TABLE III
SCREENING RESULTS OF NITROGEN MUSTARDS FROM AMINOPHENYLTHIAZOLES[a]

No.[b]	Test[c] system	Dose, mg/kg	Survivors	Cures	Animal[d] wt diff, g (T − C)	Tumor[e] wt, g, or survival[f] days, T/C	T/C, %
1	3 LE	400.0	4/4		−1.0	10.0/9.0	111
		200.0	4/4		−0.1	8.8/9.0	97
		100.0	4/4		−0.5	9.5/9.0	105
	AA	100.0	3/3				
		33.0	3/3				
		10.0	3/3				
		3.0	3/3				
	DL	200.0	7/7	3	−22.0	27.7/15.0	184
		100.0	7/7		−09.0	19/15	126
		50.0	7/7		−02.0	17/15	113
		25.0	7/7		−02.0	16/15	106
	5 WM	400.0	6/6		−10.0	0.5/3.8	13
2	3 LE	400.0	6/6		1.3	8.8/9.4	93
		200.0	6/6		0.7	8.7/9.4	92
		100.0	6/6		1.2	8.8/9.4	93
	AA	330.0	3/3				
		100.0	3/3				
		33.0	3/3				
		10.0	3/3				
	5 WM	330.0	6/6		−5.0	3.9/6.1	63
3	3 LE	400.0	4/4		0.9	8.3/9.1	91
		200.0	4/4		−0.4	8.8/9.1	96
		100.0	4/4		−1.0	9.3/9.1	102
	AA	330.0	3/3				
		100.0	3/3				
		33.0	3/3				
		10.0	3/3				
	5 WM	330.0	6/6		1.0	3.5/7.3	47
5	3 LE	400.0	4/4		−1.8	8.8/8.4	104
		200.0	4/4		−1.3	9.5/8.4	113
		100.0	4/4		0.7	8.5/8.4	101

[a] For test procedures see *Cancer Chemother. Rep.*, **25**, 1 (1962). [b] Numbers refer to those from Table II. [c] AA = toxicity; 3 LE = L 1210 lymphoid leukemia; 5 WM = Walker 256 (im); DL = Dunning leukemia (solid). [d] Av wt change of test group minus av wt change of control animals in grams; T = test; C = control. [e] Tumor wt for 5 WM test system. [f] Survival days for 3 LE and DL test systems.

recrystd (C_6H_6), yield 55%, mp 121°. *Anal.* ($C_{12}H_{16}ClNO_3$) C, H, N.

A mixt of this halo ketone (2.57 g, 0.01 mole), thiobenzamide (1.5 g, 0.011 mole), and abs EtOH (15 ml) was heated at reflux temp for 3 hr. The solvent was removed under reduced pressure, and the residue was dissolved in H_2O and decolorized. The filtrate on basifying (NH_4OH) gave the required thiazole which was recrystd (EtOH–H_2O).

All the 4-{*p*-[*N*,*N*-bis(2-hydroxyethyl)amino]phenyl}-2-substituted thiazoles were prepared similarly.

2-Phenyl-4-{*p*-[*N*,*N*-bis(2-chloroethyl)amino]phenyl}-thiazole.—To a suspension of 2-phenyl-4-{*p*-[*N*,*N*-bis(2-hydroxyethyl)amino]phenyl}thiazole (1.7 g, 0.005 mole) in C_6H_6 (15 ml) was added $POCl_3$ (2.3 g, 0.015 mole). The mixt was heated gently at reflux temp for 1 hr. The dark red soln was cooled, and the solvent was removed *in vacuo*. The oily residue was poured onto ice and left overnight, neutralized ($NaHCO_3$), and extd (Et_2O). The Et_2O exts were washed (H_2O) and dried (Na_2SO_4), and the solvent was removed. Residue crystd (hexane) gave the desired N-mustard.

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Synthesis and Pharmacology of Some Dimethoxy-Substituted Indanamines as Potential Hypoglycemic Agents. 1-Methyl-2-*N*-(dialkylaminomethyl)-5,6-dimethoxyindans

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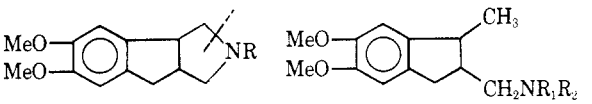
In view of reported significant oral hypoglycemic activity among hexahydroindeno[1,2-*c*]pyrroles (I) and their hypothetical degradation products, indanamines,[1] a large number of such compounds were synthesized and screened for oral hypoglycemic activity as reported earlier.[2-4] This paper is concerned with the synthesis of some dimethoxy-substituted indanamines along with the salient features of their biological activities. These compounds may be considered to have originated by the fission along the dotted lines in the indeno[1,2-*c*]pyrrole structure and subsequent alkylation at the generated basic center.



I II

Chemistry.—Ethyl 2-(3,4-dimethoxybenzyl)acetoacetate[5] was cyclized with polyphosphoric acid to ethyl 3-methyl-5,6-dimethoxyindene-2-carboxylate in 85% yield.[6] The corresponding carboxylic acid was reduced with NaHg and converted to the acid chloride; this was treated with appropriate primary or secondary amines to yield amides. The amides were converted to the desired amines by LAH reduction. The overall reaction sequence is outlined in Scheme I.

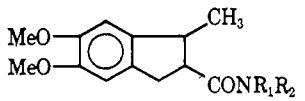
All compounds reported in Table I were prepared by a method similar to that described earlier.[1-3] They were first screened for hypoglycemic activity.[7] Blood glucose determinations were made at different intervals up to 24 hr after dosing, using tolbutamide as reference standard. Compounds **8**, **9**, and **14** showed appreciable hypoglycemic activity in both normal- and alloxan-diabetic animals.

Pharmacology.—Groups of 8 normal, healthy, male rabbits, weighing 1.5–2.0 kg were used for screening hypoglycemic activity. The animals were fasted over-

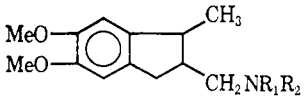
(1) S. C. Lahiri and B. Pathak, *J. Med. Chem.*, **8**, 131 (1965).
(2) S. C. Lahiri and B. Pathak, Indian Patent Application 105,586 (June 4, 1966).
(3) S. C. Lahiri and B. Pathak, *J. Pharm. Sci.*, **57**, 1013 (1968).
(4) S. C. Lahiri and N. C. De, *J. Med. Chem.*, **11**, 900 (1968).
(5) J. Koo, *J. Amer. Chem. Soc.*, **75**, 2000 (1953).
(6) J. Koo, *ibid.*, **75**, 1891 (1953).
(7) Some of these compounds also exhibited appreciable hypotensive and moderate muscle relaxant activities though they do not possess significant antimicrobial activity.

TABLE I

1-METHYL-2-*N*-(DICARBOXYAMIDO)-5,6-DIMETHOXYINDANS (IIA) AND 1-METHYL-2-*N*-(DIALKYLAMINOMETHYL)-5,6-DIMETHOXYINDANS (II)



IIA

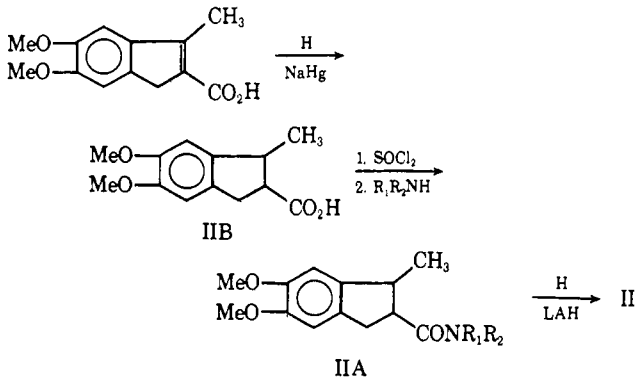


II

Compds	R_1	R_2	Bp, °C(mm)	$n^{25}D$	Formula[d]	HCl mp, °C	Av % decrease of blood sugar, 25 mg/kg dose: Normal diabetic rabbits	Av % decrease of blood sugar, 25 mg/kg dose: Alloxan-diabetic rabbits
					IIA			
1	Me	Me	163–168 (0.60)		$C_{15}H_{21}NO_3$			
2	Et	Et	170–174 (0.15)		$C_{17}H_{25}NO_3$			
3	*n*-Pr	*n*-Pr	184–190 (0.10)		$C_{19}H_{29}NO_3$			
4	*n*-Bu	*n*-Bu	193–196 (0.10)		$C_{21}H_{33}NO_3$			
5	*n*-Pr	H	186–192 (0.25)		$C_{16}H_{23}NO_3$			
6	*n*-Bu	H	195–200 (0.20)		$C_{17}H_{25}NO_3$			
					II			
7	Me	Me	122–126 (0.80)	1.5256	$C_{15}H_{23}NO_2$	192–193[a]	11.1 ± 1.0	
8	Et	Et	142–145 (1.50)	1.5185	$C_{17}H_{27}NO_2$	176–177[b]	21.4 ± 1.3	37.1 ± 3.7
9	*n*-Pr	*n*-Pr	165–168 (1.50)	1.5160	$C_{19}H_{31}NO_2$	168–170[a]	17.2 ± 2.9	35.0 ± 4.1
10	*n*-Bu	*n*-Bu	138–142 (0.10)	1.5025	$C_{21}H_{35}NO_2$	230–232[a]	11.6 ± 1.7	
11	*n*-Pr	H	137–138 (0.25)	1.5142	$C_{16}H_{25}NO_2$	175–177[a]	14.2 ± 2.3	
12	*n*-Bu	H	135–140 (0.10)	1.5140	$C_{17}H_{27}NO_2$	169–170[a]	15.1 ± 3.2	
13	Me	*n*-Pr	142–146 (0.40)	1.5150	$C_{17}H_{27}NO_2$	167–168[b]	13.3 ± 1.7	
14	Me	*n*-Bu	158–162 (0.60)	1.5120	$C_{18}H_{29}NO_2$	156–157[c]	15.6 ± 2.8	23.7 ± 3.6
Tolbutamide							22.5 ± 2.5	

[a] From EtOAc and EtOH. [b] From EtOAc. [c] Crystd from PhH. [d] All compds showed correct anal. for C, H, N.

SCHEME I



night (18 hr), H_2O being allowed *ad libitum*. After taking venous blood of the fasting rabbits, the animals were given the compounds as hydrochlorides in soln at 25 mg/kg by stomach tube and blood glucose concn was observed every hour up to 24 hr. The maximum fall of blood glucose concn was observed between the 9th and 12th hr. The blood glucose estimation was carried out following the procedure of Hagedorn and Jensen.[8] Using a set of 6 albino rats (180–200 g) and the same dose level, blood sugar lowering of similar magnitude was also observed.

Compounds **8**, **9**, and **14** which showed appreciable activity in normal animals were further tested on alloxan-diabetic rats and rabbits,[9,10] the results are shown in Table I.

(8) H. C. Hagedorn and B. N. Jensen, *Biochem. Z.*, **135**, 46 (1923); **137**, 92 (1923).

(9) J. J. Pincus, J. J. Hurwitz, and M. E. Scott, *Proc. Soc. Exp. Biol. Med.*, **86**, 553 (1954).

(10) M. A. Root and J. Ashmore, *Arch. Exp. Pathol. Pharmakol.*, **248**, 117 (1964).

Experimental Section[11]

1-Methyl-5,6-dimethoxyindan-2-carboxylic Acid (IIB).—Ethyl 2-(3,4-dimethoxybenzyl)acetoacetate[5] was cyclized with polyphosphoric acid (PPA) at 100° for 2 hr with thorough stirring to yield ethyl 3-methyl-5,6-dimethoxyindene-2-carboxylate in 85% yield. A better yield (92%) was obtained using concd H_2SO_4 (98%; previously cooled to −10°) at −5 to 0° for 30–45 min. The corresponding carboxylic acid was obtained by alkaline hydrolysis followed by acidification. The acid was reduced with NaHg, crystallized from hot H_2O, mp 133–134°. *Anal.* ($C_{13}H_{16}O_4$) C, H.

1-Methyl-5,6-dimethoxyindan-2-carbonyl Chloride.—A soln of $SOCl_2$ (1.2 moles) in dry PhH was added slowly with stirring to a suspension of IIB (1 mole) in dry PhH at room temp. The resulting mixt was heated on a water bath at 40–50° for 30 min and excess $SOCl_2$ was removed under reduced pressure. The acid chloride was found to be thermolabile and was therefore not distd.

1-Methyl-2-*N*-dialkylcarboxamido-5,6-dimethoxyindans (IIA).—The crude acid chloride (1 mole) was added dropwise with constant stirring to a mixt of an appropriate primary or secondary amine (1.5 moles) and NaOH soln (10%, 1 mole) cooled in an ice bath. The amides were extd with Et_2O or PhH and distd under reduced pressure.

1-Methyl-2-*N*-dialkylaminomethyl-5,6-dimethoxyindans (II) were prepd by the reduction of the corresponding carboxamide (1 mole) with LAH (1.2 moles) in dry Et_2O under reflux for 8–12 hr. The amines were isolated and extd with Et_2O and distd under reduced pressure. In some cases, secondary amines were methylated by heating with a mixt of HCO_2H and CH_2O at 95–100°.[12]

The bases were characterized as their hydrochlorides (Table I).

Acknowledgment.—The authors are grateful to Dr. Maxwell Gordon and Dr. Joseph Lein of Bristol Laboratories, Syracuse, N. Y., for the biological evaluation of some of these compounds in hypoglycemic, antimicrobial, and various other fields of chemotherapy.

(11) Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. All melting points are corrected and were determined in Gallenkamp apparatus. Boiling points are uncorrected.

(12) W. E. Bachmann, *Org. Syn.*, **25**, 89 (1945).