoate was 1.1 g. Recrystallization from cyclohexane gave a white product with a mp of 86-87 °C. A second recrystallization from cyclohexane raised this to 89-90 °C, which is in agreement with the literature value.



To a solution of 31.0 g crude 2,4-dimethoxyphenol in 60 mL absolute EtOH there was added a solution of 11.25 g KOH in 90 mL boiling EtOH. To this, there was then added 28 g allyl bromide which produced an immediate white precipitate of KBr. The mixture was held at reflux for 2 h and then quenched in 3 volumes of H_2O. Sufficient 10% NaOH was added to make the reaction strongly basic, and this was extracted with 3x100 mL Et_2O. Removal of the solvent under vacuum gave 33.2 g of 1-allyloxy-2,4-dimethoxybenzene, shown to be free of phenol starting material by GC analysis. Analyses must be carried out at low column temperatures (below 180 °C) on an ethylene glycol succinate substrate. If a silicone column is used, even at these low temperatures, there is considerable Claisen rearrangement taking place on the column. Low temperature distillation can be used for further purification (107-110 °C at 1.0 mm/Hg).

A 31.0 g sample of 1-allyloxy-2,4-dimethoxybenzene was gently heated with a soft flame until the internal temperature reached 215 °C. An exothermic reaction took place, with the temperature rising to 270 °C. The residue left in the flask was largely 2-allyl-4,6-dimethoxyphenol, that contained perhaps 10% of 2,4-dimethoxyphenol which resulted from the pyrolytic loss of the allyl group. This mixture was methylated without further purification.

To a solution of 30 g impure 2-allyl-4,6-dimethoxyphenol in a little absolute EtOH there was added a boiling solution of 8.7 g KOH in 75 mL absolute EtOH followed, immediately, by 22.4 g methyl iodide in a little EtOH. The mixture was held at reflux for 3 h, then added to 4 volumes of H_2O. Sufficient 10% NaOH was added to make the mixture strongly basic, and this was extracted with 4x100 mL Et_2O. Removal of the solvent gave 28 g of 1-allyl-2,3,5-trimethoxybenzene. GC analysis showed some 10% of the expected impurity, 1,2,4-trimethoxybenzene.

To a solution of 26 g crude 1-allyl-2,3,5-trimethoxybenzene in an equal weight of absolute EtOH there was added 52 g of flaked KOH. The mixture was heated on the steam bath overnight, and then quenched with much H_2O. This was extracted with 3x100 mL Et_2O which, on removal under vacuum gave 24.6 g of product. This contained, by GC analysis, largely cis- and trans-1-propenyl-2,3,5-trimethoxybenzene and the expected 1,2,4-trimethoxybenzene. This mixture was dissolved in an equal volume of pentane, and cooled in dry ice. Quick filtration gave 9.2 g of an amber solid which had a melting point of 39-41.5 °C. Recrystallization from hexane provided pure trans-1-propenyl-2,3,5-trimethoxybenzene with a mp of 44-45 °C. Evaporation of the original pentane mother liquor provided an impure sample of mixed cis- and trans- isomers.

A solution of 7.2 g trans-1-propenyl-2,3,5-trimethoxybenzene in 41 g dry acetone was treated with 3.3 g dry pyridine and, with good stirring, cooled to 0 °C. There was then added 6.9 g of tetranitromethane over the course of 1 min, and the reaction mixture was allowed to stir for an additional 2 min. The reaction mixture was then quenched with a solution of 2.2 g KOH in 40 mL H_2O. After the addition of more H_2O, the product was extracted with 3x50 mL CH_2Cl_2. Removal of the solvent under vacuum yielded 7.0 g of an impure product which would not crystallize. This was distilled under vacuum to give four fractions, all of which crystallized spontaneously. Cuts #1 and #2 (bp 100-120 °C and 120-130 °C at 2 mm/Hg) were combined, weighed 0.8 g, and after crystallization from hexane yielded white crystals with a mp of 62-63 °C. The NMR spectrum (in $CDCl_3$) was in agreement with 2,3,5-trimethoxybenzaldehyde, and the literature mp has been reported as being 62-63 °C. Cuts #3 and #4 (bp 130-170 °C and 170-175 °C at 2 mm/Hg with the bulk coming over in the latter fraction) were combined to give 3.0 g of yellow crystals. These were triturated under a little cold MeOH, and then recrystallized from MeOH to give 1.15 g of yellow crystals of 2-nitro-1-(2,3,5-trimethoxyphenyl)propene, with a mp of 87-88 °C. The forerun of the distillation contained considerable unreacted trans-1-propenyl-2,3,5-trimethoxybenzene and some 1,2,4-trimethoxybenzene, by GC analysis.

To a refluxing and stirred suspension of 1.1 g LAH in 150 mL anhydrous Et_2O and under an inert atmosphere, there was added a solution of 1.1 g 2-nitro-1-(2,3,5-trimethoxyphenyl)propene in 50 mL anhydrous Et_2O. The creamy mixture was held at reflux for 4 h, cooled, and then the excess hydride cautiously destroyed by the addition of 1.5 N H_2SO_4. There was then added 20 g potassium sodium tartrate followed by sufficient aqueous NaOH to raise the pH to >9. The Et_2O phase was separated, and the remaining aqueous phase extracted with 3x75 mL CH_2Cl_2. The organic phase and extracts were combined, and the solvent removed under vacuum yielding 0.9 g of a colorless oil. This was dissolved in 200 mL anhydrous Et_2O which was saturated with anhydrous HCl gas. There was generated a thick oil that did not crystallize. The Et_2O was decanted from this, and allowed to stand for several days in a sealed container at room temperature. There was the deposition of fine white needles of 2,3,5-trimethoxyamphetamine hydrochloride (TMA-4) weighing, after Et_2O washing and air drying, 0.31 g. The mp was 118-119 °C. Anal. ($C_{12}H_{20}ClNO_3$) C,H. The residual oil was dissolved in H_2O, made basic with NaOH, and extracted

with CH_2Cl_2. Evaporation of the solvent gave 0.40 of a white oil which was dissolved in a little MeOH containing 0.22 g oxalic acid. There was the immediate deposition of crystals of the oxalate salt of 2,3,5-trimethoxyamphetamine, with a mp of about 110 °C.

DOSAGE: greater than 80 mg.

DURATION: perhaps 6 h.

QUALITATIVE COMMENTS: (with 80 mg) "I was concerned about life issues, with much introspection, for about 6 hours. There were no subjective physical symptoms. It was comparable to about 50 micrograms of LSD, or to 120 milligrams TMA, for me."

EXTENSIONS AND COMMENTARY: That is the sum total of the knowledge of subjective effects that exist. There was such a precious small amount of the final hydrochloride salt that, by the time the needed build-up of dosage had been completed, there was just enough left for this single trial, which was conducted in South America. Based upon the volunteered comparisons to LSD and TMA, a potency for this compound has been published that states that it is 4x the potency of mescaline, or 4 M.U. The material must be re-synthesized, and re-evaluated with the now-accepted protocol.

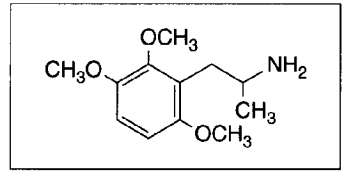
In the future re-synthesis, there will be a considerable improvement made with the several steps that are described above. The products from the preparations of the phenol, the allyl ether, the Claisen rearrangement, the methylation of the new phenol, and the isomerization to the mixture of cis- and trans-propenylbenzenes were all conducted without the benefit of a Kugel-Rohr apparatus. The products became progressively thick and blacker, and it was only by the grace of getting a solid at the trans-propenyl stage that some degree of purity could finally be obtained. All of the intermediates are certainly white oils, and when this preparation is repeated, they will be distilled at each and every stage.

This 2,3,5-orientation of the methoxy groups on the aromatic ring is far and away the most difficult tri-substitution pattern known to chemists. There just isn't any simple way to put it together. The 2-carbon phenethylamine (2,3,5-trimethoxyphenethylamine) had been synthesized quite a while ago. Its role as a substrate for liver amine oxidase in *in vitro* studies has been explored, but it has never been tried in man. Even more bizarre is the amphetamine with this oxygenation pattern, in which a methylenedioxy ring has replaced the two adjacent methoxyl groups. This is the material 2,3-methylenedioxy-5-methoxyamphetamine, or MMDA-4. Despite its theoretical appeal (being one of the six possible MMDA derivatives) and it's synthetic challenge (as with the 2,3,5-trimethoxy things above, everything is simply in the wrong position) the compound is of unknown pharmacology. This follows, quite logically, from the fact that it has never been synthesized. No one has yet put together a workable procedure that would make it. In the course of making all possible positional isomers of MMDA explicitly Schedule I drugs, the DEA has named this compound, and since it was specifically named, it was entered into the Chemical Abstracts. So it is listed in the literature, at least it is in the Chem. Abstracts. But it is in reality completely unknown. Some day, some one somewhere will have a light bulb go on over his head, and find a synthetic process that will make it. Of course, the moment it is made, an illegal act will have occurred, at least in the United States as long as the present laws remain unchanged, as it is currently a Schedule I drug.

Needless to say, the 2-carbon analog of MMDA-4, 2,3-methylenedioxy-5-methoxyphenethylamine (would 2C-MMDA-4 be a reasonable name?) is also unknown.

#161 TMA-5; 2,3,6-TRIMETHOXYAMPHETAMINE

SYNTHESIS: A solution of 100 g 1,2,4-trimethoxybenzene in 1 L hexane was cooled to 15 °C and treated with 400 mL of a 15% solution of n-butyllithium in hexane. A white precipitate formed immediately, and stirring was continued for an additional 2 h while the reaction returned to room temperature. There was then added a solution of 40 g freshly distilled propionaldehyde in 100 mL hexane. The reaction was exothermic and, as the stirring was continued, the precipitate gradually dissolved. Stirring was continued overnight at room temperature. There was then added 1 L H_2O, and the reaction was acidified with HCl. The hexane phase was separated, and the remaining aqueous phase was extracted with hexane, then with Et_2O. The pooled organic extracts were stripped of solvent under vacuum, and the residue distilled to give 60 g ethyl 2,3,6-trimethoxyphenyl carbinol, with an index of refraction $n_D^{20} = 1.5192$. Anal. ($C_{12}H_{18}O_4$) C,H. From the Et_2O extracts above, additional carbinol was obtained, containing a small amount of the starting 1,2,4-trimethoxybenzene. The two materials were readily separated by vacuum distillation, providing an additional 21 g of carbinol.



The above alcohol, 60 g of ethyl 2,3,6-trimethoxyphenyl carbinol, was stirred without solvent and cooled to 0 °C with an external ice bath. There was then added 80 g PBr_3 at a rate that maintained the temperature below 60 °C. At the end of the addition, there were added quantities of chipped ice, followed by H_2O. The reaction mixture was extracted with 3x100 mL Et_2O, and removal of the solvent provided 60 g of 1-bromo-1-(2,3,6-trimethoxyphenyl)propane which was used in the following dehydrobromination step without further purification.

A solution of the above 60 g of 1-bromo-1-(2,3,6-trimethoxyphenyl)propane

in an equal weight of EtOH was treated with 120 g of flaked KOH. The exothermic reaction was allowed to run its course with stirring continued overnight. The mixture was then quenched in H_2O and extracted with 3x200 mL CH_2Cl_2. Removal of the solvent from the pooled extracts gave a crude product which contained no starting bromo material, but which was contaminated with an appreciable quantity of the ethoxy analogue, 1-ethoxy-1-(2,3,6-trimethoxyphenyl)propane. This impure product was heated briefly to 80 °C with 50% H_2SO_4. Cooling, dilution with water, and re-extraction with 3x100 mL CH_2Cl_2 gave, after removal of the volatiles under vacuum, 1-(2,3,6-trimethoxyphenyl)propene. This was distilled to provide 7.0 g of a clear oil that was a 12:1 ratio of the trans- and cis-isomers.

A well-stirred solution of 6.8 g of the mixed isomers of 1-(2,3,6-trimethoxyphenyl)propene in 40 g of dry acetone was treated with 3.2 g pyridine and cooled to 0 °C with an external ice bath. There was then added 6.5 g tetranitromethane over the course of 1 min, the stirring was continued for an additional 2 min, and then the reaction mixture was quenched by the addition of 2.2 g KOH in 40 mL H_2O. There was additional H_2O added, and the organics were extracted with 3x75 mL CH_2Cl_2. The solvent from the pooled extracts was removed under vacuum, and the 5.3 g residue distilled at 0.2 mm/Hg. A fraction boiling at 150-170 °C proved to be largely 2,3,6-trimethoxybenzaldehyde. A second fraction (170-200 °C at 0.2 mm/Hg) also spontaneously crystallized to a yellow solid. This was recrystallized from MeOH to provide, after drying to constant weight, 2.8 g of 2-nitro-1-(2,3,6-trimethoxyphenyl)propene with a mp of 73-74 °C. Anal. ($C_{12}H_{15}NO_5$) C,H.

To a refluxing and stirred suspension of 2.4 g LAH in 300 mL anhydrous Et_2O and under an inert atmosphere, there was added a solution of 2.4 g 2-nitro-1-(2,3,6-trimethoxyphenyl)propene in 100 mL anhydrous Et_2O. The mixture was held at reflux for 4 h, cooled, and then the excess hydride cautiously destroyed by the addition of 1.5 N H_2SO_4. There was then added 40 g potassium sodium tartrate followed by sufficient aqueous NaOH to raise the pH to >9. The Et_2O phase was separated, and the remaining aqueous phase extracted with 3x100 mL CH_2Cl_2. The organic phase and extracts were combined, and the solvent removed under vacuum yielding 1.8 g of a colorless oil. This was dissolved in 200 mL anhydrous Et_2O which was saturated with anhydrous HCl gas. There was generated a thick oil that slowly crystallized. The resulting white crystalline solid was removed by filtration, providing 2.2 g 2,3,6-trimethoxyamphetamine hydrochloride (TMA-5). The mp was 124-125 °C. Anal. ($C_{12}H_{20}ClNO_3$) C,H.

DOSAGE: 30 mg or more.

DURATION: 8 - 10 h.

QUALITATIVE COMMENTS: (with 20 mg) "There appeared to be a slight stimulation. Modest eye dilation, but normal pulse. If this is the marginal edge of intoxication, then it is not a psychotomimetic, but a stimulant. Go up with care."

(with 30 mg) "Intense introspection. Comparable to about 75 micrograms of LSD, or more."

EXTENSIONS AND COMMENTARY: TMA-5, as was the case with TMA-4, has only been superficially explored. The above two quotations are from two different people, and together no more than hint at the possibility that it might be active in the several tens of milligrams.

Pharmacologists have developed quite an art in the design and evaluation of animal behavior models for the study of psychedelic drugs. They have always faced two formidable tasks, however. There is the qualitative question: is the drug a psychedelic? And there is the quantitative question: how potent is it?

The first question is addressed by taking a number of known psychedelic drugs, and searching for some animal responses that are common to all. Since there is little logic in the argument that animals can experience, let alone reveal, altered states of consciousness or fantasy fugues or colored imagery, the investigator must look for objective signs such as conditioned responses to stimuli, or unusual behavior. If one explores ten drugs that are known psychedelics, and all ten produce, say, bizarre nest-building behavior in mice, and an eleventh drug of unknown pharmacology does exactly the same thing, then the eleventh drug can be suspected of being a psychedelic drug.

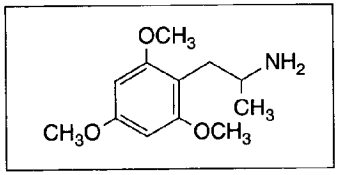
And the second question, how potent, is answered by seeing how much of the drug is required to evoke this standardized behavior. This is called the dose-response curve, in which the more drug you give, the more response you get. This curve gives confidence that the drug is indeed responsible for the activity that is seen, as well as giving a quantitative measure of that activity.

But this entire discipline depends on the acceptance of the fact that the first ten drugs are indeed psychedelic materials. And these inputs can only come from human trials. What is the validity of these assumptions with TMA-5? Not very good. The statement that it is psychedelic has actually been published in reviews solely on the basis of the above two studies; the potency has been put at some ten times that of mescaline. Mescaline is certainly an effective psychedelic drug in the 300-500 milligram range, and this factor of ten implies that TMA-5 is also a psychedelic drug and is active in the 30-50 milligram range. And indeed, both statements may be true, but confidence in these conclusions must await more extensive trials.

The two-carbon analogue of TMA-5 is 2,3,6-trimethoxyphenethylamine (or 2C-TMA-5 or 2,3,6-TMPEA). This is a known material, although there has been some controversy as to its physical properties. It has been studied in monoamine oxidase systems, and appears to be either a competitive substrate or an inhibitor of that enzyme. But as far as I know, no one has nibbled it, so its human activity is unknown.

#162 TMA-6; 2,4,6-TRIMETHOXYAMPHETAMINE

SYNTHESIS: To a solution of 100 g phloroglucinol dihydrate in 320 mL MeOH there was added 55 mL of concentrated H_2SO_4, and the clear solution held under reflux conditions overnight. After cooling, there was added 500 mL H_2O, and the bulk of the MeOH was removed under vacuum. The residual oil was extracted with Et_2O, and the removal of this left 60 g of a red oil as residue. This was dissolved in 300 g methyl sulfate (caution, this is extremely toxic through skin contact, and any exposure must be flushed thoroughly with dilute ammonium hydroxide). With good stirring, this was cautiously treated with 500 g of 40% aqueous KOH, and the exothermic reaction allowed to run its course. Extraction with 3x100 mL Et_2O gave, after evaporation of the solvent from the pooled extracts, an oil that became largely crystalline. This was suspended in 100 mL hexane, and filtered through a coarse fritted funnel. With evaporation there was obtained 57 g of 1,3,5-trimethoxybenzene as a pale amber solid that melted at 44-50 °C. A sample purified by recrystallization from EtOH had the proper mp of 54-55 °C.



A mixture of 62.9 g N-methylformanilide and 71.3 g of $POCl_3$ was allowed to stand for 0.5 h producing a light claret color. There was then added 30.9 g of 1,3,5-trimethoxybenzene and the mixture heated on the steam bath for 2 h. The reaction mixture then was poured into chipped ice, and allowed to stir for several h. The dark gummy mess was extracted with 2x100 mL Et_2O (this was discarded) and then with 4x200 mL CH_2Cl_2. The latter extracts were pooled, and stripped of solvent under vacuum yielding 14 g of an amber solid. This was recrystallized from 80 mL boiling MeOH (with decolorizing charcoal employed and filtration of the boiling solution through paper) to give 10.0 g of 2,4,6-trimethoxybenzaldehyde as a white crystalline solid with a mp of 115-116 °C. The literature values are generally one-degree ranges, and they are reported as high as 121 °C. The malononitrile adduct was prepared from a solution of 0.5 g aldehyde and 0.5 g malononitrile in 10 mL warm MeOH treated with a drop of triethylamine. There was an immediate formation of a yellow crystalline mass which was removed by filtration, washed with EtOH, and air dried. The yield of 2,4,6-trimethoxybenzalmalononitrile was 0.5 g and the mp was 174-175 °C. Anal. ($C_{13}H_{12}N_2O_3$) N.

A solution of 5 g 2,4,6-trimethoxybenzaldehyde in 20 g nitroethane was treated with 1.0 g of anhydrous ammonium acetate and held on the steam bath for 24 h. The excess solvent/reagent was stripped from the deep-red colored solution under vacuum yielding a residue that spontaneously set to a crystalline mass. This was well triturated under 5 mL MeOH, filtered, and washed with 3 mL additional MeOH to give 5.4 g of 2-nitro-1-(2,4,6-trimethoxyphenyl)propene as yellow crystals. The mp of the crude material was 135-142 °C which could be raised to 147-148 °C by recrystallization from EtOH. The use of an alternate procedure for the synthesis of this nitrostyrene, using acetic acid as solvent and a stoichiometric amount of nitroethane (and ammonium acetate as catalyst), gave very poor yields. The use of butylamine as catalyst gave considerably better results.

A suspension of 50 g LAH in 1 L anhydrous THF was placed under an inert atmosphere, stirred magnetically, and brought to a gentle reflux. There was added a total of 56.9 g 2-nitro-1-(2,4,6-trimethoxyphenyl)propene as a saturated solution in THF. This was achieved by letting the condensed THF drip through a Soxhlet thimble containing the nitrostyrene with direct addition to the reaction mixture. The solubility was extremely low. The stirred mixture was maintained at reflux for 36 h, generating a smooth creamy gray color. After being brought to room temperature, the excess hydride was destroyed by the patient addition of 50 mL H_2O, followed with 50 mL 15% NaOH (still some heat evolved) and then 150 mL additional H_2O. Stirring was continued until the insoluble salts were white and loose. These solids were removed by filtration, and the filter cake washed with additional THF. The combined filtrate and washes were stripped of solvent under vacuum, and the 73 g of pale amber residue dissolved in 200 mL IPA, neutralized with approximately 50 mL concentrated HCL, and diluted with 2 L anhydrous Et_2O. A lower, oily phase separated slowly set up as a crystalline mass. This was removed by filtration, Et_2O washed, and allowed to air dry to constant weight. The weight of 2,4,6-trimethoxyamphetamine hydrochloride was 41.3 g and the color was an off-white. There was a tendency to discolor upon air exposure. The mp was 204-205 °C which was increased to 207-208 °C upon recrystallization from IPA. The literature gives a mp of 214-215 °C for this salt after isolation and purification as the picrate salt (with a mp 212-213 °C from EtOH).

DOSAGE: 25 - 50 mg.

DURATION: 12 - 16 h.

QUALITATIVE COMMENTS: (with 25 mg) "I was outside at the California-Washington State football game, which was completely nutty. As was I. With the crowd activity, it was impossible to separate the drug's action from the environment. Later I simply sat in the car, and tried to define what the effects really were. Things were completely benign, there was ease with concepts, and writing was good and smooth. At twelve hours, comfortably down. Maybe a plus two."

(with 35 mg) "My body was tingling all over, and there were times when walking was unsteady. Thinking was a little difficult, as I was quite intoxicated most of the day (all of the day, now that I think that over). To accomplish anything, such as toasting the toast in the toaster, was difficult. And things were so funny most of the time. Setting the table for supper, six hours later, proved to be hilarious. I like to think of the day as a mixture of the mad hatter's tea party, and a trip to the moon. We were all still intoxicated at bedtime, whatever time that was. Had difficult time sleeping. If I were to repeat, would go lighter in dosage, I feel."

(with 40 mg) "This experiment was begun at noon of a cool rainy day. Almost all of the day had to be spent indoors, without benefit of sunshine, This is worth mentioning because there was, for the first eight hours of the experiment, a decided feeling of inner chill which might not have occurred so strongly had it been a warm day. Most, if not all, of the other eight subjects also reported the same chill. There was some visual sparkle which persisted throughout. At the two hour point a minor but persistent stomach queasiness came on, preceded by a diarrhea-like bowel movement. There was no impairment of speech, but there was some halting quality to all thought processes. It was easy to talk about personal matters, but there did not seem to be a significant insight increase. Appetite for food was lessened. Sleep was decidedly difficult after the effects of the material seemed otherwise gone."

(with 40 mg) "As the experience grows in intensity for the first four hours, I feel a strange mixture of plateaus, exuberance, and strong negative feelings, all replacing each other. I found myself inside a stout, hemispherical shell, curled up in the solid part, thoroughly walled off but absolute master within the shell, calling all shots, making all decisions, in complete control. Moving beyond the half-shell meant becoming vulnerable, which I refused to do. Consequently my difficulty in hearing what other people say, becoming involved in their perceptions and lives. I keep relationships shallow, pull away inside my shell rather than become involved. I like to be by myself. This was a great revelation; I had never seen it before. This material had an enormous drive. I feel extremely grateful for exposing a very deep personal problem."

(with 50 mg) "My previous try at this level produced a record that said, 'alteration of consciousness, but no visual, no anything,' and oh my, surprise! It was very, very active, visual, colorful, etc., etc. Good talking, clear and steady control of body, despite intense energy flow. Extremely funny — great humor, wonderful laughter."

EXTENSIONS AND COMMENTARY: Here is a simple and easily made compound that might well bid fair to be one of the most rewarding and pleasurable of the methoxylated amphetamines. It is fully as potent as its counterpart, TMA-2. This latter compound, with its 2,4,5-trisubstitution pattern, has served as a template from which an immense family of very active and fascinating drugs have arisen. The 2,5-dimethoxy aspect has been kept intact, and modifications in the 4-position have given rise to treasures such as DOM, DOB, DOET, DOI, and the Aleph compounds. And, of course, the entire world of the 2C-X's has exploited this same orientation.

Here, there is the blatant, parallel call from TMA-6. It can serve, as the 2,4,6-counterpart, as a similar template compound. And the first indicators are that, in keeping the 2,6-dimethoxy aspect intact, a completely analogous series could be made, again with modifications of the 4-position. These have been named the psu-series, or psi-series, as an abbreviation for the prefix, pseudo, and can be differentiated from the 2,4,5-things with the u[illegible] the Greek letter "Ψ". Thus there is the Ψ-DOM (called Z-7 in this book, and certainly an active compound), and Ψ-DOB, Ψ-DOET, Ψ-DOI, and the Ψ-ALEPH compounds. And, of course, the Ψ-2C-X counterparts. I would expect all of them to be active and, certainly, some of them interesting. They will be considerably more difficult to synthesize. However, some of them, specifically things such as Ψ-2C-T-4, have already been prepared, and are being evaluated.

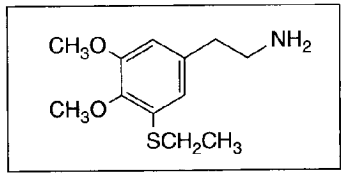
One of the guiding premises of this Book II was to make all recipes employ commercially available materials as starting materials. And in the case of TMA-6, the required benzaldehyde (2,4,6-trimethoxybenzaldehyde) is an easily obtained trade item from any of several supply houses. Why not start the recipe there? Why tell how to make it from 1,3,5-trimethoxybenzene (also presently available from commercial sources) and how to make the ether in turn, from phloroglucinol? This simply reflects a valid paranoia of our times. Today the aldehyde is available (at $2/g) and can be easily purchased. But tomorrow? What about in the year 2003? Who can tell what will, or will not, be easily available then? There might be a world-wide acknowledgment that the "war on drugs" is more destructive than any drug itself could ever be, and every law that had been written in the attempt to dictate human behavior will have been transformed into a force that truly educates and allows choice. This might really happen. But maybe, on the other hand, no fine chemicals may be permitted to be held in any hands, at any price, except for those of licensed chemists and in authorized laboratories. The black market price for the aldehyde might be $1000/g with another $1000 for protection.

But, it will be impossible to remove phloroglucinol from availability. It is available as a natural component in the free form, in sources as diverse as the cones of the *Sequoia sempervirens* (the coast redwood tree) and species of *Camillia* (that provides the leaves of our morning tea). And combined with a molecule of glucose in the form of its glucoside, it is called phlorin, and it is present in the discarded rinds of almost all citrus fruits as well as the resins from many of the *Eucalyptus* species. And one step yet further back into nature, there is a dihydrochalcone glucoside called phloridzin which practically drips out of all parts of the apple and pear trees except for the apple or pear itself. It, on base hydrolysis, gives phlorin, which on acid hydrolysis gives phloroglucinol, which when dissolved in methanol and sulfuric acid gives —. Nature is indeed most bountiful.

The phenethylamine homologue of TMA-6 is well known, but is virtually unexplored pharmacologically. The above benzaldehyde with nitromethane in glacial acetic acid containing ammonium acetate gave the appropriate beta-nitrostyrene as yellow crystals with a mp 177-177.5 °C. This, with LAH in ether, gave 2,4,6-trimethoxyphenethylamine (2,4,6-TMPEA, or 2C-TMA-6) as the picrate salt (mp 204-205 °C) or the hydrochloride salt (mp 234-235 °C). It has been shown not to be a substrate to the soluble amine oxidase from rabbit liver, a property it shares with mescaline, but whether it is or is not active in man is at present unknown.

#163 3-TME; 3-THIOMETAESCALINE; 4,5-DIMETHOXY-3-ETHYLTHIOPHENETHYLAMINE)

SYNTHESIS: A solution of 13.0 g of 3-bromo-N-cyclohexyl-4,5-dimethoxybenzylidenimine (see under MP for its preparation) in 125 mL anhydrous Et_2O in a He atmosphere was cooled with an external dry ice acetone bath to -80 °C with good stirring. To this clear pale yellow solution there was added 32 mL 1.55 M butyllithium in hexane (about a 25% excess) which was stirred for 10 min producing a fine white precipitate. There was then added 7.0 g diethyl disulfide. The dry ice bath was removed and the reaction stirred as it came to room temperature. This was then added to 300 mL dilute HCl and the aqueous phase separated and heated on the steam bath for 45 min. A yellow oil was formed with a nearly colorless aqueous overhead. This was removed by decantation, and the remaining oil was diluted with a little MeOH and additional concentrated HCl. After further heating on the steam bath, this was added to the separated phase, all was cooled and extracted with 2x50 mL CH_2Cl_2. Removal of the solvent from these pooled extracts gave 11.8 g of a residue that was distilled. The product, 3-ethylthio-4,5-dimethoxybenzaldehyde boiling at 106-125 °C at 0.4 mm/Hg and was an almost colorless oil weighing 8.3 g. Anal. ($C_{11}H_{14}O_3S$) C,H.



To a solution of 8.2 g 3-ethylthio-4,5-dimethoxybenzaldehyde in 125 mL nitromethane, there was added 1.0 g of anhydrous ammonium acetate and the mixture was heated on the steam bath for 1.5 h. The reaction mixture was stripped of nitromethane under vacuum, and the residual red oil was dissolved in 20 mL of boiling MeOH. This was decanted from a small amount of insolubles, and allowed to cool to room temperature. After considerable manipulation of a small sample with dry ice cooling, a seed of crystal was obtained, which successfully promoted crystallization of the entire MeOH solution. After standing for 1 h, the product 3-ethylthio-4,5-dimethoxy-ß-nitrostyrene was removed by filtration and, after air drying, weighed 3.2 g with a mp of 96-98 °C. Upon recrystallization from MeOH, the mp was tightened to 98-99 °C. Anal. ($C_{12}H_{15}NO_4S$) C,H.

AH was prepared in the usual manner from a suspension of 2.0 g LAH in 75 mL anhydrous THF, cooled to 0 °C and well stirred in an inert atmosphere of He, and treated with 1.33 mL of 100% H_2SO_4 added dropwise. There was added, dropwise and over the course of 10 min, a solution of 3.1 g 3-ethylthio-4,5-dimethoxy-ß-nitrostyrene in 15 mL anhydrous THF. At the end of the addition, the reaction mixture was returned to room temperature, and finally heated on the steam bath for 10 min. After cooling again, there was added enough IPA to decompose the excess hydride and sufficient 10% NaOH to convert the aluminum oxide to a white, easily filterable mass. This was removed by filtration, the filter cake washed with additional IPA, and the filtrate and washes combined and the solvent removed under vacuum. This was dissolved in 100 mL of dilute H_2SO_4, which was washed with 2x50 mL CH_2Cl_2. The aqueous phase was made basic with NaOH, extracted with 2x50 mL CH_2Cl_2, and the extracts pooled and the solvent removed under vacuum to yield a residue of a colorless oil. This was distilled at 160-170 °C at 1.0 mm/Hg yielding 2.6 g of a colorless liquid. This was dissolved in 12 mL IPA, neutralized with 24 drops of concentrated HCl and diluted with 25 mL anhydrous Et_2O. The clear solution was decanted from a little solid material, and the decantings diluted with a further 50 mL anhydrous ether. The still clear solution became cloudy after a few min, and then there was the slow formation of 3-ethylthio-4,5-dimethoxyphenethylamine hydrochloride (3-TME) as a fine white crystalline product. Removal by filtration, washing with Et_2O, and air drying yielded 2.8 g of white granular solids that melted at 171-172 °C. Anal. ($C_{12}H_{20}ClNO_2S$) C,H.

DOSAGE: 60 - 100 mg.

DURATION: 10 - 15 h.

QUALITATIVE COMMENTS: (with 60 mg) "As important as the experience was, itself, I feel that it was in the two or three days that followed that it had the most profound impact on me. It was at the time of the death of my wife's mother, and I found that I could look directly towards death and its ramifications. Including my own death. I felt very close to the Higher Powers that seemed to make their presence felt all around. And there was still the deep internal strength that was the direct product of the 3-TME experience. I feel it very strongly, still, but I have no desire to repeat the experience right away. It is almost as if the effects are still in evidence, and one should take one's time in letting it manifest all its ramifications. But it is certainly an experience one should have once a year, if not oftener."

(with 100 mg) "I was aware of the development quite early, and by the end of an hour and a half, I was in quite a remarkable state. I was extremely disinhibited, with easy verbal play and easily self-revealing, but not at too deep a level. There was great fun with a set of water colors but, when a used Kleenex became my canvas, the others failed to share my humor. I drove home at midnight with considerable care and was unable to sleep for another two hours. I would be very willing to repeat this experiment, at this level, to see if the good humor of it all was a consistent property."

(with 100 mg) "I had a sudden revelation — what I called the wet-paint theory of Christ. How does one find and identify the Messiah? It is most simple. All of life is nothing more than a freshly painted fence separating us from the rest of the world. And the fence has many, many signs on it that say: Beware. Don't Touch. Wet Paint. And if you touch too soon, indeed you get a dirty finger because the paint really is still wet. But the very first man to touch it and find it dry? There is your natural leader, your Son of God, and all those who touch later than He are the followers of the leader who first touched and found the paint dry."

EXTENSIONS AND COMMENTARY: A short unraveling of the codes used here for the various materials is very much needed. There are 3's and 4's and M's and I's and incipient confusion. Mescaline is mescaline. That much is simple. All homologs are the first letter of the homolog. Escaline is E, Proscaline is P, etc. If the group is at the three-position, then the term "meta" is used and an M preceeds the name of the homolog, i.e., ME is Metaescaline. The number (3- or 4- or 5-) gives the position of the sulfur, which is represented by the prefix "Thio" so this compound, 3-TME, has the sulfur at the 3-position, and by chance, the ethyl group there as well.

Here is a brief presentation of the needed Rosetta Stone:

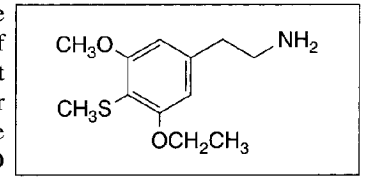
Number of ethyl groups	all three are oxygen atoms	One oxygen is replaced with sulfur
none	M	3-TM
		4-TM
one	E	3-TE
		4-TE
	ME	3-TME
		4-TME
		5-TME
two	SB	3-TSB
		4-TSB
	ASB	3-TASB
		4-TASB
		5-TASB
three	TRIS	3-T-TRIS
		4-T-TRIS

#164 4-TME; 4-THIOMETAESCALINE; 3-ETHOXY-5-METHOXY-4-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution of 5.1 g N,N,N',N'-tetramethylethylenediamine and 6.8 g of 3-ethoxyanisole was dissolved in 80 mL hexane. This was stirred vigorously under a He atmosphere and cooled to 0 °C with an external ice bath. There was added 27.5 mL of 1.6 M solution of butyllithium in hexane. The stirred reaction mixture deposited a fine white precipitate. It was warmed to room temperature and stirred for 15 min. After cooling again to 0 °C, there was added 4.6 mL of dimethyl disulfide which converted the precipitate to a creamy white material. Stirring was continued while the reaction mixture was brought up to room temperature, and continued for an additional h. All was then added to 200 mL dilute H_2SO_4. The

solids dissolved and there was the formation of two phases. These were separated, the aqueous phase extracted with with 2x75 mL Et_2O, the organic phases combined and evaporated under vacuum. The residue weighed 11.1 g and set up to a waxy solid. This was ground under 1 mL of hexane, filtered, washed sparingly with hexane, and air dried yielding 7.6 g of 3-ethoxy-2-(methylthio)anisole as white crystals. The mp was 35-36 °C which was not improved following recrystallization from hexane. Anal. ($C_{10}H_{14}O_2S$) C,H.

To a stirred solution of 7.6 g of 3-ethoxy-2-(methylthio)anisole in 100 mL CH_2Cl_2 there was added 6.2 g elemental bromine dissolved in 50 mL CH_2Cl_2. The initial dark red color gradually faded to a pale yellow and there was a steady evolution of HBr. An added crystal of iodine did not appear to increase the rate of reaction. After 4 min the color was a pale orange. The reaction mixture was extracted with H_2O containing sufficient dithionite to remove most of the residual color. The solvent was removed under vacuum leaving 12.2 g of a pale yellow fluid oil. This was distilled at 100-110 °C at 0.3 mm/Hg to yield a mixture of 4-bromo-3-ethoxy-2-(methylthio)anisole and 6-bromo-3-ethoxy-2-(methylthio)anisole as a pale yellow, highly refractory oil that was used as such in the following reaction. Anal. ($C_{10}H_{13}BrO_2S$) C,H.



To a solution of 12 mL diisopropylamine in 75 mL anhydrous THF that was stirred under an N_2 atmosphere and cooled to -10 °C with an external ice/MeOH bath, there was added in sequence 35 mL of 1.6 M butyllithium in hexane, 1.8 mL of dry acetonitrile, and 5.0 g of 4-bromo- (and 6-bromo)-3-ethoxy-2-(methylthio)-anisole. The reaction mixture changed color from yellow to red to reddish brown. Stirring was maintained for an additional 0.5 h, and then the reaction mixture was poured into 80 mL of dilute H_2SO_4. The phases were separated, and the aqueous phase was extracted with 100 mL CH_2Cl_2. The organic phases were combined, and the solvent was removed under vacuum. The oily residue was distilled at 0.2 mm/Hg yielded two fractions. The first fraction boiled at 90-115 °C and weighed 1.7 g. This material proved to be largely the unreacted bromo starting materials. The second fraction came over at 140- 170 °C, weighed 1.7 g, and it crystallized when seeded with a small crystal obtained externally with dry ice. This fraction was recrystallized from 10 mL MeOH, filtered, and washed sparingly with cold MeOH. After air drying, there was obtained 0.5 g 3-ethoxy-5-methoxy-4-methylthio-phenylacetonitrile which had a mp of 65-66 °C. Anal. ($C_{12}H_{15}NO_2S$) C,H.

A suspension of 0.5 g LAH in 50 mL anhydrous THF under N_2 was cooled to 0 °C and vigorously stirred. There was added, dropwise, 0.35 mL 100% H_2SO_4, followed by 0.45 g 3-ethoxy-5-methoxy-4-methylthiophenylacetonitrile in 10 mL anhydrous THF. The reaction mixture was stirred at 0 °C for a few min, then brought to a reflux for a few min on the steam bath. After allowing the mixture to return to room temperature, there was added IPA sufficient to destroy the excess

hydride followed by 10% NaOH to bring the reaction to a basic pH and to convert the aluminum oxide to a loose, white, filterable consistency. This was removed by filtration, and washed with 50 mL IPA. The filtrate and washes were stripped of solvent in vacuo, and the residue suspended in dilute H_2SO_4. This was washed with 2x75 mL CH_2Cl_2, made basic with aqueous NaOH, and the product extracted with 2x75 mL CH_2Cl_2. After combining these extracts, the solvent was removed under vacuum providing 1.2 g of a residue which was distilled at 132-140 °C at 0.4 mm/Hg to give 0.35 g of a colorless oil. This was dissolved in 7 mL of IPA, neutralized with 7 drops of concentrated HCl and diluted with 3 volumes of anhydrous Et_2O. The product was removed by filtration, washed with Et_2O, and air dried to give 0.30 g 3-ethoxy-5-methoxy-4-methylthiophenethylamine hydrochloride (4-TME) as white crystals with a mp of 164-165 °C. Anal. ($C_{12}H_{20}ClNO_2S$) C,H.

DOSAGE: 60 - 100 mg.

DURATION: 10 - 15 h.

QUALITATIVE COMMENTS: (with 60 mg) "There was a strange off-baseness for several hours in the middle of the day, which was replaced by a mild gastric upset in the evening. The mild mental disturbance is neither visual nor particularly interesting."

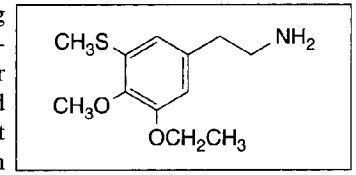
(with 100 mg) "A benign and gentle altered state became progressively sad and morbid. Nothing went together well — I could not empathize with anyone, and trying to write at the typewriter was useless. So were efforts to sleep at midnight, but this was totally relieved with 200 milligrams of Miltown. In the morning I seemed still to be off baseline, and I was extremely sleepy, with much lethargy. Even several days later there were problems trying to integrate my emotions and feelings. I am not yet completely at peace."

EXTENSIONS AND COMMENTARY: Sometimes things work well in their mysterious ways. The reports with 4-TME were more to the toxic than to the joyous side, and this by chance with a compound that could only be obtained in an atrociously small yield.

#165 5-TME; 5-THIOMETAESCALINE; 3-ETHOXY-4-METHOXY-5-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution of 10.4 g of 3-bromo-N-cyclohexyl-4-methoxy-5-ethoxybenzylidenimine (see under ME for its preparation) in 150 mL anhydrous Et_2O in a He atmosphere was cooled with an external dry ice acetone bath to -80 °C with good stirring. The addition of 52 mL 1.6 M butyllithium in hexane produced

a thick precipitate which was stirred for 5 min. There was then added 8.5 mL of dimethyl disulfide and the reaction mixture gradually became thinner and lighter. The dry ice bath was removed and the reaction allowed to come to room temperature over the course of 15 min. This was then added to 400 mL of dilute HCl. The two phases were separated, and the aqueous phase was heated on the steam bath for 1 h which generated a separate yellow oily phase. On cooling, this set to a yellow solid, which was removed by filtration, washed with H_2O, and sucked relatively free of H_2O. These yellow solids weighed 14.4 g and were ground under 20 mL of cold cyclohexane which removed almost all the color and, after filtering and air drying, there remained 12.9 g of an off-white crystalline solid that melted at 83-84 °C. Recrystallization from cyclohexane produced 3-ethoxy-4-methoxy-5-(methylthio)benzaldehyde as a white fluffy crystalline material with a melting point of 84-85 °C. Anal. ($C_{11}H_{14}O_3S$) C,H.



To a solution of 8.0 g 3-ethoxy-4-methoxy-5-(methylthio)benzaldehyde in 100 mL nitromethane, there was added 0.5 g anhydrous ammonium acetate and the mixture was heated on the steam bath for 1.5 h, at which time most of the aldehyde had disappeared and there was a sizeable quantity of nitrostyrene as well as a cascade of wrong things down to the origin, as seen by TLC on silica gel, with CH_2Cl_2. The excess nitromethane was removed under vacuum, and the residual red oil was dissolved in 25 mL of hot MeOH and decanted from a small amount of insoluble material. With cooling in an ice bath for 20 min, bright yellow crystals were formed which were removed by filtration, washed with MeOH and air dried, producing 4.1 g 3-ethoxy-4-methoxy-5-methylthio-ß-nitrostyrene which melted at 80-82 °C. This sample, on resolidification and remelting, melted at 109-110 °C. This higher-melting polymorphic form was also produced by recrystallization of the product from cyclohexane. The two polymorphs were chromatographically and analytically identical. Anal. ($C_{12}H_{15}NO_4S$) C,H.

AH was prepared in the usual manner from a suspension of 3.0 g LAH in 100 mL anhydrous THF, cooled to 0 °C, well stirred in an inert atmosphere of He, and treated with 2.0 mL of 100% H_2SO_4 added dropwise. There was then added a solution of 2.4 g 3-ethoxy-4-methoxy-5-methylthio-ß-nitrostyrene in 20 mL anhydrous THF. The reaction was exothermic, and had come nearly to a boil at the half-addition point. The reaction was cooled again to 0 °C and the remaining nitrostyrene then added. This was brought to a reflux briefly on the steam bath, then cooled again and stirred for an additional 1 h. IPA was carefully added to decompose the excess hydride followed by sufficient 10% NaOH to convert the aluminum oxide to a white, easily filterable mass. This was filtered, the filter cake washed with additional IPA, and the filtrate and washes combined and the solvent removed under vacuum. This was dissolved in 100 mL of dilute H_2SO_4, which was washed with 2x50 mL CH_2Cl_2. The aqueous phase was made basic with sodium hydroxide, extracted with 2x50 mL CH_2Cl_2, and the extracts pooled, dried over

anhydrous K_2CO_3, and stripped of solvent under vacuum to yield a nearly colorless residue. This was distilled at 125-135 °C at 0.3 mm/Hg producing 2.0 g of a water-white oil. This was dissolved in 8 mL IPA, neutralized with 23 drops of concentrated HCl and, with good stirring, diluted with 20 mL anhydrous Et_2O. The product 3-ethoxy-4-methoxy-5-methylthiophenethylamine hydrochloride (5-TME) was removed by filtration, washed with Et_2O, and air dried to provide a white solid that weighed 2.0 g and melted at 168-169 °C. Anal. ($C_{12}H_{20}ClNO_2S$) C,H.

DOSAGE: greater than 200 mg.

DURATION: unknown.

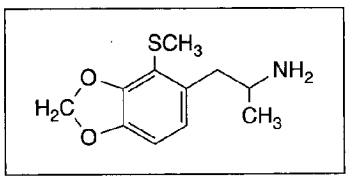
QUALITATIVE COMMENTS: (with 200 mg) "There was a noticeable tinnitus, but then that comes and goes at odd times without any reason needed. There was perhaps a brush of light-headedness at the third hour point, but other than that, nothing. No effect that can be ascribed to today's drug trial."

EXTENSIONS AND COMMENTARY: Nothing comes to mind. This, along with most of the di- and triethylated thiomescaline analogues, represents a lot of synthetic effort without useful qualitative data. If there is any activity, it would only be seen with monster dosages, and why put the body through such potential impact?

#166 2T-MMDA-3a; 3,4-METHYLENEDIOXY-2-METHYLTHIOAMPHETAMINE

SYNTHESIS: A solution of 30 g piperonal in 25 mL cyclohexylamine was brought to a boil on a hot plate, until there was no more water apparently being evolved. The resulting melt was distilled giving 45 g of N-cyclohexyl-3,4-methylenedioxybenzylidenimine boiling at 114-135 °C at 0.2 mm/Hg as a light yellow oil.

In 400 mL anhydrous Et_2O there was dissolved 40.3 g N-cyclohexyl-3,4-methylenedioxybenzylidenimine and 30 mL N,N,N',N'-tetramethylethylenediamine (TMEDA). This solution was put under an inert atmosphere, and with good stirring brought to -78 °C with an external dry ice/acetone bath, which produced a light white crystalline precipitate. There was then added 120 mL of 1.55 M butyllithium, which produced an immediate darkening and a dissolving of the fine precipitate. After 10 min stirring, there was added 20 mL of dimethyl disulfide. The color immediately vanished and there was the formation of a white precipitate. The temperature was allowed to return to ice bath temperature, and then all volatiles were removed under



vacuum. The residue was poured into 500 mL H_2O and acidified with HCl. After heating for 1 h on the steam bath, the reaction mixture was cooled, producing a gummy solid that was shown to be a complex mixture by TLC. But there was a single fluorescent spot that was the product aldehyde and it was pursued. Extraction with 3x75 mL CH_2Cl_2 gave, after pooling and stripping of the solvent, a residue which was extracted with four separate passes, each with 75 mL boiling hexane. The deposited crystals from each were separated, and all recrystallized from boiling MeOH to give 3.3 g of 3,4-methylenedioxy-2-(methylthio)benzaldehyde, with a mp of 77-80 °C.

To a solution of 3.0 g 3,4-methylenedioxy-2-(methylthio)benzaldehyde in 25 mL IPA there was added 2 mL nitroethane, 0.11 mL ethylenediamine and 0.1 mL acetic acid. This was held at reflux temperature for 18 h, and the solvents removed under vacuum. The residue showed a total of eight spots on TLC analysis, extending from the origin to the spot of the product nitrostyrene itself. Trituration of this residue under 25 mL MeOH gave a crude nitrostyrene which was, after separation, recrystallized from 20 mL of boiling MeOH. The final isolation of 1-(3,4-methylenedioxy-2-methylthiophenyl)-2-nitropropene gave 0.5 g of a product that had a mp of 94-95 °C. The mixed mp with the nitrostyrene from piperonal (mp 97-98 °C) was soundly depressed (mp 67-79 °C).

A solution of AH was prepared by the treatment of a solution of 0.5 g LAH in 10 mL THF, at 0 °C and under He, with 0.32 mL 100% H_2SO_4. A solution of 0.45 g 1-(3,4-methylenedioxy-2-methylthiophenyl)-2-nitropropene in 10 mL THF was added dropwise, and the stirring was continued for 1 h. After a brief period at reflux, the reaction mixture was returned to room temperature, and the excess hydride destroyed by the addition of IPA. The salts were converted to a filterable mass by the addition of 5% NaOH, and after filtering and washing with IPA, the combined filtrate and washings were stripped of solvent under vacuum. The residue was dissolved in dilute H_2SO_4 which was washed with 3x75 mL CH_2Cl_2. After alkalinification with 25% aqueous NaOH, the product was extracted with 2x75 mL CH_2Cl_2. The extracts were pooled, and the solvent removed under vacuum. Distillation of the residue gave a fraction that boiled at 137-150 °C at 0.3 mm/Hg and weighed 0.3 g. This was dissolved in 1.6 mL IPA, neutralized with 6 drops of concentrated HCl, warmed to effect complete solution, and diluted with 4 mL of anhydrous Et_2O. The formed crystals were collected by filtration, and after Et_2O washing and air drying to constant weight, gave 0.3 g 3,4-methylenedioxy-2-methylthioamphetamine hydrochloride (2T-MMDA-3a).

DOSAGE: greater than 12 mg.

DURATION: unknown.

EXTENSIONS AND COMMENTARY: And visions of sugar-plums danced through their heads. There are many trisubstituted amphetamine analogues that

have been documented with varying degrees of activity. There are six TMA's and if one were to systematically make every possible thio-analogue of each of these, there would be a total of sixteen thio-analogues of the TMA. Let's go for it, said I to myself. Let's get the 16 thio analogues in hand. That is where the action's at. But hold on a minute. Each and every MMDA isomer has, by definition, three possible thio analogues, so there are eighteen more possible thio compounds just with them. Sure, let's make them all! It will be an unprecedented coup for students of structure-activity relationships. Let's whip out some 34 compounds, and test them all, and maybe we will begin to understand just why those which are active are, indeed, active. And maybe not.

Anyway, this was the most manic of all manic programs ever, involving thio-analogues. And it was totally compelling. Another synthetic clue stemmed from the fact that vanillin also formed the cyclic carbonate with sodium thiocyanate and it could, in principle, be brought around in time to 3-methoxy-5,4-methylene-thiooxyamphetamine, or 5T-MMDA. That made two of the magic analogues, and only some 32 to go. What a marvelous task for a graduate student. (What a horribly dull task for a graduate student.) But in any case there was no graduate student, and this appeared to be the end of the line. Some day, let's make all these possibilities. A magnificent tour-de-force, but at the present time, not worth the effort. Other directions are more exciting and more appealing.

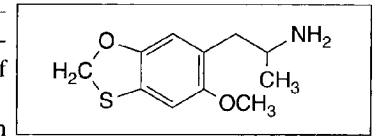
A last note of simple humor. One of the compounds used in this preparation was N,N,N',N'-tetramethylethylenediamine, which has been abbreviated TMEDA. There is a pattern, within any active inner clique of research chemists intently pursuing a goal, to begin condensing complex concepts into deceptively simple terms. We "MOM-ed the hydroxy group of the T-BOC-ed amine." I have recently heard the above tetramethyl monster referred to in the chemist's jargon as a pronounced, rather than a spelled out, word. It sounds very much like "tomato" spoken by a native of the Bronx.

#167 4T-MMDA-2; 6-(2-AMINOPROPYL)-5-METHOXY-1,3-BENZOXATHIOL; 2-METHOXY-4,5-METHYLENETHIOOXYAMPHETAMINE

SYNTHESIS: To a well-stirred solution of 120 g thiourea in 800 mL 2N HCL, there was added a solution of 100 g benzoquinone in 500 mL acetic acid over the course of 15 min. Stirring was continued for an additional 0.5 h at room temperature, and then the reaction mixture was heated on the steam bath for 1 h. With cooling in ice water, a heavy crop of crystals separated. These were removed by filtration and air dried to provide 90.1 g of 5-hydroxy-1,3-benzoxathiol-2-one (2-mercaptohydroquinone cyclic carbonate ester) with a melting point of 170.5-172.5 °C.

To a suspension of 100 g finely powdered anhydrous K_2CO_3 in 400 mL

acetone containing 50 g methyl iodide there was added 41 g 5-hydroxy-1,3-benzoxathiol-2-one, and the mixture stirred overnight at room temperature. The solids were removed by filtration, and the solvent removed under vacuum. The residue was distilled to give a fraction subliming over as a solid at an oven temperature of 110 °C at 0.1 mm/Hg. This was a yellowish solid, weighing 27.4 g and having a mp of 66-72 °C. Recrystallization from MeOH gave 5-methoxy-1,3-benzoxathiol-2-one as a white solid with a mp of 75.5-76.5 °C.



To a solution of 30 g 85% KOH in 75 mL warm H_2O, there was added an equal volume of warm MeOH followed by 16 g 5-methoxy-1,3-benzoxathiol-2-one, and the mixture was held under reflux conditions for 2 h. After cooling to room temperature, the mix was acidified with HCl and extracted with 2x100 mL CH_2Cl_2. Removal of the solvent from the pooled extracts gave a yellow oil that crystallized on standing. The product, 2-mercapto-4-methoxyphenol, weighed 14 g and had a mp of 56-57 °C.

A solution of 10 g 2-mercapto-4-methoxyphenol in 100 mL MEK was added over the course of 1 h to a vigorously stirred suspension of 25 g finely powdered anhydrous K_2CO_3 in 200 mL MEK that contained 14 g methylene bromide. The reflux was maintained for 48 h. After cooling, the mixture was freed of solids by filtration and the filter cake washed with 50 mL additional MEK. The combined washes and filtrate were stripped of solvent under vacuum, and the product distilled to give 3.3 g of 5-methoxy-1,3-benzoxathiol as a yellowing oil that had a bp of 110-120 °C at 1.7 mm/Hg. There was considerable residue in the pot, which was discarded. The NMR spectrum was excellent, with the methylene protons a two-hydrogen singlet at 5.6 ppm.

To a mixture of 3.2 g $POCl_3$ and 2.8 g N-methylformanilide that had been heated briefly on the steam bath (to the formation of a deep claret color) there was added 2.3 g 5-methoxy-1,3-benzoxathiol, and steam bath heating was continued for an additional 5 min. The reaction mixture was poured into 100 mL H_2O, and after a few minutes stirring, the insolubles changed to a loose solid. This was collected by filtration, H_2O washed and, after sucking as dry as possible, recrystallized from 30 mL boiling MeOH. This provided 1.9 g of 6-formyl-5-methoxy-1,3-benzoxathiol as brownish needles that melted at 119-120 °C.

A solution of 1.5 g 6-formyl-5-methoxy-1,3-benzoxathiol in 50 mL nitroethane was treated with 0.3 g anhydrous ammonium acetate and heated on the steam bath for 5 h. Removal of the solvent under vacuum gave a residue that crystallized. This was recrystallized from 110 mL boiling EtOH providing, after filtering and air drying, 1.3 g 5-methoxy-6-(2-nitro-1-propenyl)-1,3-benzoxathiol as San Francisco Giants-orange-colored crystals.

A solution of AH was prepared by the treatment of a solution of 1.3 g LAH in 10 mL THF, at 0 °C and under He, with 0.8 mL 100% H_2SO_4. A solution of 1.1 g of 5-methoxy-6-(2-nitro-1-propenyl)-1,3-benzoxathiol in 25 mL THF was added

dropwise, and the stirring was continued for 1 h. After a brief period at reflux, the reaction mixture was returned to room temperature, and the excess hydride destroyed by the addition of IPA. The salts were converted to a filterable mass by the addition of 5% NaOH and, after filtering and washing with IPA, the combined filtrate and washings were stripped of solvent under vacuum. The residue was dissolved in dilute H_2SO_4 which was washed with 3x75 mL CH_2Cl_2 and then, after being made basic with 25% NaOH, the product was extracted with 2x75 mL CH_2Cl_2. The extracts were pooled, and the solvent removed under vacuum. Distillation of the residue gave a fraction that boiled at 140-155 °C at 0.3 mm/Hg which weighed 0.7 g. This was dissolved in 4 mL IPA, neutralized with 14 drops of concentrated HCl, heated to effect complete solution, then diluted with 10 mL of anhydrous Et_2O. The white crystals that formed were removed, Et_2O washed, and air dried to give 0.6 g 6-(2-aminopropyl)-5-methoxy-1,3-benzoxathiol hydrochloride (4T-MMDA-2).

DOSAGE: greater than 25 mg.

DURATION: unknown.

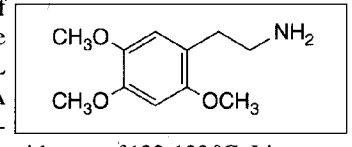
QUALITATIVE COMMENTS: (with 25 mg) "At three hours after having taken the material, I felt that there might have been a little exhilaration. And maybe a hint of tremor and of teeth clench. Perhaps this is a threshold dose."

EXTENSIONS AND COMMENTARY: There is no logical way to try to guess where the active level of this might be. In a comparison of 4-oxy with 4-thio- and with 4-alkyl (as, for example, TMA-2, PARA-DOT and DOM) the analogue with the sulfur atom lies intermediate in potency between the oxygen atom and the carbon atom. Then, perhaps, 4T-MMDA-2 should be somewhat more potent than MMDA-2. Which is where the trials have gone to, and the absence of effects therefore declares that line of reasoning invalid. What else could be used for clues? The whole benzofuran project, which had the same cyclic nature, was without activity. They had a carbon where the sulfur was of 4T-MMDA- 2, so, by that reckoning, this compound should be even less active. Maybe that is the formula to follow. The bottom line is inescapable. None of these extrapolations can hold a candle to the only experiment that can give believable findings, the actual trial of a new compound in man.

The positional isomer of the heterocyclic carbonate used here is also known. Instead of using benzoquinone as a starting material with thiourea as the sulfur source (giving the 1,4- oxygen orientation), one can start with resorcinol in reaction with ammonium thiocyanate as the sulfur source (in the presence of copper sulfate) and get the positional isomer with a 1,3- oxygen orientation. This material (also known as thioxolone, or tioxolone, or 6-hydroxy-1,3-benzoxathiol-2-one, and which is commercially available) should follow the same chemistry shown here for the 5-hydroxy analogue, and give 5T-MMDA-2 (5-(2-aminopropyl)-6-methoxy-1,3-benzoxathiole or 2-methoxy-5,4-methylenethiooxyamphetamine) as a final product. I would guess, based on the findings that compare 5-TOM with DOM, that this would be a relatively low-potency compound. At least it should be an easy one to make!

#168 TMPEA; 2,4,5-TRIMETHOXYPHENETHYLAMINE

SYNTHESIS: To a solution of 39.2 g 2,4,5-trimethoxybenzaldehyde in 160 mL nitromethane there was added 7.0 g anhydrous ammonium acetate, and the mixture was heated on the steam bath for 2 h. The excesssolvent/reagent was removed under vacuum, leaving a deeply colored residue that spontaneously crystallized. This was mechanically removed and triturated under 60 mL cold MeOH. Filtration, washing with cold MeOH and air drying, gave 49.3 g of bright orange crystals. Trial recrystallizations from EtOAc gave a mp of 132-133 °C; from CH_3CN, 130.5-131.5 °C. The entire product was recrystallized from 1.1 L boiling IPA to provide, after filtration, IPA washing, and air drying, 34.5 g of ß-nitro-2,4,5-trimethoxystyrene as yum-yum orange crystals with a mp of 132-133 °C. Literature values are usual one-degree ranges, anywhere in the area of 127-130 °C.



To a suspension of 30 g powdered LAH in 800 mL of well stirred and refluxing anhydrous THF there was added a solution of 34.9 g ß-nitro-2,4,5-trimethoxystyrene in 200 mL anhydrous THF. The mixture was maintained at reflux for an additional 36 h, cooled, and the excess hydride activity destroyed by the addition of 30 mL H_2O followed by 30 mL 15% NaOH, and finally with another 90 mL H_2O. The solids were removed by filtration, washed with THF, and the pooled mother liquor and washings stripped of solvent under vacuum. The residue was dissolved in CH_2Cl_2, washed with both 5% NaOH and then H_2O, removing much of the color. It was then extracted with 3x75 mL N HCl. The pooled red-colored acid extracts were washed with CH_2Cl_2, made basic with 25% NaOH, and extracted with 3x75 mL CH_2Cl_2. Removal of the solvent gave some 25 g of residue which was dissolved in 100 mL IPA and neutralized with concentrated HCl. The crystalline mass that formed was diluted with an equal volume of Et_2O, and the solids removed by filtration. Washing with cold IPA, followed by Et_2O and air drying, gave 17.7 g of 2,4,5-trimethoxyphenethylamine hydrochloride (TMPEA) as a white product. The reported melting point was 187-188 °C.

DOSAGE: greater than 300 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with less than 300 mg) "Since it was not easy, however, to judge the extent of a 'Rausch'-action from experiments on animals, some injections of beta-2,4,5-trimethoxyphenethylamine were administered to the author, and finally a control test was carried out with an equal quantity of mescaline. The action of both these substances in these experiments agreed only to a limited extent with the effects described for mescaline by, for example, Beringer. It must be remembered, however, in this connection, that the quantities used by Beringer were larger than the doses administered in these experiments. Nevertheless, it may be concluded that the pharmacological action of beta-2,4,5-trimethoxyphenethylamine agrees to a large extent with that of mescaline. However, the new compound had more unpleasant secondary effects (nausea) and did not bring about the euphoristic state caused by mescaline."

(with 300 mg) "Under double blind conditions, I was unable to distinguish this from a placebo. Both were without any of the changes described after the ingestion of psychotomimetic drugs."

(with 200 mg, followed after 45 minutes, with 100 mg mescaline) "The normally modest effects known to be due to mescaline alone at this level, were strongly potentiated with the earlier taking of 2,4,5-TMPEA. The effects were stronger as well as longer lived."

EXTENSIONS AND COMMENTARY: The code letters used for this drug are not as ambiguous as they might seem at first glance. A large number of the 2-carbon homologues are given names based on the code for the 3-carbon compound. On that basis, this should be 2C-TMA-2, since it is the 2-carbon counterpart of TMA-2. But since the first of the trimethoxyphenethylamines already had a trivial name, mescaline, the code TMPEA was unassigned. So, here is the logical place to use it.

There have been just two reports published of self-experimentation with TMPEA, and these comments are taken from them.

The first is presented here, word for word, as it was originally published (this was in 1931). It leaves much to be desired. The administration was by injection (intramuscular injection?). The dose was not given, but it was less than those reported by Beringer in his studies with mescaline, and this latter experimenter's published levels were all between 300 and 500 milligrams. What can one conclude from all this? Only that TMPEA apparently did not measure up to mescaline in his comparisons.

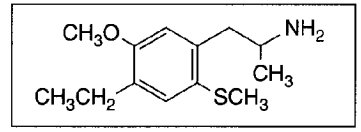
The second, reported some 40 years later, is not really contradictory. Here the TMPEA was administered orally, and the subject surrounded himself with a battery of psychological tests. This might allow statistics to provide an aura of validity to the observations. But the comments are pretty self-explanatory. The drug was not active in its own right, but when employed preliminary to mescaline, greatly enhanced the effects of the latter.

This is an area of research that deserves more attention. The simple compound that results from the stripping of all three of the O-methyl groups from

TMPEA is the extremely potent neurotoxin, 6-hydroxydopamine. When it is administered to an otherwise intact experimental animal, it produces sympathectomy, effectively destroying the sympathetic nervous system. And some of the methyl groups of TMPEA are known to be stripped off through the normal metabolic processes that occur in the liver. There are many fascinating psychedelics that have a signature of methoxyl groups para to one-another. It is known that they, too, can lose a methyl group or two. It would be intriguing to see if there was some biochemical overlap between the metabolism of some of these centrally active drugs and the metabolic fate of 6-hydroxydopamine. But in a test animal, of course, rather than in man.

#169 2-TOET; 4-ETHYL-5-METHOXY-2-METHYLTHIOAMPHETAMINE

SYNTHESIS: A mixture of 24.4 g ortho-ethylphenol and 18.9 mL methyl iodide was added to a solution of 15.6 g 85% KOH in 100 mL hot MeOH. The mixture was kept at reflux temperature overnight, stripped as much as possible of the MeOH, and poured into 1 L H_2O. An excess of 5% NaOH was added and this was extracted with 3x75 mL CH_2Cl_2. The pooled extracts were washed with 1% NaOH, and the solvent removed under vacuum to give 32.8 g of a pale amber oil. This was distilled at 55-65 °C at 0.4 mm/Hg to yield 22.0 g of 2-ethylanisole as a colorless oil.



To a 21.7 g sample of 2-ethylanisole, well stirred but without solvent, there was added, 1 mL at a time, 21 mL of chlorosulfonic acid. The color progressed from white to yellow, and finally to deep purple, with the evolution of much HCl. The exothermic reaction mixture was allowed to stir until it had returned to room temperature (about 0.5 h). It was then poured over 400 mL cracked ice with good mechanical stirring, which produced a mass of pale pink solids. These were removed by filtration, washed well with H_2O, and air dried to give about 27 g of 3-ethyl-4-methoxybenzenesulfonyl chloride as an off-white solid that retained some H_2O. A sample recrystallized from cyclohexane had a mp of 44-46 °C. A sample treated with ammonium hydroxide provided white crystals of 3-ethyl-4-methoxybenzenesulfonamide which could be recrystallized from H_2O to give tufts of crystals with a mp of 97-98 °C. Anal. ($C_9H_{13}NO_3S$) C,H.

In a 2 L round bottomed flask equipped with a mechanical stirrer there was added 200 mL cracked ice, 45 mL of concentrated H_2SO_4, 26.7 g of still moist 3-ethyl-4-methoxybenzenesulfonyl chloride, and 45 g elemental zinc dust. With external heating, an exothermic reaction set in and the temperature was maintained at reflux conditions for 4 h. After cooling to room temperature, the reaction mixture was filtered and the insolubles washed alternately with H_2O and with CH_2Cl_2. The

mother liquors and washings were diluted with sufficient H_2O to allow CH_2Cl_2 to become the lower phase. These phases were separated, and the aqueous phase extracted with 3x100 mL CH_2Cl_2. The original organic phase and the extracts were pooled, washed with H_2O, and the solvent removed to give 15.7 g of a smelly amber oil. This was distilled at 72-84 °C at 0.3 mm/Hg to give 12.1 g of 3-ethyl-4-methoxythiophenol as a water-white oil. The infra-red was perfect (with the SH stretch at 2562, OCH_3 at 2837 and 1061, and with fingerprint peaks at 806, 880, 1052, (1061), 1142 and 1179 cm^{-1}). Anal. ($C_9H_{12}OS$) C,H.

To a solution of 11.7 g of 3-ethyl-4-methoxythiophenol and 6.5 mL methyl iodide in 100 mL MeOH there was added, with good stirring and a bit at a time, a solution of 5.5 g 85% KOH in 25 mL hot MeOH. The mixture was held at reflux on the steam bath for 1.5 h, and then stripped of volatiles under vacuum. The residues were added to 400 mL H_2O, made strongly basic with 5% NaOH, and extracted with 3x75 mL CH_2Cl_2. The pooled extracts were back-washed with 1% NaOH, and the solvent removed under vacuum. The 13.2 g residue was distilled giving 2-ethyl-4-(methylthio)anisole as a fraction boiling at 78-85 °C at 0.2 mm/Hg. The weight was 11.6 g for an isolated yield of over 90% of theory. The mp was at about 0 °C. The infra-red showed no SH or other functionality, but an OCH_3 at 2832 and 1031, and a fingerprint spectrum with peaks at 808, 970, (1031), 1051, 1144 and 1179 cm^{-1}. Anal. ($C_{10}H_{14}OS$) C,H.

A solution of 11.2 g 2-ethyl-4-(methylthio)anisole and 9 g dichloromethyl methyl ether in 200 mL dry CH_2Cl_2 was treated with 13 g anhydrous aluminum chloride, added a bit at a time. The color progressed from pink to claret to deep claret, with a modest evolution of HCl. Stirring was continued for 1 h, then the reaction was quenched by the cautious addition of 250 mL H_2O. The two phase mixture was stirred an additional hour and then separated. The aqueous phase was extracted with 2x100 mL CH_2Cl_2. The organics were pooled, washed with 5% NaOH, then with saturated brine, and the solvent removed under vacuum. The residue was an amber oil weighing 13.7 g. This was distilled at 0.2 mm/Hg. A first fraction was a yellow oil boiling at 90-100 °C, and weighing 2.9 g. It was a mixture of starting anisole and the desired benzaldehyde. A second fraction, boiling at 100-130 °C was a viscous yellow oil weighing 4.8 g. By TLC it was free of starting anisole, and contained a sizeable quantity of a second benzaldehyde. From this fraction, seed crystal was obtained, and when the oil was dissolved in an equal volume of MeOH, the seed took, producing a yellow solid. This was filtered and air dried, to give 2.2 g of 4-ethyl-5-methoxy-2-(methylthio)benzaldehyde with a mp of 62-63 °C. A small sample from MeOH was almost white, and melted at 61-62 °C. The mixed mp with 4-ethyl-2-methoxy-5-(methylthio)benzaldehyde (57-58 °C) was severely depressed (37-44 °C). A cooled solution of the first fraction of the distillation, in MeOH, provided an additional 1.6 g product, with a mp 59-61 °C. The combined mother liquors gave additional product for an overall weight of 5.3 g. Anal. ($C_{11}H_{14}O_2S$) C,H.

A solution of 1.9 g 4-ethyl-5-methoxy-2-(methylthio)benzaldehyde in 75 mL nitroethane was treated with 0.3 g anhydrous ammonium acetate, and held on the steam bath for 2.5 h. The excess solvent/reagent was removed under vacuum, and the deep orange oil residue was dissolved in 10 mL boiling MeOH. As this cooled, there was the spontaneous generation of crystals. After cooling in an ice bath for a few h, these were removed by filtration, washed with MeOH, and air dried to constant weight. A total of 1.4 g of 1-(4-ethyl-5-methoxy-2-methylthiophenyl)-2-nitropropene was obtained as canary-yellow crystals melting at 83-84 °C which was not improved by recrystallization from MeOH. Anal. ($C_{13}H_{17}NO_3S$) C,H.

To a solution of 1.5 g LAH in 30 mL anhydrous THF that was cooled to 0 °C and stirred under a He atmosphere, there was added, slowly, 1.05 mL freshly prepared 100% H_2SO_4 (prepared by adding 0.9 g 20% fuming H_2SO_4 to 1.0 g 96% concentrated H_2SO_4). This was followed by the addition of a solution of 1.4 g 1-(4-ethyl-5-methoxy-2-methylthiophenyl)-2-nitropropene in 20 mL THF, over the course of 10 min. The color of the nitrostyrene solution was discharged immediately upon addition. With continued stirring, this was allowed to come to room temperature, and then to a gentle reflux for 2 h. After cooling again to room temperature, the excess hydride was destroyed by the addition of IPA. Sufficient 5% NaOH was added to generate the inorganic salts as a loose filterable mass, and these were removed by filtration. The filter cake was well washed with additional IPA, and the combined mother liquors and washes were stripped of solvent under vacuum. The residue was dissolved in 100 mL dilute H_2SO_4, washed with CH_2Cl_2, made basic with 5% NaOH, and extracted with 2x75 mL CH_2Cl_2. Removal of the solvent gave a residue that was distilled at 102-117 °C at 0.15 mm/Hg. The colorless liquid that distilled (0.7 g) was dissolved in 6 mL IPA and neutralized with 11 drops of concentrated HCl. The solids that formed were dissolved by heating the mixture briefly to a boil, and this clear solution was diluted with 20 mL anhydrous Et_2O. The white crystals of 4-ethyl-5-methoxy-2-methylthioamphetamine hydrochloride (2-TOET) weighed 0.6 g and had a mp of 164-167 °C. Anal. ($C_{13}H_{22}ClNOS$) C,H.

DOSAGE: greater than 65 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 50 mg) "After about an hour and a half, I found myself a little light-headed. And maybe a feeling of being physically a bit fragile. I ate something, but there was not much joy in eating. And the next day there was some residual fragility, whatever that means. Ahead with caution."

(with 65 mg) "During the day this was barely noticeable, but pleasant."

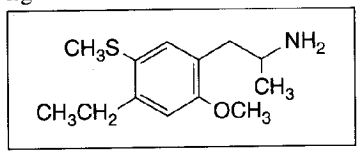
EXTENSIONS AND COMMENTARY: It seems as if the sulfur in the 2-position makes things less interesting, and less potent, than when it is in the 5-position. 2-TOM required twice the dosage of 5-TOM, and here it appears that it could well take a dosage of twice that required for 5-TOET, to get 2-TOET off the ground. There

is an understandable reluctance to push on upwards in dosage with a new and unknown compound, when there are feelings of physical discomfort that outweigh the mental effects. There is nothing tangible here. In the complete report of the 50 milligram trial, there is a mention of an inability to effect erection, and this with the light-headedness and disinterest in food, all suggest some involvement with the sympathetic nervous system. And with these subtle effects persisting into the next day, why push higher? Instinct said to leave it alone. So I left it alone.

The 2-carbon analogue, 2C-2-TOET, was made from the same aldehyde intermediate. The appropriate nitrostyrene came smoothly from the aldehyde and nitromethane, and gave glistening pumpkin-orange crystals from methanol, that melted at 93-94 °C. Anal. ($C_{12}H_{15}NO_3S$) C,H. The final phenethylamine hydrochloride salt was prepared from its reduction with aluminum hydride in THF, and was isolated in the usual manner. It was a white crystalline mass that melted at 226-227 °C. It, as with the other 2-carbon analogues of the TOMs and TOETs, remains untasted as of the moment.

#170 5-TOET; 4-ETHYL-2-METHOXY-5-METHYLTHIO-AMPHETAMINE

SYNTHESIS: A solution of 25 g 3-ethylphenol in 100 mL Et_2O was equipped with a magnetic stirrer, and cooled to 0 °C with an external ice bath. There was added 16 mL DMSO. Then, a total of 15 mL chlorosulfonic acid was added dropwise, over the course of 30 min. The reaction was allowed to return to room temperature and stirred overnight. The overhead Et_2O phase was removed by decantation, and the light-colored residue was dissolved in 100 mL IPA. The clear solution spontaneously generated white crystals which were allowed to stand for 1 h, removed by filtration, and lightly washed with IPA. After air-drying, this crop of dimethyl-(2-ethyl-4-hydroxyphenyl)-sulfonium chloride weighed 20.0 g and had a mp of 168-170 °C without obvious effervescence. A solution of 19.8 g of this sulfonium salt in 200 mL H_2O was diluted with 500 mL MeOH, and there was added 30 g NaOH. This was heated to reflux on the steam bath. There was an initial deposition of some white solids, but after 36 h the solution was almost clear. The excess MeOH was removed under vacuum, and the non-volatiles were poured into 1 L H_2O. This was acidified with HCl, and extracted with 3x100 mL CH_2Cl_2. The extracts were pooled, and the solvent removed under vacuum. The residue, 12.6 g of an amber oil, was distilled at 95-120 °C at 0.3 mm/Hg to give 10.0 g of 3-ethyl-4-(methylthio)phenol as an off-white oil. This spontaneously crystallized to a solid that had a mp of 47-49 °C. Recrystallization of an analytical sample from cyclohexane gave a mp of 47-48 °C.



To a solution of 9.7 g 3-ethyl-4-(methylthio)phenol in 50 mL MeOH there was added a solution of 4.6 g 85% KOH in 50 mL hot MeOH. There was then added 5.4 mL methyl iodide and the mixture was held at reflux on the steam bath for 18 h. Removal of the solvent under vacuum gave a residue that was poured into 1 L H_2O and made strongly basic by the addition of 5% NaOH. This was extracted with 3x75 mL CH_2Cl_2, and the extracts were pooled and the solvent removed under vacuum. There remained 11.0 g of an almost white oil with a startling apple smell. This oil was distilled at 78-88 °C at 0.3 mm/Hg to give 7.9 g 3-ethyl-4-(methylthio)-anisole as a white oil. Anal. ($C_{10}H_{14}OS$) C,H.

A mixture of 7.8 g $POCl_3$ and 6.9 g N-methylformanilide was heated on the steam bath for a few min, until there was the development of a deep claret color. This was added to 7.7 g 3-ethyl-4-(methylthio)anisole and the mixture was heated on the steam bath for 2 h. This was poured into 400 mL H_2O and stirred overnight, which produced an oily phase with no signs of crystals. The entire reaction mixture was extracted with 3x75 mL CH_2Cl_2, and the pooled extracts washed with H_2O. Removal of the solvent under vacuum gave 9.2 g of a residue. This was suspended in 25 mL hexane, and after 1 h standing, the overhead clear solution was decanted from the settled sludge. This hexane solution was stripped of solvent under vacuum, giving 7.7 g of an oil that by TLC was a mixture of starting ether and desired aldehyde. This was distilled at 0.25 mm/Hg to give three fractions, the first boiling at 75-100 °C (2.7 g) and the second at 100-115 °C (2.6 g). These were largely starting ether and aldehyde, and were chemically processed below. A third fraction, boiling at 120-140 °C, solidified in the receiver, weighed 1.6 g, and was largely the desired aldehyde. Cuts #1 and #2 (5.3 g of what was mostly recovered aldehyde) were resubmitted to the Vilsmeier reaction. A mixture of 5.4 g $POCl_3$ and 4.7 g N-methylformanilide was heated on the steam bath until it became claret-colored. The recovered aldehyde was added, and the mixture was heated overnight on the steam bath. This was poured into 500 mL H_2O. The heavy tar that was knocked out was extracted with 3x75 mL CH_2Cl_2, and the solvent was removed from the pooled extracts under vacuum. Some 5.8 g of residue was obtained, and this was heated to 120 °C at 0.2 mm/Hg to remove all materials lower boiling than the desired aldehyde. The very dark pot was extracted with 3x50 mL boiling hexane, and removal of the solvent from these pooled extracts under vacuum gave 0.9 g of a yellow oil. This was distilled at 0.2 mm/Hg to give a fraction boiling at 130-140 °C which spontaneously crystallized. This pressed on a porous plate gave almost white crystals with a mp of 55-57 °C. Recrystallization from 0.3 mL cyclohexane provided 0.3 g of 4-ethyl-2-methoxy-5-(methylthio)benzaldehyde with a mp of 57-58 °C. The total yield was 1.9 g. Anal. ($C_{11}H_{14}O_2S$) C,H.

To a solution of 1.2 g 4-ethyl-2-methoxy-5-(methylthio)benzaldehyde in 25 mL nitroethane there was added 0.25 g anhydrous ammonium acetate and the mixture was heated on the steam bath. The initial color was green, but this quickly changed to the more usual yellow which darkened as the reaction mixture was heated. After 1.5 h heating, the excess solvent/reagent was removed in vacuo. The

yellow residue was dissolved in 10 mL hot MeOH and allowed to stand in the refrigerator overnight. There was an orange oil layer formed underneath the MeOH. A small sample of this was scratched externally with dry ice, and seed was obtained. The orange oil layer slowly set to crystals which, after a few h, were removed by filtration to give 1.3 g of a slightly sticky orange solid with a mp of 43-45 °C. This was recrystallized from 8 mL boiling MeOH to give, after cooling, filtering, and air drying to constant weight, 1.1 g of 1-(4-ethyl-2-methoxy-5-methylthiophenyl)-2-nitropropene as electrostatic yellow crystals melting at 59-60 °C. Anal. ($C_{13}H_{17}NO_3S$) C,H.

A solution of 1.0 g LAH in 25 mL tetrahydrofuran was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 0.6 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 1.1 g of 1-(4-ethyl-2-methoxy-5-methylthio)-2-nitropropene in a small amount of THF. After 10 min further stirring, it was brought up to room temperature and allowed to stand for several days. The excess hydride was destroyed by the cautious addition of IPA followed by sufficient 15% NaOH to give a white granular character to the aluminum oxide, and to assure that the reaction mixture was basic. This was filtered, and the filter cake washed first with THF and then with IPA. The filtrate and washings were pooled and stripped of solvent under vacuum providing a pale amber residue. This was dissolved in 50 mL of dilute H_2SO_4 and washed with 2x50 mL CH_2Cl_2. The aqueous phase was made basic with 5% NaOH, and extracted wit 2x50 mL CH_2Cl_2. These extracts were pooled, stripped under vacuum, and distilled at 0.15 mm/Hg. The fraction with a bp of 102-128 °C weighed 0.4 g and was a colorless liquid. This was dissolved in a small amount of IPA, neutralized with concentrated HCl and diluted with anhydrous Et_2O to provide the 4-ethyl-2-methoxy-5-methylthioamphetamine hydrochloride (5-TOET) which weighed 0.6 g and melted at 146-147 °C. Anal. ($C_{13}H_{22}ClNOS$) C,H.

DOSAGE: 12 - 25 mg.

DURATION: 8 - 24 h.

QUALITATIVE COMMENTS: (with 8 mg) "After my totally freaky experience on the very closely related compound in this series, 5-TOM, I intended to approach this with some caution. Three milligrams was without effects, so I tried eight milligrams. I was a little light-headed, and saw sort of a brightness around trees against the blue sky. Noticed movement on couch in living room, and there was some activity in the curtains, almost 2C-B like. In the evening writing was still difficult, and there was eye dilation but minimal nystagmus. My sleep was fitful, but certainly there was no hint of the 5-TOM storm."

(with 18 mg) "This was too much. There was an exhausting visual hallucinatory tinsel, continuous movement, and there was no escape. It popped into an LSD-like thing, strong, restless, constantly changing, with too much input. I had to take a Miltown to calm down enough for an attempt at sleep. In the morning, a day later, I was still 1.5 + and tired of it. It was the next day after that before I was completely clear."

(with 20 mg) "This has the makings of a superb, extraordinary material. I didn't get to a full plus two, maybe something around a plus one and three quarters. The eyes-closed fantasy was exceptional, with new dimensions. The nature of the fantasy, the feeling that one had about the fantasy figures and landscapes, was the essence of joy, beauty, lovingness, serenity. A glimpse of what true heaven is supposed to feel like. Or maybe a button in the brain was pushed which has not been pushed by previous chemicals. Insight? Don't know yet. I was able to function without difficulty with eyes closed or open. Erotic absolutely exquisite. In fact, the entire experience was exquisite. Next day, same sense of serene, quiet joy/beauty persisted for most of the day. A true healing potential. Onwards and upwards. This one could be extraordinary."

(with 30 mg) "Tried to focus on cosmic questions, and succeeded. Very little fantasy images for the first 2-3 hours. After that, lovely interacting, music okay but not vital. On this compound the Brahms Concerto #1 gave vivid 'memory' impressions of house and vegetable garden, like a primitive painting. Tremendous nostalgia for a place I've never seen."

EXTENSIONS AND COMMENTARY: With the extraordinary experience that had been observed with one person with 5-TOM, this ethyl homologue was not only run up with special caution, but that individual ran his own personal titration. And he proved to be perhaps twice as sensitive to 5-TOET than any of the other subjects. An approach to what might just be some unusual metabolic idiosyncrasy on the part of his liver, is discussed in the recipe for TOMSO.

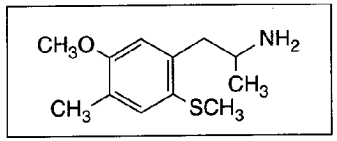
The initials of TOET progressed quite logically from TOM, in an exact parallel with the relationship between the corresponding sulfur-free analogues, where the ethyl compound is DOET and the methyl counterpart is DOM. "T" for "thio" which is the chemical nomenclature term for the replacement of an oxygen atom with a sulfur atom. And, as has been discussed in the text of this volume, the peculiarities of pronunciation in this series are interesting, to say the least. TOM is no problem. But TOET could have any of several pronunciations such as "Two-it", or "Tow-it", or "Too-wet", but somehow the one syllable term "Twat" became regularly used, and the family was generally referred to as the "Toms and Twats." The almost-obscene meaning of the latter was progressively forgotten with usage, and has led to some raised eyebrows at occasional seminars when these compounds are discussed. And not only at seminars. Once at the between-acts intermission at the Berkeley Repertory Theater, the topic came up and the phrase was used. There was a stunned silence about us within the circle of hearing, and we seemed to have been given a little extra room immediately thereafter.

As with the other members of the TOM's and TOET's, the phenethylamine homologue of 5-TOET was synthesized, but had never been started in human

evaluation. The aldehyde from above, 4-ethyl-2-methoxy-5-(methylthio)-benzaldehyde, was condensed with nitroethane (as reagent and as solvent) and with ammonium acetate as catalyst to give the nitrostyrene as spectacular canary-yellow electrostatic crystals with a mp of 91-92 °C. Anal. ($C_{12}H_{15}NO_3S$) C,H. This was reduced with aluminum hydride (from cold THF-dissolved lithium aluminum hydride and 100% sulfuric acid) to the phenethylamine 4-ethyl-2-methoxy-5-methylthiophenethylamine (2C-5-TOET) which, when totally freed from water of hydration by drying at 100 °C under a hard vacuum, had a mp of 216-217 °C. Anal. ($C_{12}H_{20}ClNOS$) C,H.

#171 2-TOM; 5-METHOXY-4-METHYL-2-METHYLTHIO-AMPHETAMINE

SYNTHESIS: To a solution of 64.8 g of o-cresol and 56 g dimethyl sulfoxide in 300 mL Et_2O, cooled with an external ice bath with vigorous stirring, there was added 40 mL chlorosulfonic acid dropwise over the course of 30 min. The cooling bath was removed, and the two phase mixture was mechanically stirred at room temperature for 12 h. The Et_2O phase was then discarded, and the deep red residue that remained was thoroughly triturated under 300 mL IPA, producing a suspension of pale pink solids. These were removed by filtration, washed with an additional 150 mL IPA, and allowed to air dry. The yield of dimethyl (4-hydroxy-3-methylphenyl)sulfonium chloride was 31.6 g and, upon recrystallization from aqueous acetone, had a mp of 155-156 °C, with effervescence. Anal. ($C_9H_{13}ClOS$) C,H,S. This analysis established the anion of this salt as the chloride, whereas the literature had claimed, without evidence, that it was the bisulfate. The thermal pyrolysis of 31.0 g of dimethyl (4-hydroxy-3-methylphenyl)sulfonium chloride resulted first in the formation of a melt, followed by the vigorous evolution of methyl chloride. The open flame was maintained on the flask until there was no more gas evolution. This was then cooled, dissolved in 200 mL CH_2Cl_2, and extracted with 3x100 mL of 5% NaOH. The aqueous extracts were pooled, acidified with concentrated HCl, and extracted with 3x75 mL CH_2Cl_2. The solvent was removed under vacuum, and the residue distilled at 100-110 °C at 0.5 mm/Hg yielding 22.0 g of 2-methyl-4-(methylthio)phenol as a white crystalline solid with a mp 36-37 °C.



To a solution of 25.5 g 2-methyl-4-(methylthio)phenol in 100 mL MeOH there was added a solution of 12 g 85% KOH in 60 mL hot MeOH, followed by the addition of 12.4 mL methyl iodide. The mixture was held at reflux for 16 h. The solvent was removed under vacuum, and the residue added to 400 mL H_2O. This was made basic with 25% NaOH and extracted with 3x100 mL CH_2Cl_2. The extracts

were pooled, the solvent removed under vacuum giving 28.3 g of a light, amber oil as residue. This was distilled at 72-80 °C at 0.5 mm/Hg to provide 2-methyl-4-(methylthio)anisole as a pale yellow oil. Anal. ($C_9H_{12}OS$) C,H. The same product can be made with the sulfonyl chloride and the thiol as intermediates. To 36.6 g 2-methylanisole there was added, with continuous stirring, a total of 38 mL chlorosulfonic acid at a modest rate. The exothermic reaction went through a complete spectrum of colors ending up, when the evolution of HCl had finally ceased, as deep amber. When it had returned again to room temperature, the reaction mixture was poured over a liter of cracked ice which, on mechanical stirring, produced a mass of white crystals. These were removed by filtration, washed with H_2O, and sucked as dry as possible. The wet weight yield was over 40 g and the mp was about 49 °C. Recrystallization of an analytical sample of 4-methoxy-3-methylbenzenesulfonyl chloride from cyclohexane gave white crystals with a mp of 51-52 °C. A small sample of this acid chloride brought into reaction with ammonium hydroxide produced the sulfonamide which, after recrystallization from EtOAc, melted at 135-136 °C. To a slurry of 300 mL cracked ice and 75 mL concentrated H_2SO_4 in a round-bottomed flask equipped with a reflux condenser, there was added 43 g of the slightly wet 4-methoxy-3-methylbenzenesulfonyl chloride followed by 75 g elemental zinc dust. The temperature was raised to a reflux which was maintained for 2 h. The reaction mixture was cooled and filtered, with the finely ground filter cake being washed alternately with H_2O and with CH_2Cl_2. The combined mother liquor and washings were diluted with 1 L H_2O, the phases separated, and the aqueous phase extracted with 100 mL CH_2Cl_2 which was added to the organic phase. This was washed with 100 mL H_2O, and the solvent removed under vacuum. The residue was a pale amber oil weighing 27.3 g and it slowly set up to a crystalline mass that smelled of banana oil. A portion of this, pressed on a porous plate, gave a waxy solid with a mp of 39-43 °C which, on recrystallization from MeOH, gave 4-methoxy-3-(methyl)thiophenol with a mp of 45-46 °C. Anal. ($C_8H_{10}OS$) C,H. A solution of 24 g of the crude thiol in 100 mL MeOH was treated with a solution of 17 g KOH 85% pellets in 100 mL hot MeOH, and to this there was added 16 mL of methyl iodide. This was held at reflux on the steam bath for 1.5 h, then stripped of solvent under vacuum, added to 1 L H_2O, and made strongly basic with 25% NaOH. Extraction with 3x100 mL CH_2Cl_2, pooling of the extracts, and removal of the solvent, gave an amber oil weighing 22.6 g. This was distilled at 70-80 °C at 0.7 mm/Hg to give 16.3 g of 2-methyl-4-(methylthio)anisole as a white oil, identical in all respects to the product that came from the sulfonium salt pyrolysis above.

A solution of 22.1 g 2-methyl-4-(methylthio)anisole and 17.5 g dichloromethyl methyl ether in 600 mL CH_2Cl_2 was vigorously stirred, and treated with 24.5 g anhydrous aluminum chloride added portion-wise over the course of 1 min. Stirring was continued for 20 min while the color developed to a dark red. There was added 500 mL H_2O with caution, and stirring was continued until the initial yellow solids redissolved and there were two distinct phases formed. These were separated, and the aqueous phase was extracted with 3x100 mL CH_2Cl_2. The

original organic phase and the pooled extracts were combined and washed with 5% NaOH. The organic solvent was removed under vacuum. The residue was distilled, giving two major fractions. A forerun (85-95 °C at 0.5 mm/Hg) proved to be largely starting ether. The major fraction (8.4 g, boiling at 95-120 °C) consisted of two materials, both benzaldehydes. Crystallization of this fraction from 30 mL cyclohexane provided, after filtering, washing and air drying, 2.9 g of 5-methoxy-4-methyl-2-(methylthio)benzaldehyde as a pale yellow crystalline solid with a mp of 69-70 °C. Anal. ($C_{10}H_{12}O_2S$) C,H. The mother liquor from this crystallization contained a slower-moving component, 2-methoxy-3-methyl-5-(methylthio)benzaldehyde, which was best separated by preparative gas chromatography. The proof of the structure of the major aldehyde above was obtained by its reductive conversion to 2,5-dimethyl-4-(methylthio)anisole with amalgamated zinc and HCl. The details are given in the recipe for 5-TOM.

To 4 mL glacial acetic acid there was added 1.0 g 5-methoxy-4-methyl-2-(methylthio)benzaldehyde, 0.35 g anhydrous ammonium acetate, and 0.8 g nitroethane, and the mixture was heated on the steam bath for 4 h. Another 0.5 g of nitroethane was added, and the heating continued for an additional 4 h. Standing at room temperature overnight allowed the deposition of spectacular orange crystals which were removed by filtration, washed lightly with acetic acid, and air dried. This product melted at 82-83 °C. Recrystallization from 10 mL boiling MeOH gave 0.7 g of 1-(5-methoxy-4-methyl-2-methylthiophenyl)-2-nitropropene with a mp of 83-84 °C. Anal. ($C_{12}H_{15}NO_3S$) C,H. The alternate method for the formation of nitrostyrenes, the reaction of the benzaldehyde in nitroethane as both reagent and solvent, with ammonium acetate as a catalyst, gave a gummy product that could be purified only with severe losses. The overall yield with this latter method was 24% of theory.

A solution of 1.5 g LAH in 75 mL THF was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.0 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 3.0 g 1-(5-methoxy-4-methyl-2-methylthiophenyl)-2-nitropropene in 20 mL anhydrous THF. After a few min further stirring, the temperature was brought up to a gentle reflux on the steam bath, and then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of IPA followed by sufficient 5% NaOH to give a white granular character to the oxides, and to assure that the reaction mixture was basic. The reaction mixture was filtered, and the filter cake washed first with THF and then with IPA. The filtrate was stripped of solvent under vacuum providing a light yellow oil. This was dissolved in 100 mL dilute H_2SO_4 and then washed with 2x50 mL CH_2Cl_2. The aqueous phase was made basic with 5% NaOH and extracted with 2x50 mL CH_2Cl_2. These were pooled, the solvent removed under vacuum, and the residue distilled at 105-130 °C at 0.25 mm/Hg to give 1.6 g of a white oil. This was dissolved in 8 mL IPA, neutralized with 24 drops of concentrated HCl which formed crystals spontaneously. Another 20 mL of hot IPA was added to effect complete solution, and then this was diluted with anhydrous Et_2O. On cooling fine

white crystals of 5-methoxy-4-methyl-2-methylthioamphetamine hydrochloride (2-TOM) separated. These weighed 1.55 g and had a mp of 195-196 °C. Anal. ($C_{12}H_{20}ClNOS$) C,H.

DOSAGE: 60 - 100 mg.

DURATION: 8 - 10 h.

QUALITATIVE COMMENTS: (with 60 mg) "There is a superb body feeling, and food tasted excellent but then it just might have been excellent food. By the tenth hour, there were absolutely no residues, and I had the feeling that there was no price to pay. Venture up a bit with confidence."

(with 80 mg) "For me this was excellent, in a down-to-earth, humorous, matter-of-fact universe-perspective sense. Very pleasant feeling, although there was a strong body awareness below the waist (not the erotic thing, but rather a slight heaviness, and the next day I came down with a G.I. cold). Very good feeling, and I sense that the depth of the experience is way out there where the big questions lie. I found it easy to go out of body (in the good sense) into a warm, loving darkness. Sliding down by 6, 7th hour, and had no trouble sleeping. Fully scripted dreams, vivid. Very, very good. Want to try 100 mg."

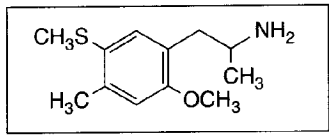
(with 80 mg) "Completely foul taste. The effects were quite subtle, and I found this to be a strange but friendly ++. There was much eyes-closed fantasizing to music, even to Bruchner, whom I found unexpectedly pleasant. There was a feeling of tenseness at the twilight of the experience."

EXTENSIONS AND COMMENTARY: There is a most extraordinary loss of potency with the simple substitution of a sulfur atom for an oxygen atom. DOM is fully active at the 5 or so milligram area, whereas 2-TOM is active at maybe the 80 milligram area, a loss of potency by a factor of x15 or so. And the duration is quite a bit shorter. It might take a fair amount of learning to become completely at peace with it, but it might be worth the effort. And there are none of the disturbing hints of neurological and physical roughness of 5-TOM.

Again, as with the other TOM's and TOET's, the two-carbon homologue of this has been synthesized but not yet evaluated. The common intermediate benzaldehyde, 5-methoxy-4-methyl-2-(methylthio)benzaldehyde was condensed with nitromethane and ammonium acetate to give the nitrostyrene which, upon recrystallization from ethanol, had a melting point of 118-118.5 °C. Anal. ($C_{11}H_{13}NO_3S$) C,H. Reduction with aluminum hydride in THF gave the crystalline free base which, as the hydrochloride salt, melted at 233-234 °C. Anal. ($C_{11}H_{18}ClNOS$) C,H. Quite logically, it has been called 2C-2-TOM.

#172 5-TOM; 2-METHOXY-4-METHYL-5-METHYLTHIO-AMPHETAMINE

SYNTHESIS: To a solution of 6.6 g KOH pellets in 100 mL hot EtOH there was added a solution of 15.4 g methylthio-m-cresol (3-methyl-4-(methylthio)phenol, Crown-Zellerbach Corporation) in 25 mL EtOH. This was followed by the addition of 17 g methyl iodide, and the mixture was held at reflux on the steam bath for 16 h. The reaction mixture was poured into 400 mL H_2O, acidified with HCl, and extracted with 4x50 mL CH_2Cl_2. These were pooled, washed with 3x50 mL 5% NaOH, once with dilute HCl, and then the solvent was removed under vacuum. The residue was 3-methyl-4-(methylthio)anisole, a clear pale yellow oil, weighing 12.7 g. Distillation at 150-160 °C at 1.7 mm/Hg, or at 80-90 °C at 0.25 mm/Hg, did not remove the color, and gave a product with no improvement in purity.



To a mixture of 82 g $POCl_3$ and 72 g N-methylformanilide that had been heated on the steam bath for 10 min, there was added 33.6 g 3-methyl-4-(methylthio)phenol, and heating was continued for an additional 2 h. This was poured into 1.2 L H_2O, producing a brown gummy crystalline mass that slowly loosened on continued stirring. This was filtered off, washed with additional H_2O, and sucked as dry as possible. This was finely ground under 60 mL of cold MeOH, refiltered, and air dried to give 17.8 g of a nearly white crystalline solid with a mp of 94-96 °C. Recrystallization from 50 mL boiling MeOH gave a product of higher purity, but at some cost in yield. With this step there was obtained 13.4 g of 2-methoxy-4-methyl-5-(methylthio)benzaldehyde with a mp of 98-99 °C. An additional recrystallization from IPA increased this mp by another degree. From this final recrystallization, a small amount of material was left as an insoluble residue. It was also insoluble in acetone, but dissolved readily in CH_2Cl_2. It melted broadly at about 200 °C and was not identified. Proof of the structure of 2-methoxy-4-methyl-5-(methylthio)benzaldehyde was obtained by its successful reduction (with amalgamated Zn in HCl) to 2,5-dimethyl-4-(methylthio)anisole. This reference convergence compound was prepared separately from 2,5-dimethylanisole which reacted with chlorosulfonic acid to give the 4-sulfonyl chloride derivative, which was in turn reduced to the 4-mercapto derivative (white crystals from MeOH, with a mp of 38 °C sharp). This, upon methylation with methyl iodide and KOH in MeOH, gave 2,5-dimethoxy-4-(methylthio)anisole (white crystals from MeOH, with a mp of 67-68 °C). The two samples (one from the aldehyde reduction, and the other from this independent synthesis), were identical in all respects.

A solution of 1.9 g 2-methoxy-4-methyl-5-(methylthio)benzaldehyde in 40 mL nitroethane was treated with 0.5 g anhydrous ammonium acetate and heated under reflux, with stirring, with a heating mantle for 3.5 h, at which time TLC analysis showed no unreacted aldehyde and only a trace of slow moving materials. Removal of the excess nitroethane under vacuum gave a yellow plastic film (the wrapping of the magnetic stirrer had dissolved off) which was extracted first with 35 mL boiling MeOH, then with 2x35 mL boiling IPA. Separately, the MeOH extract and the combined IPA extracts, on cooling, deposited 0.6 g each of fluffy needles. The mother liquors were combined and allowed to evaporate to about 15 mL final volume, providing another 0.4 g crude product. All three samples melted at 101-102 °C. These were combined, and recrystallized from 50 mL boiling MeOH to provide, after filtering and air drying, 1.4 g of 1-(2-methoxy-4-methyl-5-methylthiophenyl)-2-nitropropene as bright yellow crystals with a mp of 102-102.5 °C. Anal. ($C_{12}H_{15}NO_3S$) C,H.

A solution of 2.0 g LAH in 100 mL anhydrous THF was cooled, under He, to 0 °C with an external ice bath. With good stirring there was added 1.28 mL 100% H_2SO_4 dropwise, to minimize charring. This was followed by the addition of 1.35 g 1-(2-methoxy-4-methyl-5-methylthiophenyl)-2-nitropropene in 50 mL anhydrous THF over the course of 5 min. After a few min further stirring, the temperature was brought up to a gentle reflux on the steam bath, and then all was cooled again to 0 °C. The excess hydride was destroyed by the cautious addition of 5 mL IPA followed by sufficient 5% NaOH to give a white granular character to the oxides, and to assure that the reaction mixture was basic (about 5 mL was used). The reaction mixture was filtered, and the filter cake washed first with THF and then with IPA. The combined filtrate and washings were stripped of solvent under vacuum and the residue dissolved in 150 mL dilute H_2SO_4. This was washed with 3x50 mL CH_2Cl_2 (the color stayed in the organic layer), made basic with aqueous NaOH, and extracted with 2x50 mL CH_2Cl_2. After the solvent was removed under vacuum, the residue was distilled at 110-125 °C at 0.4 mm/Hg to give 0.9 g of a colorless oil. This was dissolved in 4 mL IPA, neutralized with about 11 drops of concentrated HCl, and then diluted with 20 mL anhydrous Et_2O. After about a ten second delay, white crystals formed. These were removed by filtration and air dried, to give 0.6 g of 2-methoxy-4-methyl-5-methylthioamphetamine hydrochloride (5-TOM) as white crystals with a mp of 156-157 °C. A second crop obtained from the mother liquors on standing weighed 0.3 g and melted at 150-156 °C. Anal. ($C_{12}H_{20}ClNOS$) C,H.

DOSAGE: 30 - 50 mg.

DURATION: 6 - 10 h.

QUALITATIVE COMMENTS: (with 35 mg) "There was an awful lot of visual activity, and in general I found the day quite good, once I got past the early discomfort."

(with 40 mg) "I knew that I was sinking into a deep reverie after an hour into it. I was not totally unconscious since I seemed to respond to external stimuli (at least most of the time). But I certainly wasn't all that much there. The experience dominated completely. At one point (perhaps the peak?) I remember seeing

a very quiet sea with a horizontal shoreline and a clear sky. This image seemed to come back rather frequently. At other times I would see a set of disjointed horizontal lines on this beach. These lines reminded me of spectral lines. For a short period of time I thought they were some kind of expression of my energy levels that I didn't understand. In retrospect, I suspect the horizontal lines were only expressions of how my mind was reacting to the material. I don't remember talking to anyone until I had started to come down from the experience. I eventually could see real images, but they were greatly distorted. It was as if I was looking at Cubism paintings by Picasso, having intense and strange colorations. As I came back into the real world, I realized that I had had an extraordinary trip. I had not been afraid at any time. The experience seemed unique, but quite benign. The experience for my fellow travelers was probably much more anxious. I wasn't particularly interested in food when I came down. I slept well. I was quite lethargic the next day. It really took me another day to integrate back into normal life. Would I repeat it? Possibly, but at a way smaller dose."

(with 50 mg) "The body was complete whacked, and the mental simply didn't keep up with it. There was some early nausea going into it, and my sinuses never cleared, and I somehow became irritable and angry. In fact, the impatience and grimness lasted for a couple of days. There were some visual events that might have been interesting to explore, but too much other stuff got in the way."

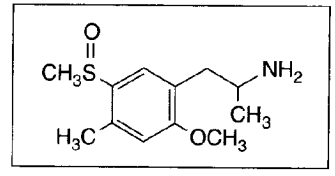
(with 50 mg) "There was much eyes-closed fantasy, and quite a bit of it with erotic undertones. In efforts to direct my actions, I found it difficult to find the point of initiation of a task. Reading and writing both impossible. I am somehow de-focused. But art work became quite rewarding. The experience was heavy going in, but rich coming out. Good dosage."

EXTENSIONS AND COMMENTARY: The bottom line is that 5-TOM is a pretty heavy-duty experience, with more negative reports than positive ones. I have received no mentions of a completely ecstatic time, and not even very many neutral experiences. The consensus is that it wasn't worth the struggle. Some cramping, some nausea, and a generalized discomfort. And that one case of a catatonic response. An approach to possible individual variation in the metabolic handling of the sulfur atom is the rationale for the preparation of the compound TOMSO, and it is discussed there.

The two-carbon homologue of 5-TOM has been prepared. It uses, of course, the same aldehyde, but the condensation was with nitromethane which yielded the nitrostyrene as an orange powder with a melting point of 118-119 °C from methanol. This was reduced with LAH in ether containing anhydrous $AlCl_3$, giving 2-methoxy-4-methyl-5-methylthiophenethylamine hydrochloride as white crystals with a melting point of 257-258 °C. It has been named 2C-5-TOM, but it has not yet been entered into the screening program so it is pharmacologically still a mystery.

#173 TOMSO; 2-METHOXY-4-METHYL-5-METHYLSULFINYLAMPHETAMINE

SYNTHESIS: A suspension of 12.7 g 1-(2-methoxy-4-methyl-5-methylthiophenyl)-2-nitropropene (see under 5-TOM for its preparation) in 50 mL warm acetic acid was added to a suspension of 22.5 g electrolytic grade elemental iron in 100 mL warm acetic acid. The temperature was raised cautiously until an exothermic reaction set in, and the mixture was maintained under reflux conditions as the color progressed from yellow to deep brown to eventually colorless. After coming back to room temperature, the somewhat gummy mixture was poured into 1 L H_2O, and all insolubles were removed by filtration. These were washed with CH_2Cl_2, and the aqueous filtrate was extracted with 3x100 mL CH_2Cl_2. The washes and extracts were combined, washed with 5% NaOH until the bulk of the color was removed and the washes remained basic, and the solvent was then removed under vacuum. The residue, 11.6 g of a pale amber oil that crystallized, was distilled at 110-120 °C at 0.4 mm/Hg to give 9.9 g 2-methoxy-4-methyl-5-methylthiophenylacetone with a mp of 41-42 °C. This was not improved by recrystallization from hexane. Anal. ($C_{12}H_{16}O_2S$) C,H.



To a solution of 7.3 g 2-methoxy-4-methyl-5-methylthiophenylacetone in 35 mL methanol there was added 7.3 mL 35% hydrogen peroxide, and the mixture held under reflux conditions for 40 min. All volatiles were removed under vacuum, and the residue suspended in 250 mL H_2O. This was extracted with 3x50 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. The residue, 8.6 g of an oily solid, was recrystallized from 10 mL boiling toluene to provide, after filtering and air drying, 5.4 g of 2-methoxy-4-methyl-5-methylsulfinylphenylacetone as a white solid with a mp of 89-89.5 °C. Anal. ($C_{12}H_{16}O_3S$) C,H.

To a vigorously stirred solution of 5.2 g of 2-methoxy-4-methyl-5-methylsulfinylphenylacetone in 70 mL MeOH there was added 17 g anhydrous ammonium acetate followed by 1.0 g sodium cyanoborohydride. HCl was added as needed to maintain the pH at about 6 as determined with damp universal pH paper. No further base was generated after 3 days, and the reaction mixture was poured into 500 mL H_2O. After acidification with HCl (caution, highly poisonous HCN is evolved), this was washed with 2x100 mL CH_2Cl_2, made strongly basic with NaOH, and then extracted with 3x100 mL CH_2Cl_2. The pooled extracts were stripped of solvent under vacuum, and the residue weighed 7.1 g and was a pale amber oil. This was distilled at 150-160 °C at 0.3 mm/Hg to give a colorless oil weighing 4.4 g. A solution of this in 13 mL IPA was neutralized with 30 drops of concentrated HCl and the resulting solution warmed and diluted with 20 mL of warm anhydrous Et_2O. White crystals separated immediately and, after filtering, ether washing and air drying, provided 4.4 g of 2-methoxy-4-methyl-5-methylsulfinylamphetamine hydrochloride (TOMSO) that melted at 227-229 °C after vacuum drying for 24 hrs.

Anal. ($C_{12}H_{20}ClNO_2S$) C,H. The presence of two chiral centers (the alpha-carbon of the amphetamine side chain and the sulfoxide group at the 5-position of the ring) dictates that this product was a mixture of diastereoisomeric racemic compounds. No effort was made to separate them.

DOSAGE: greater than 150 mg (alone) or 100 - 150 mg (with alcohol).

DURATION: 10 - 16 h.

QUALITATIVE COMMENTS: (with 100 mg) "There were no effects at all, and it was at the so-called surprise pot-luck birthday lunch for the department chairman that I ate a little and had two glasses of Zinfandel. I shot up to an immediate ++ and this lasted all afternoon. I went to San Francisco by BART, and walked up Market Street and saw all the completely bizarre faces. I was absolutely unable to estimate the age of anybody who was female, at least by looking at her face. All aspects, both child-like and old, seemed to be amalgamated into each face, all at the same time. There was remarkable time-slowing; overall the experience was favorable. That certainly was not the effect of the alcohol in the wine. Food poisoning? No. It must have been the TOMSO that had been kindled and promoted to something."

(with 150 mg) "At best there is a threshold and it is going nowhere. At the third hour I drank, over the course of an hour, a tall drink containing 3 oz. of vodka. Soon I was clearly somewhere, and three hours later I was a rolling plus three. This lasted until well after midnight, and was not an alcohol response."

EXTENSIONS AND COMMENTARY: This entire venture into the study of TOMSO was an outgrowth of the extraordinary response that had been shown by one person to 5-TOM. There were two obvious approaches that might throw some light on the reason for this dramatic sensitivity. One would be to see if he was unusually capable of metabolizing sulfur-containing molecules, and the second would be to assume he was, and to try to guess just what product he had manufactured with his liver.

The individual sensitivity question was addressed in a tidy and direct manner. Why not study a simple sulfur-containing model compound that would probably be metabolized only at the sulfur and that would itself probably be pharmacologically inactive in its own rights? Sounded OK to me, so I made up a goodly supply of 4-tert-butyl thioanisole, which proved to be a gorgeous white crystalline solid. It seemed quite logical that this would be metabolized at the sulfur atom to produce either or both the sulfoxide and the sulfone. So I treated a methanol solution of this with a little hydrogen peroxide and distilled the neutral extracts at 100-115 °C at 0.2 mm/Hg to give the sulfoxide as a solid that melted at 76-77 °C from hexane: Anal. ($C_{11}H_{16}OS$) C,H. On the other hand, if a solution of the thioanisole in acetic acid containing hydrogen peroxide was heated on the steam bath for a few hours and then worked up, a new solid was isolated that proved to be the sulfone (a negative Fries-Vogt test). This was obtained as white crystals with a mp of 94-95 °C from aqueous methanol. Anal. ($C_{11}H_{16}SO_2$) C,H. And I found that these three compounds separated well from one another by GC, and that they could be extracted from urine. Everything was falling into place. My thought was to determine a safe (inactive) level of the parent thioanisole, and determine the distribution of metabolites in my urine, and then in the urine of several other people, and then finally in the urine of the person who was the intense reactor to 5-TOM. I found that there were no effects, either physical or psychological, at an oral dose of 60 milligrams of 4-tert-butyl-thioanisole. But then everything fell apart. There was not a detectable trace of anything, neither parent compound nor either of the potential metabolites, to be found in my urine. The material was obviously being completely converted to one or more metabolites, but the sulfoxide and sulfone were not among them. It would be fun, someday, to methodically trace the fate of this compound.

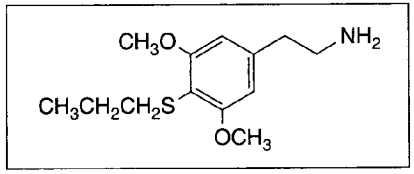
So, on to the second approach. What might the active metabolite of 5-TOM actually be? The sulfoxide seemed completely reasonable, and that encouraged the synthesis of TOMSO. This name was given, as it is the sulfoxide analogue (SO) of 5-TOM. And since only one of these analogues has been made, the "5" distinction is not needed. But it is apparent that this approach to the finding of an explanation for the idiosyncratic sensitivity to 5-TOM also failed, in that TOMSO itself appeared to be without activity.

But the fallout of this study was the uncovering of an unusual property that alcohol can occasionally have when it follows the ingestion of certain inactive drugs. Or if it is used at the tail end of an experience with an active drug. Usually some alcohol has been employed as a softener of the residual effects of the day's experiment, or as a social habit to accompany the post-mortem discussions of a day's experiences, and perhaps as a help to sleeping. But if there is a rekindling of the effect, rather than the sedation expected, then the verb "to tomso" can be used in the notes. It represents the promotion of an inactive situation into an active one, with the catalysis of alcohol. But the effect is not that of alcohol. Might the extreme sensitivity of some alcoholics to even a small amount of alcohol be due to some endogenous "inactive" factor that is promoted in this way into some centrally florid toxicity? I remember seeing proposals of some tetrahydroisoquinolines as potential mis-metabolites in efforts to explain the toxicity of alcohol. Maybe they are nothing more than psychedelics that are thought to be inactive, but which might be ignited with a glass of wine. And the person is tomsoing with his small amount of alcohol.

#174 TP; THIOPROSCALINE; 3,5-DIMETHOXY-4-(n)-PROPYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution was made of 12.1 g N,N,N',N'-tetramethylethylenediamine and 13.8 g of 1,3-dimethoxybenzene in 200 mL 30-60 °C petroleum ether. This was

stirred vigorously under a He atmosphere and cooled to 0 °C with an external ice bath. There was added 66 mL of 1.6 M butyllithium in hexane which produced a white granular precipitate. The reaction mixture was brought up to room temperature for a few minutes, and then cooled again to 0 °C. There was then added 15.8 g of di-(n)-propyl disulfide which changed the granular precipitate to a creamy appearance. Stirring was continued while the reaction mixture was brought up to room temperature and finally up to reflux. The reaction mixture was then added to 600 mL of dilute H_2SO_4. The two phases were separated, and the aqueous phase extracted with 2x75 mL Et_2O. The organic phases were combined, and the solvent removed under vacuum. The residue was 24.2 g of a pale amber liquid which was distilled at 0.35 mm/Hg to give two fractions. The first boiled at 85-90 °C, weighed 0.5 g and appeared to be recovered dipropyl disulfide. The product 2-(n)-propylthio-1,3-dimethoxybenzene boiled at at 105-125 °C, and weighed 20.8 g. A small sample recrystallized from hexane had a mp of 27-28 °C. Anal. ($C_{11}H_{16}O_2S$) C,H.



To a stirred solution of 19.8 g of 2-(n)-propylthio-1,3-dimethoxybenzene in 200 mL CH_2Cl_2 there was added 15.4 g elemental bromine dissolved in 100 mL CH_2Cl_2. The reaction was not exothermic, and it was allowed to stir for 1 h. The reaction mixture was washed with H_2O containing sodium hydrosulfite (which rendered it nearly colorless) and finally washed with saturated brine. The solvent was removed under vacuum leaving 33.5 g of a pale yellow liquid. This was distilled at 112-120 °C at 0.3 mm/Hg to yield 4-bromo-2-(n)-propylthio-1,3-dimethoxybenzene as a pale yellow oil. Anal. ($C_{11}H_{15}BrO_2S$) C,H.

To a solution of 16.8 g diisopropylamine in 100 mL anhydrous THF that was stirred under a N_2 atmosphere and cooled to -10 °C with an external ice/MeOH bath, there was added in sequence 75 mL of 1.6 M butyllithium in hexane, 3.0 mL of dry CH_3CN, and 8.7 g of 4-bromo-2-(n)-propylthio-1,3-dimethoxybenzene which had been dissolved in 20 mL THF. The bromo compound was added dropwise over the course of 5 min. The color became deep red-brown. Stirring was maintained for a total of 30 min while the reaction came to room temperature. It was then poured into 750 mL dilute H_2SO_4, the organic layer separated, and the aqueous phase extracted with 2x100 mL CH_2Cl_2. These extracts were pooled, washed with dilute H_2SO_4, and the solvent was removed under vacuum yielding a residue that was distilled. Two distillation cuts were taken at 0.3 mm/Hg. The first fraction boiled at 110-138 °C and weighed 0.7 g and was discarded. The second fraction came over at 148-178 °C and weighed 3.0 g. By thin layer chromatography this fraction was about 80% pure, and was used as such in the following reduction. A small sample was ground under methyl cyclopentane yielding white crystals of 3,5-dimethoxy-4-(n)-propylthiophenylacetonitrile with a mp of 35.5-37.5 °C.

A solution of LAH in THF (15 mL of a 1 M solution) under N_2 was cooled

to 0 °C and vigorously stirred. There was added, dropwise, 0.4 mL 100% H_2SO_4, followed by 2.7 g 3,5-dimethoxy-4-(n)-propylthiophenylacetonitrile dissolved in 10 mL anhydrous THF. The reaction mixture was stirred at 0 °C for a few min, then brought to a reflux for 30 min on the steam bath. After cooling back to room temperature, there was added IPA to destroy the excess hydride and 10% NaOH to bring the reaction to a basic pH and converted the aluminum oxide to a loose, white, filterable consistency. This was removed by filtration and washed with both THF and IPA. The filtrate and washes were stripped of solvent under vacuum, the residue added to 1 L dilute H_2SO_4. This was washed with 2x75 mL CH_2Cl_2, made basic with aqueous NaOH, extracted with 3x75 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. The residue was distilled at 137-157 °C at 0.3 mm/Hg to give 1.3 g of a colorless oil. This was dissolved in 10 mL of IPA, neutralized with 20 drops of concentrated HCl and, with continuous stirring, diluted with 50 mL anhydrous Et_2O. The product was removed by filtration, washed with Et_2O, and air dried to give 1.4 g of 3,5-dimethoxy-4-(n)-propylthiophenethylamine hydrochloride (TP) as bright white crystals with a mp of 164-165 °C. Anal. ($C_{13}H_{22}ClNO_2S$) C,H.

DOSAGE: 20 - 25 mg.

DURATION: 10 - 15 h.

QUALITATIVE COMMENTS: (with 18 mg) "There was very little effect until more than two hours, when I came inside out of the cold and jumped to an immediate +1. It is hard to define, and I am quite willing to have it develop more, and if not, quite willing to go higher next time. I got into several quite technical conversations, but through it all I was aware of a continuous alteration. There was a drop at the seventh hour, and nothing at all was left at twelve hours."

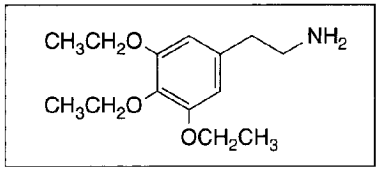
(with 27 mg) "My body feels heavy. This is not a negative thing, but it is there. I feel a heavy pressure at the back of the neck, which is probably unresolved energy. The nervous system seems to be somehow vunerable. Towards the end of the experience I considered a Miltown, but settled on an aspirin, and I still couldn't sleep for about 24 hours. The imagery is extremely rich and there is quite a bit of eyes-open visual, but mostly eyes closed. I think the rewards are not worth the body price. Sometime again, maybe lower?"

EXTENSIONS AND COMMENTARY: There is a high potency here, but clearly there are signs of increased toxicity as well even over the ethyl homologue, TE. The butyl compound (see TB) was the last of this series of phenethylamines and as is noted there, the physical problems lessen, but so do the psychedelic properties. The three-carbon amphetamine homologues are completely unexplored. The most reasonable starting material for these would be 4-thiosyringaldehyde, with S-alkylation and then the conventional nitroethane coupling followed with LAH reduction. The most appealing target as a potential psychedelic would be the

methylthio homologue (3,5-dimethoxy-4-methylthioamphetamine, 3C-TM) or, as a potential euphoriant, the butylthio homologue (3,5-dimethoxy-4-(n)-butylthio-amphetamine, 3C-TB). I am not sure that these alkylthio analogues would justify the labor needed to make them.

#175 TRIS; TRESCALINE; TRISESCALINE; 3,4,5-TRIETHOXYPHENETHYLAMINE

SYNTHESIS: A solution of 16.9 g of ethyl 3,4,5-triethoxybenzoate in 25 mL THF was added to a well stirred suspension of 8 g LAH in 150 mL THF. The mixture was heated at reflux for 24 h and and, after cooling, treated with IPA to destroy the excess hydride. There was then added sufficient 25% NaOH to produce a granular, white form of the aluminum oxide. This was removed by filtration, the filter cake washed with IPA, and the filtrate and washes were combined and stripped of solvent under vacuum. The residue weighed 12.2 g and was distilled at 120-140 °C at 0.4 mm/Hg to yield 8.6 g of 3,4,5-triethoxybenzyl alcohol that spontaneously crystallized. It had a mp of 29-30 °C and was free of the parent ester carbonyl absorption at 1709 cm^{-1} in the infra-red.



This product 3,4,5-triethoxybenzyl alcohol was suspended in 30 mL concentrated HCl, heated briefly on the steam bath, cooled to room temperature, and suspended in a mixture of 75 mL CH_2Cl_2 and 75 mL H_2O. The phases were separated, and the aqueous phase extracted with another 75 mL CH_2Cl_2. The organic fractions were combined, washed first with H_2O and then with saturated brine. Removal of the solvent under vacuum yielded an off-white oil that was distilled at 112-125 °C at 0.4 mm/Hg to provide 7.5 g of 3,4,5-triethoxybenzyl chloride that spontaneously crystallized. The crude product had a mp of 34-37 °C which was increased to 37.5-38.5 °C upon recrystallization from hexane. Anal. ($C_{13}H_{19}ClO_3$) C,H.

A solution of 4.5 g 3,4,5-triethoxybenzyl chloride in 10 mL DMF was treated with 5.0 g sodium cyanide and heated for 1 h on the steam bath. The mixture was then poured into 100 mL H_2O and the oily phase that resulted immediately crystallized. This was filtered off, washed well with H_2O, air dried, and distilled at 128-140 °C at 0.25 mm/Hg to yield 3.7 g of 3,4,5-triethoxyphenylacetonitrile which melted at 54-56.5 °C. There was a sharp nitrile band at 2249 cm^{-1}. Anal. ($C_{14}H_{19}NO_3$) C,H.

To 18.8 mL of a 1 M solution of LAH in THF under N_2, vigorously stirred and cooled to 0 °C, there was added, dropwise, 0.50 mL 100% H_2SO_4. This was followed by 3.6 g 3,4,5-triethoxyphenylacetonitrile in 10 mL anhydrous THF over the course of 5 min. The reaction mixture was brought to room temperature and stirred for a few min, and finally held at reflux on the steam bath for 1 h. After cooling back to room temperature, there was added about 2 mL IPA (to destroy the excess hydride) followed by sufficient 15% NaOH to make the aluminum oxide granular and white, and the organic solution basic. The solids were removed by filtration, and washed with IPA. The filtrate and washes were stripped of solvent under vacuum, the residue added to 400 mL dilute H_2SO_4. This was washed with 2x75 mL CH_2Cl_2, the aqueous phase made basic with aqueous. NaOH, and the product extracted with 2x75 mL CH_2Cl_2. These extracts were pooled, the solvent removed under vacuum, and the residue distilled at 115-135 °C at 0.4 mm/Hg to give a white oil. This was dissolved in a few mL of IPA, neutralized with concentrated HCl, and diluted with anhydrous Et_2O to the point of turbidity. When the crystal formation was complete, the product was removed by filtration, washed with Et_2O, and air dried to give 2.8 g 3,4,5-triethoxyphenethylamine hydrochloride (TRIS) as white crystals with a mp of 177-178 °C.

DOSAGE: greater than 240 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 240 mg) "No effects were noted at any time following 240 milligrams of trisescaline. This would have been a thoroughly active level of the trimethoxy counterpart, mescaline."

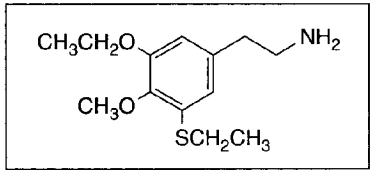
EXTENSIONS AND COMMENTARY: With the progressive diminution of human potency with increased ethylation of the mescaline molecule, there is no suprise in finding that this base is devoid of activity. Studies done years ago in the cat at a dosage of 25 mg/Kg (i.m.) gave none of the expected, and looked for, signs of behavioral changes (pilomotor activity, pupillary dilation, growling, hissing, aggressive behavior, withdrawal, or salivation) that are often seen with the less bulky substituents. It was without action.

More lengthy substituents in the 3,4,5-positions (with combinations of ethyls and propyls, for example) are presently unknown compounds, and there is small incentive to make them.

#176 3-TSB; 3-THIOSYMBESCALINE; 3-ETHOXY-5-ETHYLTHIO-4-METHOXYPHENETHYLAMINE

SYNTHESIS: A solution of 13.4 g 3-bromo-N-cyclohexyl-4-methoxy-5-ethoxy-benzylidenimine (see under ME for its preparation) in 150 mL anhydrous Et_2O was placed in a He atmosphere, well stirred, and cooled in an external dry ice/acetone

bath to -80 °C. There was the formation of a granular precipitate. There was then added 28 mL of 1.6 N butyllithium in hexane over the course of 5 min, and the mixture (which had turned quite creamy) was stirred for 15 min. This was followed by the addition of 5.5 g diethyl disulfide over the course of 1 min. The mixture was allowed to come to room temperature over the course of 1 h, and then added to 100 mL of dilute HCl. The Et_2O phase was separated and the solvent removed under vacuum. The residue was dissolved in 50 mL MeOH, combined with the original aqueous phase, and the entire mixture heated on the steam bath for 0.5 h. The aqueous solution was cooled to room temperature, extracted with 3x100 mL CH_2Cl_2, the extracts pooled, and the solvent removed under vacuum. The residue was distilled at 132-140 °C at 0.3 mm/Hg to yield 9.1 g of 3-ethoxy-5-ethylthio-4-methoxybenzaldehyde as a white oil that, on standing for several months, spontaneously crystallized. A small bit of the crystalline solid was wastefully recrystallized from MeOH to provide white crystals with a mp of 31.5-32.5 °C. Anal. ($C_{12}H_{16}O_3S$) C,H. The crude distillate was used in the following reactions.



Several attempts were made to prepare the nitrostyrene from this aldehyde and nitromethane. The most successful, but still inadequate, procedure is described here. A solution of 1.0 g 3-ethoxy-5-ethylthio-4-methoxybenzaldehyde in 10 mL nitromethane was treated with about 150 mg of anhydrous ammonium acetate and heated on the steam bath. The course of the reaction was followed by TLC. The bulk of the aldehyde had disappeared in 45 min, and there were several UV-absorbing spots visible. Removal of the excess nitromethane under vacuum gave an orange oil which, when rubbed under cold MeOH, gave 200 mg of yellow solids. This was (by TLC) a mixture of nitrostyrene, starting aldehyde, and several slow-moving scrudge impurities. Recrystallization from MeOH gave a poor recovery of a yellow solid with a mp of 102.5-104 °C but this was still contaminated with the same impurities. Several repetitions of this synthetic procedure gave little if any of the desired 3-ethoxy-5-ethylthio-4-methoxy-ß-nitrostyrene.

A suspension of 5.4 g methyltriphenylphosphonium bromide in 30 mL anhydrous THF was placed under a He atmosphere, well stirred, and cooled with an external water bath. There was then added 10 mL of 1.6 N butyllithium in hexane which resulted in the generation of a bright pumpkin color. The initial heavy solids changed into a granular precipitate. There was then added 2.4 g of 3-ethoxy-5-ethylthio-4-methoxybenzaldehyde in a little THF. An initial gummy phase became granular with patient swirling and stirring. After 30 min, the reaction was quenched in 500 mL H_2O, the top hexane layer separated, and the aqueous phase extracted with 2x75 mL of petroleum ether. The organic fractions were combined, washed with H_2O, dried over anhydrous K_2CO_3, and the solvents removed under vacuum to give the crude 3-ethoxy-5-ethylthio-4-methoxystyrene as a yellow mobile liquid.

A solution of 2 mL of borane-methyl sulfide complex (10 M BH_3 in methyl sulfide) in 20 mL THF was placed in a He atmosphere, cooled to 0 °C, treated with 4.2 mL of 2-methylbutene, and stirred for 1 h while returning to room temperature. To this there was added a solution of the impure 3-ethoxy-5-ethylthio-4-methoxystyrene in a little anhydrous THF. This was stirred for 1 h. The excess borane was destroyed with 1 mL MeOH, followed by the addition of 3.8 g elemental iodine, followed in turn by a solution of 0.8 g NaOH in hot MeOH added over the course of 5 min. The color gradually faded, and became a pale lime green. This was added to 300 mL dilute aqueous sodium thiosulfate which was extracted with 2x100 mL petroleum ether. The extracts were pooled, and the solvent evaporated under vacuum to provide crude 1-(3-ethoxy-5-ethylthio-4-methoxyphenyl)-2-iodoethane as a residue.

To this crude 1-(3-ethoxy-5-ethylthio-4-methoxyphenyl)-2-iodoethane there was added a solution of 3.7 g potassium phthalimide in 50 mL anhydrous DMF, and all was heated on the steam bath. The reaction seemed to be complete after 15 min (as seen by TLC) and the addition of a second batch of potassium phthalimide in DMF produced no further change. After adding to 500 mL of dilute NaOH, the aqueous phase was extracted with 2x75 mL Et_2O. These extracts were combined, washed first with dilute NaOH and then with dilute H_2SO_4, dried over anhydrous K_2CO_3, and the solvent removed under vacuum which provided an amber oil as residue. This was triturated under cold MeOH giving white solids which were recrystallized from 20 mL MeOH. Thus there was obtained 0.9 g of 1-(3-ethoxy-5-ethylthio-4-methoxyphenyl)-2-phthalimidoethane as white crystals that melted at 79-80.5 °C. A small sample was recrystallized from EtOH to give large flat needles with a mp of 81-82 °C. Anal. ($C_{21}H_{23}NO_4S$) C,H.

A suspension of 0.8 g of the crystallized 1-(3-ethoxy-5-ethylthio-4-methoxyphenyl)-2-phthalimidoethane in 25 mL of n-butanol was treated with 2 mL of 66% hydrazine, and the mixture was heated on the steam bath for 0.5 h. Initially all went into solution, and then there was the separation of solids that resembled cottage cheese. The reaction mixture was added to 150 mL dilute H_2SO_4. The solids were removed by filtration, and the filtrate was washed with 3x50 mL CH_2Cl_2. These washes were discarded. The H_2O phase was then made basic with aqueous NaOH, extracted with 2x75 mL CH_2Cl_2, and the solvent from these pooled extracts removed under vacuum. The residue was distilled at 135-155 °C at 0.3 mm/Hg to give 0.45 g of a colorless oil. This was dissolved in 2.5 mL IPA, neutralized with 5 drops of concentrated HCl, and diluted with 10 mL anhydrous Et_2O. The solution became cloudy, and then deposited lustrous white plates. These were removed by filtration, washed with additional Et_2O, and air dried to give 0.4 g of 3-ethoxy-5-ethylthio-4-methoxyphenethylamine hydrochloride (3-TSB) with a mp of 153.5-154.5 °C. Anal. ($C_{13}H_{22}ClNO_2S$) C,H.

DOSAGE: greater than 200 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 200 mg) "No effects whatsoever, neither mental nor physical."

EXTENSIONS AND COMMENTARY: The elephant labored and brought forth a mouse. A lot of work for a material without activity.

I have used the term "scrudge" in this and other recipes, without defining it. With this aldehyde, as with most aldehydes in this nitrostyrene synthesis reaction where there is no ortho-substituent on the benzaldehyde, the reaction progress should be carefully followed by thin-layer chromatography. As the aldehyde disappears from the reaction mixture, the nitrostyrene appears, but there is usually the development of one or more slower moving components as seen by TLC. Such a wrong-product is called scrudge. The reaction should be continuously titrated, and stopped when there is a favorable balance between the aldehyde being mostly gone, the nitrostyrene being mostly made, and the slower-moving scrudge components being not yet too plentiful. Methylene chloride is an excellent solvent to try first, with silica gel plates and UV detection. The nitrostyrene is always the fastest moving component of the reaction mixture and often fluoresces a dull purple. The starting aldehyde is the second spot and usually fluoresces white or pale yellow. The scrudge spots then occur in a cascade from the aldehyde to the origin. A maddening property is that they are yellow or brown colored, and in the probe mass spectrograph they can crack to give rise to what appears to be the right nitrostyrene. Usually, they are high melting.

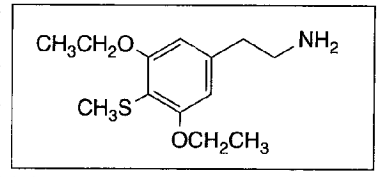
In this preparation, there was not one but several scrudges, and little if any nitrostyrene. The same was true for the other of the diethyl compounds such as 3-TASB, 5-TASB and 3-T-TRIS. Thus, it is preferable to circumvent this usual synthetic step by using the Wittig reaction instead, as described here.

#177 4-TSB; 4-THIOSYMBESCALINE; 3,5-DIETHOXY-4-METHYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution of 12.1 g N,N,N',N'-tetramethylethylenediamine and 16.6 g of 1,3-diethoxybenzene was made in 200 mL 30-60 °C petroleum ether. This was stirred vigorously under a N_2 atmosphere and cooled to 0 °C with an external ice bath. There was added 66 mL of 1.6 M butyllithium in hexane. The stirred reaction mixture became a little cloudy and then gradually formed a white granular precipitate. This was brought to room temperature, stirred for 0.5 h, and returned again to 0 °C. There was added 9.45 g of dimethyl disulfide which converted the loose precipitate to a creamy texture. The reaction was exothermic. After being held 0.5 h at reflux temperature, the reaction mixture was added to 600 mL dilute H_2SO_4. There was the immediate formation of white solids which were insoluble in either phase. The petroleum ether phase was separated, and the aqueous phase extracted

with 3x100 mL Et_2O. The organics were combined, and the solvents removed under vacuum. There was obtained as residue 24.8 g of a slightly oily crystalline solid that, after trituration under 30 mL cold hexane, filtering, and air drying, weighed 16.9 g. This product, 2,6-diethoxythioanisole, had a mp of 71-72 °C which was not improved by recrystallization from methylcyclopentane. Anal. ($C_{11}H_{16}O_2S$) C,H.

To a stirred solution of 16.7 g of 2,6-diethoxythioanisole in 175 mL CH_2Cl_2 there was added 13 g elemental bromine dissolved in 100 mL CH_2Cl_2. After stirring at ambient temperature 1 h, the dark solution was added to 150 mL H_2O containing 1 g of sodium dithionite. Shaking immediately discharged the residual bromine color, and the organic phase was separated. The aqueous phase was extracted once with 100 mL CH_2Cl_2, the pooled extracts washed first with H_2O, and then with saturated brine. Removal of the solvent under vacuum provided 28.6 g of a pale yellow oil with several globs of H_2O present. This wet product was distilled at 118-125 °C at 0.25 mm/Hg to yield 3-bromo-2,6-diethoxythioanisole as a white oil weighing 21.5 g. It could not be crystallized. Anal. ($C_{11}H_{15}BrO_2S$) C,H.



To a solution of 19.3 g diisopropylamine in 75 mL hexane under a He atmosphere there was added 100 mL of 1.6 M butyllithium. The viscous mixture was loosened by the addition of 200 mL anhydrous THF, and this stirred mixture was cooled with an external ice bath. There was then added 4.0 mL of dry CH_3CN, and 11.6 g of 3-bromo-2,6-diethoxythioanisole (which had been diluted with a little anhydrous THF). The deep red brown reaction mixture was stirred for 0.5 h, and then poured into 1 L dilute H_2SO_4. This was extracted with 3x75 mL CH_2Cl_2, the extracts pooled, washed with H_2O, dried with anhydrous K_2CO_3, and the solvent was removed under vacuum. The residue was distilled at 0.3 mm/Hg yielding two fractions. The first fraction boiled at 120-140 °C and weighed 1.2 g. This fraction partially crystallized, but was not investigated further. The second fraction was 3,5-diethoxy-4-methylthiophenylacetonitrile, which came over at 135-160 °C, was a yellow liquid, weighed 3.2 g, but did not crystallize.

A solution of LAH in anhydrous THF (30 mL of a 1.0 M solution) under N_2 was cooled to 0 °C and vigorously stirred. There was added, dropwise, 0.78 mL 100% H_2SO_4, followed by 3.0 g 3,5-diethoxy-4-methylthiophenylacetonitrile diluted with a little anhydrous THF. The reaction mixture was stirred at 0 °C for a few min, then brought to reflux on the steam bath for 1.5 h. After cooling back to room temperature, there was added IPA to destroy the excess hydride and 10% NaOH to bring the reaction to a basic pH with the conversion of aluminum oxide to a loose, white, filterable consistency. This was removed by filtration, and washed first with THF followed by IPA. The filtrate and washes were stripped of solvent under vacuum, the residue added to 1 L dilute H_2SO_4. This was washed with 2x75 mL CH_2Cl_2, made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. After combining, the solvent was removed under vacuum providing an orange oil. This

was distilled at 135-160 °C at 0.4 mm/Hg to give a light yellow oil. This was dissolved in 20 mL of IPA, and neutralized with 32 drops of concentrated HCl producing white crystals spontaneously. These were dissolved by bringing the IPA suspension to a boil on the steam bath and, with stirring, diluted with 80 mL of warm anhydrous Et_2O. There was the immediate formation of crystals which were removed by filtration, washed with an IPA/Et_2O mixture, and then with Et_2O. After air drying there was obtained 1.5 g of 3,5-diethoxy-4-methylthiophenethylamine hydrochloride (4-TSB) as white crystals. The mp was 194.5-196 °C. Anal. ($C_{13}H_{22}ClNO_2S$) C,H.

DOSAGE: greater than 240 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 80 mg) "There was a real effect about three hours into this experiment — a little bit spacey while I was talking to Mr. X. But the talk went well, and we were all really friendly. There was no hint that he suspected anything. A couple of hours later, nothing."

(with 160 mg) "Twinges at a couple of hours, but the rest of the day disappointing as to any effect from the drug."

(with 240 mg) "No effects at all."

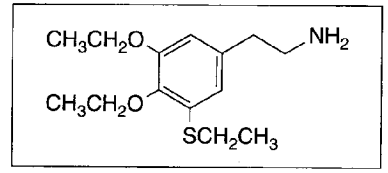
EXTENSIONS AND COMMENTARY: Here is an excellent presentation of a report that shows false positives or maybe false negatives. Something at low levels. Nothing at higher levels. Always tend to trust the absence of an effect in preference to the presence of an effect, if one of the two observations is presumed to be in error.

#178 3-T-TRIS; 3-THIOTRESCALINE; 3-THIOTRISESCALINE; 3,4-DIETHOXY-5-ETHYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution of 11.5 g 3-bromo-N-cyclohexyl-4,5-diethoxybenzylidenimine (see under ASB for its preparation) in 150 mL anhydrous Et_2O was placed in a He atmosphere, well stirred, and cooled in an external dry ice acetone bath to -80 °C. There was light formation of fine crystals. There was then added 25 mL of 1.6 N butyllithium in hexane and the mixture stirred for 15 min. This was followed by the addition of 5.8 g diethyl disulfide over the course of 20 min during which time the solution became increasingly cloudy with the eventual deposition of an insoluble gummy phase. The mixture was allowed to come to room temperature over the course of 1 h, and then added to 400 mL of dilute HCl. The organic phase was separated and stripped of solvent under vacuum. This residue was combined with the original aqueous phase, and the mixture was heated on the steam bath for

2 h. The aqueous mixture was cooled to room temperature, extracted with 3x100 mL CH_2Cl_2, the extracts pooled, washed with H_2O, and the solvent removed under vacuum to yield 11.0 g of an amber oil. This was distilled at 130-150 °C at 0.2 mm/Hg to yield 7.2 g of 3,4-diethoxy-5-(ethylthio)benzaldehyde as a white oil that spontaneously crystallized. The crude product had a mp of 52-57 °C that increased to 57-58 °C upon recrystallization from EtOH. Anal. ($C_{13}H_{18}O_3S$) C,H.

A solution of 14.9 g methyltriphenylphosphonium bromide in 200 mL anhydrous THF was placed under a He atmosphere, well stirred, and cooled to 0 °C with an external ice water bath. There was then added 27.6 mL of 1.6 N butyllithium in hexane which resulted in the generation of a yellow color which was at first transient, and then stable. The reaction mixture was brought up to room temperature, and 6.8 g 3,4-diethoxy-5-(ethylthio)benzaldehyde in 50 mL THF was added dropwise dispelling the color, and the mixture was held at reflux on the steam bath for 1 h. The reaction was quenched in 800 mL H_2O, the top layer separated, and the aqueous phase extracted with 2x75 mL of petroleum ether. The organic fractions were combined and the solvents removed under vacuum to give 12.0 g of the crude 3,4-diethoxy-5-ethylthiostyrene as a deep yellow oil.



A solution of 5.6 g of borane-methyl sulfide complex (10 M BH_3 in methyl sulfide) in 45 mL THF was placed in a He atmosphere, cooled to 0 °C, treated with 11.6 g of 2-methylbutene, and stirred for 1 h while returning to room temperature. To this there was added the crude 3,4-diethoxy-5-ethylthiostyrene in 25 mL THF and the stirring was continued for 1 h. The excess borane was destroyed with about 2 mL MeOH. There was then added 11.4 g elemental iodine followed by a solution of 2.2 g NaOH in 40 mL hot MeOH. This was followed by sufficient 25% NaOH to minimize the residual iodine color (about 4 mL was required). The reaction mixture was added to 500 mL H_2O containing 4 g sodium hydrosulfite. This was extracted with 3x75 mL petroleum ether, and the pooled extracts stripped of solvent under vacuum to yield 24.5 g of crude 1-(3,4-diethoxy-5-ethylthiophenyl)-2-iodoethane as a viscous yellow oil.

This crude 1-(3,4-diethoxy-5-ethylthiophenyl)-2-iodoethane was added to a solution of 11.1 g potassium phthalimide in 80 mL DMF, and all was heated on the steam bath for 1.5 h. It was then flooded with 600 mL H_2O, made basic with NaOH, and extracted with 3x100 mL Et_2O. Removal of the solvent under vacuum provided 18.5 g of a residue that was dried to a constant weight by heating under vacuum (0.2 mm/Hg). The solid residue was ground under MeOH, and then recrystallized from MeOH providing 1-(3,4-diethoxy-5-ethylthiophenyl)-2-phthalimidoethane as white granular crystals, with a mp of 86.5-87.5 °C. Anal. ($C_{22}H_{25}NO_4S$) C,H.

The recrystallized 1-(3,4-diethoxy-5-ethylthiophenyl)-2-phthalimidoethane was dissolved in n-butanol, treated with 66% hydrazine, and the mixture

heated on the steam bath for 1.5 h. This was then added to dilute H_2SO_4, the butanol separated, the aqueous phase washed with 2x75 mL Et_2O. After being made basic with aqueous NaOH, the aqueous phase was extracted with 3x75 mL CH_2Cl_2 and the solvent removed under vacuum to provide a pale amber oil. This was distilled at 140-155 °C at 0.25 mm/Hg to give about 1 g of a white oil. The distillate was dissolved in 5 mL IPA, neutralized with concentrated HCl, and treated with 10 mL anhydrous Et_2O to give a solution from which a white crystalline product slowly separated. These crystals, 3,4-diethoxy-5-ethylthiophenethylamine hydrochloride (3-T-TRIS) weighed 1.1 g and had a mp of 161-162 °C. Anal. ($C_{14}H_{24}ClNO_2S$) C,H.

DOSAGE: greater than 160 mg.

DURATION: unknown.

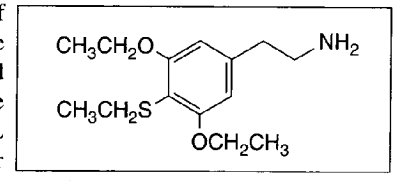
QUALITATIVE COMMENTS: (with 160 mg) "There were no effects. At the 9th or 10th hour after having taken the material I was aware of some neurological irritability. I will not try this at any higher dosage, and let me stretch things a bit by a few percent in good conscience and say that this is less active than mescaline. This would allow it to be reported as < 1 M.U."

EXTENSIONS AND COMMENTARY: The term "M.U." pops up here and there in a lot of the earlier literature on these phenethylamines. It stands for "mescaline units" and was used to give a quantitative measure for the relative potency of a compound. Since it became obvious quite early in these studies that mescaline, although the prototypic compound, was probably going to remain the least potent, it seemed reasonable to use it as a bench mark of unity. By dividing the dose needed of mescaline (to produce central effects) by the dose needed of another drug, one would generate a number that represented just how many times more potent this new drug was than mescaline. I used this term in a very early review of the one-ring psychotomimetics, and it served satisfactorily for quite a while.

Its intrinsic worth proved, however, to be its very limitation. It was quickly apparent that the principal value, to behavioral researchers, of the reports of new hallucinogenic drugs, was not in the nature of their action but in the amount of stuff needed to produce that action. This was an essential axis against which the animal pharmacologist could plot his findings. A number was wanted, and the mescaline unit was just that number. Sadly, the major question that is asked by most academic researchers in their evaluation of the psychedelic materials is, "How much does it take," rather than "What does it do." The marvelous nuances of action, the subtle variations of effect, are dismissed as being hopelessly subjective and thus without scientific worth. But they are, I believe, of great worth. That is exactly what this book is all about.

#179 4-T-TRIS; 4-THIOTRESCALINE; 4-THIOTRISESCALINE; 3,5-DIETHOXY-4-ETHYLTHIOPHENETHYLAMINE

SYNTHESIS: A solution of 12.1 g N,N,N',N'-tetramethylethylenediamine and 16.6 g of 1,3-diethoxybenzene was made in 200 mL 30-60 °C petroleum ether. This was stirred vigorously under a He atmosphere and cooled to 0 °C with an external ice bath. There was added 66 mL of 1.6 M butyllithium in hexane. The stirred reaction mixture became a little cloudy and then gradually formed a white granular precipitate. This was brought to room temperature, stirred for 0.5 h, and returned again to 0 °C. There was added 12.8 g of diethyl disulfide which seemed to produce an exothermic reaction. After being held for a few min at reflux temperature, the reaction mixture was added to 600 mL dilute H_2SO_4 which produced two clear phases. The petroleum ether phase was separated, and the aqueous phase extracted with 2x75 mL Et_2O. The organics were combined, and the solvents removed under vacuum. There was obtained as residue 24 g of a viscous oil. This was distilled at 93-110 °C at 0.3 mm/Hg yielding 21.5 g 1,3-diethoxy-2-ethylthiobenzene which spontaneously crystallized. Grinding under a small amount of hexane, filtering, and hexane washing provided 18.5 g of white crystals with a mp of 26-27 °C. Anal. ($C_{12}H_{18}O_2S$) C,H.



To a stirred solution of 17.3 g of 1,3-diethoxy-2-ethylthiobenzene in 175 mL CH_2Cl_2 there was added 11.8 g elemental bromine dissolved in 100 mL CH_2Cl_2. There was an immediate loss of color, and the obvious evolution of HBr gas. After stirring at ambient temperature for 1 h, the dark solution was added to 150 mL H_2O containing 1 g of sodium dithionite. Shaking immediately discharged the residual bromine color, and the organic phase was separated, The aqueous phase was extracted once with 75 mL CH_2Cl_2, the pooled extracts washed first with H_2O, and then with saturated brine. Removal of the solvent under vacuum provided 34.2 g of a pale yellow oil with several globs of H_2O that were mechanically removed. This wet product was distilled at 105-125 °C at 0.35 mm/Hg to yield 4-bromo-1,3-diethoxy-2-ethylthiobenzene as an off-white oil weighing 21.6 g. It could not be crystallized. Anal. ($C_{12}H_{17}BrO_2S$) C,H.

To a solution of 20.2 g diisopropylamine in 200 mL anhydrous THF that had been cooled to -10 °C under a He atmosphere with an external ice/MeOH bath, there was added 125 mL of a 1.6 M solution of butyllithium in hexane. There was then added, in sequence, 5.1 mL of dry CH_3CN followed by the dropwise addition of 15.3 g 4-bromo-1,3-diethoxy-2-ethylthiobenzene diluted with a little anhydrous THF. There was only a modest color development. Analysis by thin-layer chromatography showed that the reaction components were largely starting bromide and only a little product nitrile. An additional 2.5 mL dry CH_3CN was added, followed immediately by a solution of lithium diisopropylamide prepared separately from 14

mL isopropylamine in 50 mL hexane treated with 60 mL butyllithium solution. There was an immediate darkening of color. After 15 min stirring, the bromo starting material was gone, by TLC analysis. The reaction mixture was then poured into 1 L dilute H_2SO_4. The organic phase was separated and the aqueous fraction extracted with 2x100 mL CH_2Cl_2. These extracts were pooled, washed with H_2O, dried with anhydrous K_2CO_3, and the solvent was removed under vacuum. The residue was distilled at 0.3 mm/Hg yielding two fractions. The first fraction boiled at 124-145 °C and gave an amber liquid weighing 2.4 g. It was largely starting bromo compound with a little nitrile, and was not processed further. The second fraction distilled at 140-190 °C and weighed 6.2 g. Although this was largely product nitrile, it was quite complex by chromatographic analysis. It was redistilled at 0.3 mm/Hg and several fractions taken. The material collected at 145-165 °C weighed 3.2 g and was approximately 80% 3,5-diethoxy-4-ethylthiophenylacetonitrile by TLC assay. This was used in the subsequent reduction. The earlier fraction in this second distillation (130-145 °C) weighed 2.1 g but contained only 50% product nitrile by TLC analysis, and was discarded.

A solution of LAH in anhydrous THF under N_2 (20 mL of a 1.0 M solution) was cooled to 0 °C and vigorously stirred. There was added, dropwise, 0.53 mL 100% H_2SO_4, followed by 3.0 g 3,5-diethoxy-4-ethylthiophenylacetonitrile diluted with a little anhydrous THF. The reaction mixture was stirred at room temperature for 1 h, and then at reflux on the steam bath for an additional 0.5 h. After cooling back to room temperature, there was added IPA to destroy the excess hydride and 10% NaOH to bring the reaction to a basic pH and convert the aluminum oxide to a loose, white, filterable consistency. This was removed by filtration, and washed first with THF followed by IPA. The combined filtrate and washes were stripped of solvent under vacuum, the residue added to 1 L dilute H_2SO_4. This was washed with 2x75 mL CH_2Cl_2, made basic with 25% NaOH, and extracted with 3x100 mL CH_2Cl_2. After combining, the solvent was removed under vacuum providing a residue that was distilled. A fraction boiling at 135-150 °C at 0.3 mm/Hg weighed 1.2 g and was a light yellow oil. This was dissolved in 20 mL of IPA, and neutralized with 17 drops of concentrated HCl which produces white crystals spontaneously. These were dissolved by bringing the IPA suspension to a boil on the steam bath and, with stirring, there was added 40 mL of hot anhydrous Et_2O. There was the immediate formation of crystals which were removed by filtration, washed with an IPA/Et_2O mixture, followed by Et_2O. After air drying there was obtained 1.0 g of 3,5-diethoxy-4-ethylthiophenethylamine hydrochloride (4-T-TRIS) as sparkling white crystals. The mp was 177-178 °C. Anal. ($C_{14}H_{24}ClNO_2S$) C,H.

DOSAGE: greater than 200 mg.

DURATION: unknown.

QUALITATIVE COMMENTS: (with 120 mg) "Maybe there is some physical effect? There is a slight tingling or numbing of my hands and fingers, and a certain amount of gas. It is certainly negative on the mental side, but go up slowly due to the physical."

(with 200 mg) "There was a passing awareness at the third hour. Otherwise, no effects, either mental or physical."

EXTENSIONS AND COMMENTARY: As with the sulfur-free counterpart, the phenethylamine with three ethyl groups hanging out from it is not active in man. It doesn't matter where the sulfur is, since the 3-T-TRIS isomer is also without action. The labor of making the amphetamine analogues of these triethylated things seems hardly worth the effort.