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**Preparation of Lysergic Acid Amides**

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This invention relates to the preparation of lysergic acid amides and to a novel intermediate compound useful in the preparation of said amides.

Although only a few natural and synthetic amides of lysergic acid are known, they possess a number of different and useful pharmacologic properties. Especially useful is ergonovine, the N-(1(+)-1-hydroryisopropyl) amide of d-lysergic acid, which is employed commercially as an oxytocic agent.

Attempts to prepare lysergic acid amides by the usual meth­ods of preparing amides, such as reacting an amine with lysergic acid chloride or with an ester of lysergic acid have been unsuccess ful. United States Patents No. 2,090,429 and No. 2,090,430, des­cribe processes of preparing lysergic acid amides and although these processes are effective to accomplish the desired conversion of lysergic acid to one of its amides, they are not without certain disadvantages.

By my invention I have provided a simple and convenient method of preparing lysergic acid amides which comprises react­ing lysergic acid with triflouroacetic anhydride to produce a mixed anhydride of lysergic and triflouroacetic acids, and when reacting the mixed anhydride with a nitrogenous base having at least one hydrogen linked to nitrogen. The resulting amide of lysergic acid is isolated from the reaction mixture by conventional means.

The reaction of the lysergic acid and the trifluoroacetic anhydride is a low temperature reaction, that is, it must be carried out at a temperature below about 0°C. The presently preferred temperature range is about -15°C. to about -20°C. This range is sufficiently high to permit the reaction to proceed at a desirably fast rate, but yet provides an adequate safeguard against a too rapid reaction which would result in a high reaction temperature and consequent excessive decomposition of the mixed anhydride.

The reaction is carried out in a suitable dispersing agent, that is, one which is inert with respect to the reactants. The ly­sergic acid is relatively insoluble in dispersants suitable for carrying out the reaction, so it is suspended in the dispersant.

Two gals. of trifluoroacetic anhydride are required per   
mol. of lysergic acid for the rapid and complete conversion of the

lysergic acid into the mixed anhydride. It appears that one molecule of theride associates with orfavors an ionic adduct with one molecule of the lysergic which contains a basic nitrogin atom and that it is the adduct ch reacts with a second molecule of trifluoroacetic andydride to form the mixed anhydride along with one molecule of trifluoroacetic acide. The conversion of the Lysergic acid into the mixed anhydride. It appears that one molecule of the anhydride associates with or favors an ionic adduct with one molecule of the lysergic which contains a basic nitrogen atom and that it is the adduct which reacts with a second molecule of trifluroacetic anhydride to form the mixed anhydride along with one molecule of trifluoroacetic acid. The conversion of the lysergic acid to the mixed anhydride occurs within a relatively short time, but to insure a complete conversion the reaction is allowed to proceed for about one to three hours.

The mixed anhydride of lysergic and trifluoroacetic acids is relatively unstable, especially at room temperature and above, and must be stored at a low temperature. This temperature instability of the mixed anhydride makes it desirable that it be converted into a lysergic acid amide without unnecessary delay. The mixed anhydride itself, since it contains a lysergic acid group, also can exist in the reaction mixture in large part as an ionic adduct with trifluoracetic anhydride or trifluoracetic acid. It is important for maximum yield of product, that the lysergic acid employed in the reaction be dry. It is most convenient to dry the acid by heating it at about 105 – 110oC in a vacuum of about 1 mm of mercury or less for a few hours, although any other customary means of drying can be used.

The conversion of the mixed anhydride into an amide by reacting the anhydride with the nitrogenous base, such as an amino compound, can be carried out at room temperature or below. Most conveniently the reaction is carried out by adding the cold solution of the mixed anhydride to the amino compound or a solution thereof which is at about room temperature. Because of the acidic components present in the reaction mixture of the mixed anhydride, about five mols or equivalents of the amino compound are required per mole or equivalent of mixed anhydride for maximal conversion of the mixed anhydride to the amide. Preferably a slight excess over the five mols is employed to insure complete utilization of the mixed anhydride. If desired, a basic substance capable of neutralizing the acid components present in the reaction mixture, but incapable of interfering with the reaction, can be utilized. A strongly basic tertiary amine is an example of such a substance. In such case, about one equivalent of the amino compound to be converted to a lysergic acid amide, as well as any unconverted; lysergic acid, can be recovered from the reaction mixture and can be re-employed in other conversions. A preferred method for carrying out the process of this invention is as follows: Dry lysergic acid is suspended in a suitable vehicle as acetonitrile, and the suspension is cooled to about -15°C. or -20°C. To the suspension is then added slowly a solution of about two equivalents of trifluoroacetic anhydride dissolved in acetonitrile

and previously cooled to about - 20°C. The mixture is maintained at a low temperature for about one to three hours to insure the completion of the formation of the mixed anhydride of lysergic and trifluoroacetic acids.

The solution of the mixed anhydride is then added to about five equivalents of the amino compound which is to be reacted with the mixed anhydride. The amino compound need not be previously dissolved in a solvent, although it is usually convenient to use a solvent. The reaction is carried out with the amino compound or solution of amino compound at or about room temperature or below. The reaction mixture is allowed to stand at room temperature for one or two hours, preferably in the dark, and the solvent is then removed by evaporation in vacuo at a temperature which desirably is not greatly in excess of room temperature. The viscous residue consisting of the amide together with excess amine and amine salts, is taken up in a mixture of chloroform and water. The water is separated and the chloroform solution which contains the amide is washed several times with water to remove excess amine and the various amine salts formed in the reaction, including that of any unconverted lysergic acid. The chloroform solution is then dried and evaporated, leaving a residue of the lysergic acid amide. The amide so obtained can be purified by any conventional procedure.

Dispersants suitable for the purpose of this invention are those which are liquids at the low temperatures employed for the reaction and are of such an inert nature that they will not react preferentially to the lysergic acid with trifluoroacetic anhydride. Among suitable dispersants are acetonitrile, dimethylformamide, propionitrile, and the like. Additional suitable agents will readily be apparent from the foregoing enumeration. Of those listed above, acetonitrile is preferred since it is non -reactive and mobile at the temperature used, and is relatively volatile and hence readily separable from the reaction mixture by evaporation in vacuo.

A wide variety of nitrogenous bases such as amino cdmpound:, can be reacted with the mixed anhydride to form a lysergic acid amide. As previously stated, the amino compound must contain a hydrogen atom attached to nitrogen to permit amide formation. Illustrative amino compounds which can be reacted are ammonia, hydrazine, primary amines such as glycine, ethanolamine, di-glycylglycine, norephedrine, aminopropanol, butanolamine, di-ethylamine, ephedrine, and the like.

When an alkanolamine such as ethanolamine or aminopropanol is reacted with the mixed anhydride of lysergic and trifluoroacetic acids, the reaction product contains not only the desired hydroxy amide but also, to a minor extent, some amino ester. These two isometric substances arise because of the bi-functional nature of the reacting alkanolamine. Ordinarily the amino ester amounts to

no more than 25-30 per cent of the total amount of reaction Product but in cases where the amino group is esterically hindered, the proportion of amino ester will increased. The amino ester can readily be converted to the desired hydroxy amide , and the over-all yield of the latter increased by treating the amino ester or the mixture of amide and ester with alcoholic alkali to cause the rearrangement of the amino ester to the desired hydroxv amide. Most conveniently the conversion is carried out by dissolving the amino ester or mixture containing the amino ester in a minimum amount of alcohol and adding to the mixture a twofold amount of 4 N alcoholic potassium hydroxide solution. The mixture is allowed to stand at room temperature for several hours, the alkali is neutralized with acid, and the lysergic acid amide is then isolated and purified.

It should be understood that, as used herein, the term "lysergic acid" is used generically as inclusive of any o a the four possible stereoisomeys having the basic lysergicrll of acid structure. Isomers of the lysergic acid series can be separated or interconverted by means known to the art.

This invention is further illustrated by the following specific examples.

EXAMPLE-1

Preparation of the mixed anhydride of lysergic and trifluoroacetic acids;

5.36 g. of d-lysergic acid are suspended in 125 ml, of acetonitrile and the suspension is cooled to about -20°C. To this suspension is added a cold (-20°C.) solution of 8.82g, of tri-fluoroacetic anhydride in 75 ml. of acetonitrile. The mixture is allowed to stand at -20°C, for about 1-1/2 hours during which e the suspended material dissolves, and the d-lysergic acid is converted to the mixed anhydride of lysergic and trifluoroacetic acids. The mixed anhydride can be separated in the fat 11 1 of an oil by evaporating the solvent in vacuo at a temperature below about 0°C.

EXAMPLE 2

Preparation of d-lysergic acid N-diethylaminoethyl amide:

A solution of the mixed anhydride of lysergic acid and tri-fluoroacetic acid in 200 ml. of acetonitrile is obtained by reacting 5.36 g. d-lysergic acid and 8.82 g. trifluoroacetic anhydride in accordance with the procedure of example 1. The acetonitrile solution containing mixed anhydride is added to 150 ml. of acetoni-trile containing 7.6 g. of diethylamine. The mixture is held in the dark at room temperature for about two hours. The acetonitrile is evaporated in vacuo leaving a residue which comprises the "norm.al‘i" and "iso" forms of d-lysergic acid N, N-diethyl amide together.dwal:‘ some lysergic acid, the diethylamine salt of trifluoroacetic nfia like by-products. The residue is dissolved in a mixture of I is I of chloroform and 20 ml. of ice water. The chloroform layer is

separated, and the aqueous layer is extracted with four 50 ml. portions of chloroform. The chloroform extracts are combined and are washed four times with about 50 ml. portions of cold water in order to remove residual amounts of amine salts. The chloroform layer is then dried over anhydrous sodium sulfate, and the chloroform is evaporated in vacuo. A solid residue of 3.45 gm. comprising the "normal" and "iso" forms of d-lysergic acid. N,N-diethylamide is obtained. This material is dissolved in 160 nil, of a 3-to-1 mixture of benzene and chloroform, and is chromatographed over 240 g. of basic alumina. As the chroma-togram is developed with the same solvent, two blue fluorescing zones appear on the alumina column. The more rapidly moving zone is d-lysergic acid N,N-diethylamide which is eluted with about 3000 ml. of the same solvent as above, the course of the elution being followed by watching the downward movement of the more rapidly moving blue fluorescing zone. The eluate is treated with tartaric acid to form the acid tartrate of d-lysergic acid N,N-diethyl amide which is isolated. The acid tartrate of d-lysergic acid N,N-diethyl amide melts with decomposition at about 190-196°C.

The d-iso-lysergic acid N,N-diethyl amide which remains absorbed on the alumina column as the second fluorescent zone is removed from the column by elution with chloroform. The "iso" form of the amide is recovered by evaporating the chloro-form eluate to dryness in vacuo.

EXAMPLE 3

Preparation of d-lysergic acid N-diethylaminoethyl amide:

A solution of the mixed anhydride of lysergic acid and tri-fluoroacetic acid is prepared from 2.68 g. of d-lysergic acid and 4.4 g. of trifluoroacetic acid anhydride in 100 ml. of acetoni-trile by the method of Example 1. This solution is added to 6.03 g. of diethylaminoethylamine. The reaction mixture is kept in the dark at room temperature for 1-1/2 hours. The acetonitrile is evaporated, and the residue treated with chloroform and water as described in Example 2. The residue comprising d-iso-lysergic acid N-diethylaminoethyl amide is dissolved in several ml. of ethyl acetate, and the solution is cooled to about 00C. whereupon d-iso-lysergic acid N-diethylaminoethyl amide separates in crystalline form. The crystalline material is filtered off, and the filtrate reduced in volume to obtain an additional amount of crystalline amide. Recrystallization from ethyl acetate of the combined fractions of crystalline material yields d-iso-lysergic acid N-diethylaminoethyl amide melting at about 157-158°C. The optical rotation is as follows:

[X]- d26 =+372o (c.=1.3 in pyridine

**Syntheses of Psilocin and Psilocybin**

Translated rolfVonEckartsburg

Hofman, Heim, Brack, Kobel, rey, Ott, Petrailke, and Troxler “Psilocybin and psilocin ,zwelpaychotrpeWirkstoffeausmexikanischenRauschpilzen,”HeveticaChemicaActa Vol. 42, p-1570-1571, 1959.

((4- Benzyloxy-indolyl-(3)))- glyoxylsaure-dimethylamid(V)

To a solution of 50 grams 4- Benzyl –oxy-indol (IV) in 1,2 liters dry ether one lets drop while stirring it well and at a temperature of 1 to 5 degrees c., 40 ml. Oxalylchlorid and keeps stirring after the mixture has been accomplished for an additional one hour at temperature of 5 to 10 degrees C orange – red solution. Following this it was cooled further with a mixture of ice and table salt and slowly a solution of 100gDimethylamin in 100ml of ether was added by slow dripping. After continuing for an additional one half hour, the stirring at room temperature , the ppt , was filtered off by suction using washing with either and then with much water . The mixture of Benzol and methanol and was brought to crystallization through an addition in portions of petrol – ether. Prisms from smp 146-150OC. yield 52.6 gram (73%). The color reaction according to KELLER is blush – green.

C19H18O3N2 Ber. C70.8 H 5.6 O 14.9 N 8.7%

(322.4) Gef. 70.6 5.7 14.6 8.7

A solution of 52.5 grams (V) in one liter abs. Dioxan was dripped under lively strirring into a boiling (seething solution of 66g LIMA into one liter of the same solvent and continued stirring for 17 hours at the same temperature. Following this, the complex was decomposed as well as the superfluous reduction-substance under good cooling with ice using Methanol, then 500 ml of saturated sodium sulfate solution was added, the precipitation sucked off and' thoroughly washed with Methanol and Dioxan. The filtrate is put "wine-sour" and side-products are removed through shaking with ether. Following this the basal -alcaline reaction product was withdrawn (drawn out after alcalization with NaOH by means of Chloroform. Out of this Chloroform extract, dried through potash and concentrated to a small volume, (VD crystallized following addition in portions of petrol-ether in fine needles of smp. 125- 126 degrees C. yield of crystallization '33. grams. Fromthe motherlye" after a chromatographic cleaning with 300gAl2O3 through which (VI) was distilled by means of Benzol whichcontained 0.2%

alcohol, an additional 7.7 grams of pure amalgamate was gained. Total yield 85% of Th.

C19 H22 ON2  Ber. C 77.5 H 7.5 0 5.4 O5.4 N0.9.5%

(294.4) Gef. 77.6 7.4 5.5

4 –Hydroxy-W -N,N -dimethyl tryptamin ( Psiloc in) (II)

A solution of 37.5 grams (VI) in 1.2 liters of Methanol was "shaken" on an Aluminum-oxide-carrier under addition of 20 grams of 5% Palladium catalyst with Hydrogen, in which process during 12 hours the theoretically computed quantity of 3.2 liters were absorbed.

Out of the concentrated solution which was filtered from the catalyst and reduced to a small volume there crystallized **(II)** in hexagonal plates of smp. 173-176. Yield 21g (81%). Color reaction of Keller blue-green.

C12H16ON2 Ber. C 70.6 H 7.9 N 13.7%

(204.3) Gef. 70.4 8.3 14.1

The synthetic substance agrees in all properties, particularly also in the I.R.spectrum with natural psilocin.

**4** -Dibenzyl -phosphoryloxy -W -N,N -dimethyltryptamin (VII)

6.3 grams **(II)** were dissolved in 30.5 ml IN methanolic NaOH, the solution under nitrogen dried and vaporized and the residue dried for 3 hours in a high vacuum at 40°C. The residue was dissolved in 100 ml t-Amylalcohol, added to this was a solution of Dibenzyl­phosphoryl-clorid in 30m1 CC14 which was made fresh from 8.3 grams Dibenzyl phosphit. This was shaken for two hours at room temperature. Then it was boiled down, the residue absorbed in Chloroform-alcohol 9:1, filtered from NaCI and the filtrate chroma­tographed at a column of 750 grams of A1903. With the same solution-mixture 6.8 grams (VII) were "eruired". From Chloroform-Alcohol crystals of smp. 238-240°C.

C26 H29 O4N2P Ber. C 67.2 H 6.3 N 6.0 P 6.7%

(465.5) Gef. 67.1 6.7 6.2 6.4

O-Phosphoryl -4 -hydroxy -W -N,N -dimethyltryptamin (Psilocybin)

(1)

A solution of 6.8 grams (VII) in 100 ml Methanol was shaken on an Al A1 carrier with Hydrogen until saturation after 5 grams of 5% Pa alum catalyst had been added. The boiled down residue of the solution which had been cleaned from the catalyst was let into 200 ml water and the undissolved side-products were filtered out. The

watery solution was steamed dry and the residue was absorbed in a little Methanol from which (I) separated itself in fine prisms. - When the change-in-crystallization from water was made we obtained soft needles from smp. 220-228°C. Yield 3.0 grams (42%)

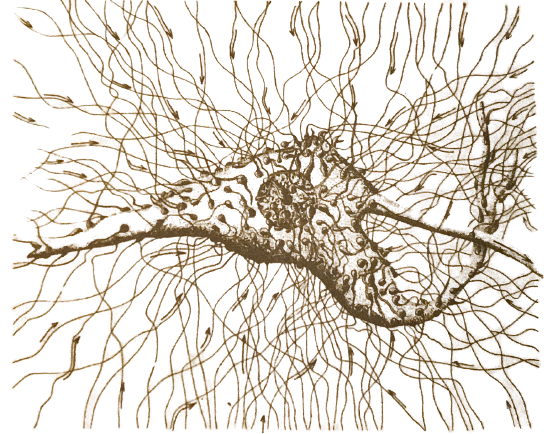
Color reaction of KELLER , violet.

C12 H17 O4 N2 P Ber. C 50.7 H 6.0 N 9.9 P 10.9**%**

(284.3) Gef. 50.5 6.1 9.5 10.8

The synthetic product agrees in all properties, particularly also in the **I.R.** spectrum with the psilocybin isolated from the mush\_room.

**The aim of the higher yogas is to advance the evolution of man beyond the illusory glamor of sangsario pr worldly existence, so that karmic necessity of rebirth in the human state comes to an end.**

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**MOTOR NEURON is the nerve cell that carries electrical impulses to activate muscle fibers. The cell body *(top)* fans out into a number of twigs. the dendrites, which make synaptic contact with other nerve fibers**

**Synthesis of Mescaline**

Makepeace U. Tsao, "A New Synthesis of Mescaline," Journal of the American Chemical Society, Vol. 73, p. 5495-5496 (Nov. 1951)

The cactus alkaloid, mescaline, B-(3.4,5 Timethoxyphenylethyl­amine, has been studied for some years, because of its most interesting effects on the psychic states of human subjects. Since the elucidation of the chemical structure of the alkaloid through the j synthesis by Spath91 7a few other methods of preparation have been published. A simple synthesis utilizing lithium aluminum hydride is presented in this report. The synthesis may be outlined as follows: gallic acid-3,4,5-Trimethoxybenzoic acid,-methyl ester of 3,4,5-Trimethoxybenzyl alcohol-3,4,5-Trimethoxybenzyl chloride - 3,4,5-Trimethoxyphenylacetonitril-Mescaline.

Experimental:

Methyl Ester of 3,4,5-Trimethoxybenzoic acid: To a solution pre­pared from 100 *g* of 3,4,5-Trimethoxybenzoic acid (0.47 Mole), 20g of sodium hydroxide, 55g of sodium carbonate and 300 ml of water is added, with stirring, 94m1 of methyl sulfate (0.94 Mole) during the course sof 20 minutes. The reaction mixture is refluxed for one-half hour. The crude ester (65g, 61%) precipitates from the cold mixture. From the filtrate 38g of starting material is re­covered upon acidification with diluted HC1. The ester is further purified by solution in the minimum amount of methanol and treat­ment with norite. Usually it is necessary to repeat this treatment to obtain a colorless crystalline product that melts at 80-82°. Semmler9, who employed a different process, reported m.p. 83- 84°.

3,4,5-Trimethoxybenyl alcohol: To a suspension of 4.6 g. (0.12 Mole) of lithium aluminum hydride in 200 ml of anhydrous ether is added, in the course of 30 min., a solution of 22.6g (0.1 Mole) of the methyl ester of 3,4,5-Trimethoxybenzoic acid in 300m1 of ether. The solid which forms is carefully decomposed first with 50m1 of ice-water. After decantation of the ether, 250 ml of ice-, cold 10% Sulfuric acid is added. The product is extracted with 150m1 of ether. The combined extracts, after drying over sodium sulfate, are freed of ether and the residue distilled; b.p. 135-137° (0.25mm); yield 14.7g (73%). This compound was obtained by a different method by Marx 1u; b.p. 228° (25mm).

3,4,5-Trimethoxybenzyl chloride: A mixture of 25g of 3,4,5- Trimethoxybenzyl alcohol and 125m1 of ice -cold concentrated HC1 is shaken vigorously until a homogeneous solution is obtained. In a few minutes turbidity develops, followed by a heavy precipita-

tion of gummy product. After 4 hours and dilution with 100ml of ice -water, the aqueous layer is decahted and extracted with three 50m1 portions of benzene. Then the gummy organic residue is dissolved in the combined benzene extracts. The benzene solution is washed with water and dried over sodium sulfate.

The benzene solution is transferred to a distilling flask and the benzene is removed under diminished pressure. The red semisolid residue is suspended in a small amount of ice -cold ether and filtered through a chilled funnel. The crystalline product, after washing with small portions of cold ether, weighs 9.7g combined filtrates on standing in refrigerator yield more crystals. The total yield is 13.0g. (48%). After four recrystallizations from benzene, colorless needles are obtained; m.p. 60-62°.

Anal. Calcd. for C10 H13 O3 ' Cl: C,55.42. H,6.05. Found: 0,55.55; H, 6.13.

This compound is extremely soluble in ether, alcohol and acetone, but slightly soluble in petroleum ether. Standing at room temperature for a few weeks causes the crystals to turn into a red semisolid. An alcoholic solution of pure material gives an instantaneous precipitation with alcoholic silver nitrate.

3,4,5-Trimethoxyphenylacetonitrile - A mixture of 9g of potassium cyanide is 35m1 of water and 60m1 of methanol and 9.7g of 3,4,5- Trimethoxybenzyl chloride is heated for 10 min. at 90°. The solvents are partially removed under diminished pressure. The residue is then extracted with 90m1 of ether in three portions. The combined extracts are washed with water and dried over sodium sulfate. After the removal of the drying agent the ether solution is warmed on a steam-bath and the ether is removed with a stream of air. On chilling, the residue yields scale-like crystals. Re-crystallization from ether gives rectangular prism; Yield 2.5g (27970): m.p. 76-77°. Baker and Robinson 12 reported a melting point of 77 degrees for this compound. Mescaline - In 150m1 of anhydrous ether is suspended 0.85g of lithium aluminum hydride powder. With stirring, 2.0g of 3,4,5- Trimethoxyphenylacetonitrile in 150m1 of anhydrous ether was added during the course of 15 min. After 25 min. stirring, 10m1 of ice-water is dropped in carefully. Then a mixture of lOg of sulfuric acid in 40m1 of water is added at a moderate rate. The aqueous layer is separated and treated with concentrated sodium hydroxide. The brown oil is extracted with three portions of 30m1 each of ether. The combined extracts are washed once with water and dried over stick potassium hydroxide. To the

decanted ether solution is added a mixture of 1g of sulfuric acid and 25m1 of ether. The white precipitate is washed several times with ether; yield 1.2g (40%). After two recrystallizations form 95% ethanol, the colorless long thin plates soften at 172° and melt at 183°.

A sample of mescaline acid sulfate prepared from the natural source and kindly furnished by Dr. Seevers of the Department of Pharma-cology softens at 170° and melts at 180°. The picrate, prepared from the acid sulfate, melts at 217° (dec.), after three recrystal-lizations from ethanol. The chloroplatinate prepared from free base melts at 184 -185°. Spath gave the following melting points: sulfate, 183-186°; picrate, 216-218°; Chloroptinate, 187-188°.

1. E. Spath, Monatsh., 40, 129 (1919)
2. K. H. Slotta and H. Heller, Ber. 6313, 3029 (1930)
3. H. Frisch and E. Waldman, German Patent 545, 853 July 3, 1930, C.A. 26, 3521°

(1932)

1. K. Kindler and W. Peschke, Arch. Pharm, 270, 410 (1932)
2. K. H. Slotta and G. Szuzker, J. prakt chem. 137 339 (1933)
3. G. Hahn and H. Wassmuth, Ber. 67, 711 (1934)
4. G. Hahn and F. Rumpf, Ibid., 7113, 2141 (1939)
5. H. Blatt, "Organic Synthesis." Coll. Vol I. 2nd ed., John Wiley and Sans, Inc. N.Y., N.Y. 1946, p.537
6. F. W. Semmler, Ber., 41, 1774 (1908)
7. M, Marx, Ann. 263, 254 (1891)
8. All M.P.'s are uncorrected.
9. Baker and R. Robinson, J. Chem Soc., 160 (1929).

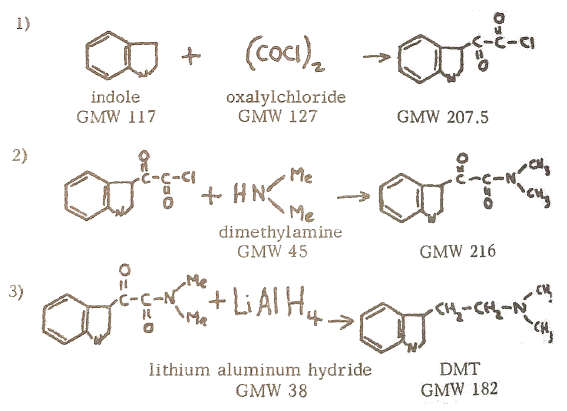
Editor's note: The next -to -last step, 3,4,5-Trirnethoxyphenylacetoni trile, can be ordered directly from Aldrich Chemical Co., 2371 N. 30th St., Milwaukee, Wisc.

**SYNTHESIS OF N,N-DIMETHYL TRYPTAMINE (DMT)**

MATERIALS: I liter dry dioxane OR tetrahydrofurao\* 25grams , indole; 50gms, oxalyl chloride, 100grns.. dimethylamine;300 Ibs (1-1/2 liters) dry ether; 20gms. of lithium aluminum hydride LiAlHA); benzene; methanol; technical (undried) ethyl ether. Petroleum ether; sodium sulfate (anhydrous); chloroform ,ace tone.

APPARATUS: 2000m1. flask (or 2 qt. wide-mouth Mason jar); suction filtration equipment; 8.5cm Bruchner funnel; filter flask and trap; vacuum source (a forced-water suction pump is least expensive); 800 ml. flask; 100m1. graduated cylinder; capillary dropping tubes; ice bath; water bath; filter paper; additional flasks or glasses; rubber tubing; spatula or spoon; corks.

\*The second intermediate is more soluble in dioxane, but dioxane is much more poisonous than tetrahydrofuran, and if the final product is to be used in solution, THF should be used.

EQUATIONS

PROCEDURES (1) 25gms. indole is dissolved in 1 lb. (1 liter) of dry ethyl ether in a 2000 ml. flask, and the solution cooled to as close to 0°C. as possible in an ice bath. (2) 50m1 dry oxalylchloride (usually in 2 small bottles of 25 ml. each) is cooled in an ice bath

to 0-5° and added slowly to the indole solution. The reactionis rapid and strongly exothermic, so care must be taken to avoid splattering or boiling over. Oxalylchloride is nasty stuff - on contact with water (or moisture of skin) it forms chloric acids, which burn. (COO), is used in considerable excess to avoid the double linking ottwo indole groups through the two carbonyl groups: ind-CO-CO-ind.

When this reaction appears complete (cessation of bubbling after about 30 minutes), the solution is cooled further by adding table salt to the ice bath and a 0°C. solution of 100gms of dry dimethyl¬amine in 100m1 of dry ethyl ether is slowly added. (This solution must be carefully prepared because dimethylamine is extremely volatile. Cool both liquids to 0°C. in the salted ice bath, break the glass tube seal of the dimethylamine bottle at the base, and pour the contents in a continuous stream into the chilled ether. Avoid the liquid's backing up in the tube - the "gurgling" pro¬duced when a small mouthed bottle is upended-because dimethyl¬amine will volatilize and boil over). After the dimethylamine has been added, remove the flask from the ice bath and stir vigorously until the solution reaches room temperature.

The result of the first two steps should be a dense, pure white, insoluble precipitate. Very often, yellow and/or reddish-orange streaks will appear in the product or on the sides of the flask (apparently chloric slats or unreacted by-products) and the solution should be stirred until these impurities are minimized or disappear. The precipitate is filtered by suction and flask and filtered products are washed twice each with ether and water (wash with ether first - regular technical or "wet" ether can be used.) The raw product when dry is redissolved in the least possible volume of a 50% methanol-to 50% benzene solution in the 800m1 beaker-cover the raw product with about 1/2 inch of the methanol -benzene solvent and heat the solution in a water bath, adding more solvent if necessary, until all the solid material goes into a liquid phase. On cooling, needle-like crystals of great purity should sep¬arate (if they do not, scratch, then add a small amount of petro-leum ether). Final yield of the second intermediate should be around 25 gms., about 70%. (3) The dried crystals are dissolved in the least possible volume of dioxane or tetrahyrofuran, and slowly added (at room temperature) to 20 gms. of lithium hydride, like¬wise dissolved in the least possible volume of the same solvent. CAUTION: LiA1H4 is one of the most reactive reducing agents known. Anything that comes in contact with it must be carefully

dried, and care must be taken not to inhale LiA1H4 dust or touch it without wearing rubber gloves. (See "Handling Procedures" in the manual put out by Metal Hydrides, Inc.).

The latter solution should be prepared by weighing out the LiAIH4 to be used (measurement can be rough because LiAIH4 is used in considerable excess) and adding it slowly to 200m1 the THF or dioxane. Humid days should be avoided, as LiAIH4 will ignite in air (actually the hydride reduces water vapor to 1-1,2 which is ignited by its own heat of evolution). When all the LiAIH4 has been added, the solution should be stirred vigorously and then heated in a water bath, with periodic stirring for several hours. An aspirator tube should be used, if possible, to avoid accumulation of ether vapor. When the reaction is complete, the solution (and unreacted hydride) are again cooled to about 0°C. and neutralized with chilled 1 methanol (Water or ice can be used directly, but the reaction is much more violent). Neutralization results in a dense white precipitate of metallic oxides.

1. If the product is to be used in solution (by application to ' tobacco or other medium) it can be left in ether (THF rather than dioxane) solution. After neutralization the solution is simply filtered and washed with THF and methanol, the filtrate saved and concentrated by boiling off excess solvent. The filtrate contains the dissolved product, but also many impurities. These are harmless if smoked (after evaporating off the mother liquor) but under no circumstances should this solution be swallowed or injected'.
2. If pure DMT is desired, the product must be crystallized. Following neutralization with methanol, 500 ml. of saturated sodium sulfate solution is added, and the precipitate sucked dry and thor­oughly washed withTHF (or dioxane). The filtrate is then acidified with a few ml. of .1m HCI solution and the reaction by-products removed through shaking with ether in a separatory funnel. The lower level is drawn off and neutralized with .lm NaOH, then shaken with chloroform. The chloroform layer is dried through anhydrous sodium sulfate, concentrated, and from it DMT crystallizes upon addition of some petroleum ether. The final yield is about 10 gms., and another 5-6 gms. can be obtained by chromatographing the mother liquors with 99.8% benzene - 0.2% methanol solution 014through 300 gms. of alumina.

NOTES ON USE:

I. Smoking is probably the most efficient method of using DMT because little of the final product is lost (as in recrystallization). The ether (THF) solution-(A) above is dripped onto a conical pile of the medium and the THF allowed to evaporate (excess THF can cause headache, nausea, and it is highly flammable). Evaporation takes about 1 hour, and results in hard lumps of medium which should be broken by rolling between the fingers. Often it is most efficient to "cure" the medium directly in a pipe bowl - lumps can