Synthesis and Pharmacology of Some Pyrroles and Indan Amines: Hexahydro Indeno (1,2-*c*) Pyrroles and Indan Amines

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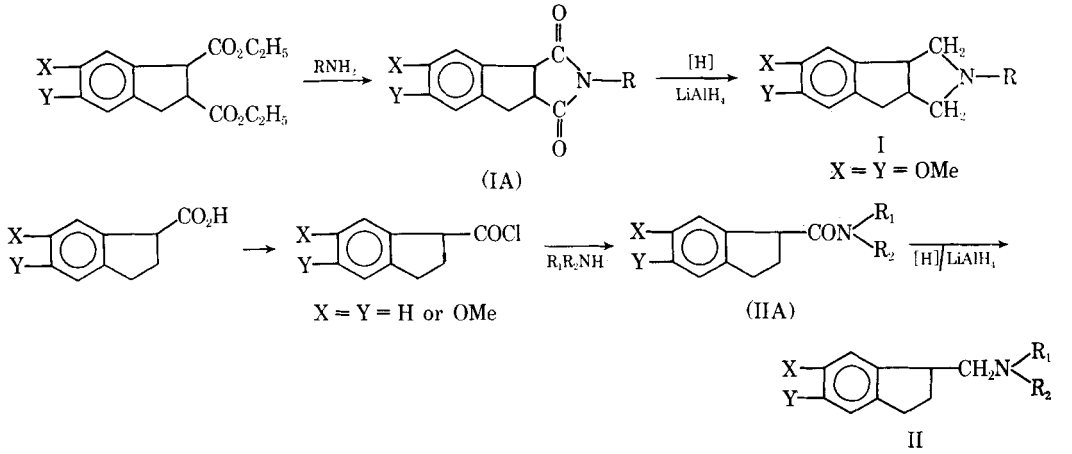
Syntheses and pharmacology of a number of 1,2,3,3*a*,8,8*a*-hexahydro 5:6-dimethoxy indeno (1,2-*c*) pyrroles, 1-*N*-dialkyl amino methyl indans and 1-*N*-dialkyl amino methyl 5:6-dimethoxy indans were described. A few of these compounds showed oral hypoglycemic activity.

THIS PAPER, which is an extension of a previous one (1), is concerned with the syntheses of a few compounds of the types I and II and presents in summary form the salient features of their pharmacological activities.

RESULTS AND DISCUSSION

Chemistry—The reaction sequences leading to the formation of compounds I and II are shown n Scheme I:



Scheme I

Ethyl 5:6-dimethoxy indan 1,2-dicarboxylate (2) was heated with appropriate amine in a sealed tube to yield imides. The imides were reduced to indan pyrrolidines (I) by $LiAlH_4$ (3).

3-Carboxy indan-1-one (4) and its 5:6-dimethoxy derivative (5) were reduced to the corresponding carboxy acids by Clemmensen reduction (6, 7). The acids were converted to acid chlorides by thionyl chloride and were subsequently treated with appropriate primary or secondary amines to yield amides. The amides were converted to desired amines by $LiAlH_4$ reduction. In some cases, methylation of the secondary amines was carried out following a procedure of Bachmann (8). The hydrochloride salts were used for the pharmacological evaluation of hypoglycemic activity.

Structure Activity Relationship—Results of investigation of hypoglycemic activity of the compounds tested so far are summarized in Tables I and II. A close scrutiny of the above results revealed the following facts that among the compounds of the type I, substitution at N atom has some direct bearing on activity. Maximum activity was attained in the *n*-propyl or *n*-butyl substitution and activity disappeared in the *n*-amyl compound. The activity, however, reappeared in the *n*-hexyl compound of this series. Cyclohexyl or benzyl substitution also showed appreciable activity. Methoxy substitution at 5 and 5:6 positions of the aromatic ring also improved the activity in general (Table II). These compounds, however, were more effective against alloxan-induced diabetic animals than that of normal animals, and in a few cases they showed better response than the known standard drugs such as tolbutamide or chlorpropamide. One striking feature of these compounds is their slow onset of action and longer duration.

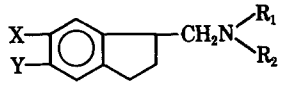
Among 1-*N*-dialkyl aminomethyl indans (Table I), activity was found to be very poor and methoxy substitution in the aromatic ring lowered the activitity in general. However, these compounds showed slight to moderate hypotensive, analgesic, and muscle-relaxant activities.

Complete pharmacology as well as mode of action of a few potent compounds along with their toxicology will be published soon. [1-Methyl-2-*N*-dialkyl aminomethyl indans and their 5:6 dimethoxy derivatives, however, showed appreciable hypoglycemic activity in both normal and alloxan-induced diabetic rabbits (9).]

Pharmacology Method—Normal, healthy, male rabbits, weighing between 1.5–1.8 Kg. were selected. Eight rabbits were used in each set. The animals were kept on fasting for 18 hr. prior to administration of the compound. Water was, however, allowed *ad libitum*. After taking the venous blood of the fasting rabbits, the animals were given the compounds (in the form of hydrochloride in aqueous solution) at the rate of 25 mg./Kg. of body weight by stomach tube and blood glucose concentration

Received August 4, 1967 from the Department of Applied Chemistry, University College of Science and Technology, Calcutta University, Calcutta 9, India.
Accepted for publication January 18, 1968.

TABLE I—1-*N*-DI-ALKYL AMINO METHYL INDANS (II)



(II)

(X = Y = H, or OMe)

X	Y	R_1	R_2	B.p., °C., mm.	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found	n_D	M.p., HCl	Activity 25 mg./Kg.
H	H	Me	Me	80–82/1	$C_{12}H_{17}N$	82.4	82.3	9.7	9.6	8.0	7.8	1.520	237–238[a]	±
H	H	Et	Et	98–100/1	$C_{14}H_{21}N$	82.7	82.6	10.3	10.3	6.9	6.7	1.509	124–126[b]	+++
H	H	*n*-Pr	*n*-Pr	110–114/.8	$C_{16}H_{25}N$	83.1	82.9	10.8	10.6	6.0	5.9	1.503	108–109[b]	++
H	H	*n*-Bu	*n*-Bu	105–110/.35	$C_{18}H_{29}N$	83.4	83.2	11.2	11.1	5.4	5.4	1.495	100–102[b]	++
H	H	H	*n*-Pr	80–85/.15	$C_{13}H_{19}N$	82.5	82.4	10.0	9.9	7.9	8.0	1.515	127–129[a]	++
H	H	H	*n*-Bu	98–102/.35	$C_{14}H_{21}N$	82.7	82.5	10.3	10.2	6.9	6.8	1.525	231–233[b]	++
H	H	Me	*n*-Pr	86–90/.25	$C_{14}H_{21}N$	82.7	82.6	10.3	10.1	6.9	6.8	1.509	131–132[b]	++
H	H	Me	*n*-Bu	128–132/2	$C_{15}H_{23}N$	82.9	82.7	10.6	10.6	6.4	6.3	1.503	138–139[a]	++
OMe	OMe	Me	Me	118–122/.6	$C_{14}H_{21}NO_2$	71.5	71.4	8.9	8.9	5.9	5.8	1.530	157–158[b]	−
OMe	OMe	Et	Et	120–122/.1	$C_{16}H_{25}NO_2$	73.0	72.9	9.5	9.4	5.3	5.4	1.526	140–142[b]	±
OMe	OMe	*n*-Pr	*n*-Pr	138–142/.1	$C_{18}H_{29}NO_2$	74.2	74.1	9.9	9.8	4.8	4.7	1.518	126–127[c]	−
OMe	OMe	*n*-Bu	*n*-Bu	144–148/.6	$C_{20}H_{33}NO_2$	75.2	75.0	10.3	10.2	4.8	4.7	1.509	230–232[a]	−
OMe	OMe	H	*n*-Pr	130–132/.4	$C_{15}H_{23}NO_2$	72.3	72.2	9.2	9.2	5.6	5.5	1.528	138–139[c]	±
OMe	OMe	H	*n*-Bu	152–156/.8	$C_{16}H_{25}NO_2$	73.0	72.9	9.5	9.4	5.3	5.3	1.523	143–145[a]	±
OMe	OMe	Me	*n*-Pr	149–151/.6	$C_{16}H_{25}NO_2$	73.0	72.8	9.5	9.3	5.3	5.3	1.516	131–132[a]	+
OMe	OMe	Me	*n*-Bu	163–166/.4	$C_{17}H_{27}NO_2$	73.3	73.2	9.7	9.8	5.0	4.9	1.511	134–135[a]	++

[a] Crystallized from ethyl acetate and ethanol. [b] Crystallized from ethyl acetate. [c] Crystallized from benzene. [d] − = inactive; ± = questionable; + = very slight; ++ = slight; +++ = moderate.

TABLE III—1-*N*-DI-ALKYL CARBOXY AMIDO INDANS (II-a)

(X = Y = H, or OMe)

Compd. Type	X	Y	R_1	R_2	B.p., °C., mm.	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found	n_D^{30}
IIA	H	H	Me	Me	140–145/0.8	$C_{12}H_{15}NO$	76.2	76.1	7.9	7.8	7.4	7.2	1.554
IIA	H	H	Et	Et	215–220/1.5	$C_{14}H_{19}NO$	77.4	77.2	8.7	8.7	7.4	7.2	1.529
IIA	H	H	*n*-Pr	*n*-Pr	234–240/1.5	$C_{16}H_{23}NO$	78.3	78.1	9.4	9.3	5.7	5.7	1.521
IIA	H	H	*n*-Bu	*n*-Bu	206–210/1	$C_{18}H_{27}NO$	79.1	79.0	9.9	9.8	5.1	5.0	1.511
IIA	H	H	H	*n*-Pr	204–206/1 m.p. 57–59[a]	$C_{13}H_{17}NO$	76.8	76.6	8.4	8.3	6.9	6.8	
IIA	H	H	H	*n*-Bu	207–210/1.5 m.p. 60–62[a]	$C_{14}H_{19}NO$	77.4	77.2	8.7	8.5	6.4	6.3	
IIA	OMe	OMe	Me	Me	163–165/.06	$C_{14}H_{19}O_3N$	67.4	67.2	7.6	7.5	5.6	5.5	1.546
IIA	OMe	OMe	Et	Et	160–166/.05	$C_{16}H_{23}O_3N$	69.3	69.1	8.3	8.2	5.0	5.0	1.538
IIA	OMe	OMe	*n*-Pr	*n*-Pr	212–215/.2	$C_{18}H_{27}O_3N$	70.8	70.6	8.8	8.6	4.6	4.5	1.533
IIA	OMe	OMe	*n*-Bu	*n*-Bu	196–202/.08	$C_{20}H_{31}O_3N$	72.0	71.9	9.3	9.1	4.2	4.1	1.513
IIA	OMe	OMe	H	*n*-Pr	m.p. 92–93[b]	$C_{15}H_{21}O_3N$	68.4	68.3	7.9	7.7	5.3	5.2	
IIA	OMe	OMe	H	*n*-Bu	m.p. 115–117[b]	$C_{16}H_{23}O_3N$	69.3	69.2	8.3	8.2	5.0	5.0	

[a] Crystallized from petroleum ether, 60–80°. [b] Crystallized from a mixture of benzene and petroleum ether, 60–80°.

TABLE II—ORAL HYPOGLYCEMIC ACTIVITY OF 1,2,3,3*a*,8,8*a*,-HEXAHYDRO INDENO (1,2-*c*) PYRROLES

(I)

(X = Y = H, OMe, X = H, Y = OMe)

X	Y	R	Hypoglycemic Effect at a Dose of 25 mg./Kg.[d]
H	H	Me[a]	+
H	H	Et[a]	±
H	H	*n*-Pr[a]	++
H	H	*n*-Bu[a]	+++
H	H	*n*-Am[a]	−
H	H	*n*-Hex[b]	++
H	H	Cyclo-hex[b]	+++
H	H	Benzyl[b]	++
H	OMe	Me[c]	−
H	OMe	Et[c]	+
H	OMe	*n*-Pr[c]	+++
H	OMe	*n*-Bu	+++
H	OMe	*n*-Am[c]	−
H	OMe	*n* Hex[c]	++
OMe	OMe	Me[a]	±
OMe	OMe	Et[a]	−
OMe	OMe	*n*-Pr[a]	+++
OMe	OMe	*n*-Bu[a]	++++
OMe	OMe	*n*-Hex	+++
OMe	OMe	Cyclo-hex	+++
OMe	OMe	Benzyl	+++
Tolbutamide			++++

[a] See Ref. 3. [b] See Ref. 1. [c] See Ref. 11. [d] − = no activity; ± = questionable; + = very slight; ++ = slight; +++ = moderate; ++++ = marked.

was observed at different hours up to 24 hr. The maximum fall of blood glucose concentration was observed in between the 9th–12th hour. The blood glucose estimation was carried out in a manner as described by Hagedorn and Jensen (10). The hypoglycemic activity of the compounds tested were detailed in Tables I and II.

EXPERIMENTAL[1]

***N*-Substituted 5:6-Dimethoxy Indan 1,2-Dicarboximides (Ia)**—A mixture of 5:6-dimethoxy indan 1,2-dicarboxylate (2) (0.05 mole) and an appropriate amine (0.1 mole) was heated in a sealed tube for 8–12 hr. at 150° and the imide isolated following a similar procedure as reported earlier (1,3).

N-*n*-Hexyl 5:6-dimethoxy indan 1,2-dicarboximide was boiled at 188–190°/0.8 mm.

Anal.—Calcd. for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.5; N, 4.2. Found: C, 68.7; H, 7.4; N, 4.2.

N-Benzyl 5:6-dimethoxy indan 1:2-dicarboximide was boiled at 210–215°/0.15 mm.

Anal.—Calcd. for $C_{20}H_{19}NO_4$: C, 71.2; H. 5.6; N, 4.1. Found: C, 71.2; H, 5.5; N, 4.2.

N-Cyclohexyl 5:6-dimethoxy indan 1,2-dicarboximide was crystallized from petroleum ether (60–80°); m.p. 118–120°.

Anal.—Calcd. for $C_{19}H_{23}NO_4$: C, 69.3; H, 6.6; N, 4.2. Found: C, 69.2; H, 6.5; N, 4.2.

1,2,3,3a,8,8a-Hexahydro 5:6-Dimethoxy 2-Alkyl Indeno (1,2-*c*)Pyrroles (I)—The appropriate imides were reduced by refluxing with $LiAlH_4$ with absolute

[1] All melting points are corrected and determined in Gallenkamp apparatus. Boiling points are uncorrected.

ether and amines were separated in the usual manner.

1,2,3,3*a*,8,8*a*-Hexahydro 5:6-dimethoxy *N*-*n*-hexyl indeno (1,2-c) pyrrole was boiled at 186–188°/0.6 mm.

Anal.—Calcd. for $C_{19}H_{29}NO_2$: C, 75.2; H, 9.6; N, 4.6. Found: C, 75.1; H, 9.5; N, 4.5. Hydrochloride (hygroscopic) was crystallized from ethyl acetate, m.p. 118–120°.

1,2,3,3*a*,8,8*a*-Hexahydro 5:6-dimethoxy *N*-cyclohexyl indeno (1,2-*c*) pyrrole was boiled at 192–195°/0.6 mm.

Anal.—Calcd. for $C_{19}H_{27}NO_2$: C, 75.7; H, 8.9; N, 4.6. Found: C, 75.6; H, 8.7; N, 4.5. Hydrochloride was crystallized from a mixture of ethyl acetate and absolute ethanol, m.p. 200–202°.

1,2,3,3*a*,8,8*a*-Hexahydro 5:6-dimethoxy *N*-benzyl indeno (1,2-*c*) pyrrole was boiled at 192–196°/0.4 mm.

Anal.—Calcd. for $C_{20}H_{23}NO_2$: C, 77.6; H, 7.4; N, 4.5. Found: C, 77.4; H, 7.3; N, 4.4. Hydrochloride salt crystallized from ethyl acetate, m.p. 172–173°.

1-Chlorocarboxy Indans—Indan 1-carboxy acid (5, 6) was converted to acid chloride by reacting with thionyl chloride. It boiled at 140–145°/1.5 mm. (74%).

Anal.—Calcd. for $C_{10}H_9ClO$: C, 65.9; H, 4.6; Cl, 19-11. Found: C, 65.9; H, 4.88; Cl, 19.01.

1-Chlorocarboxy 5:6-Dimethoxy Indan—A mixture of 3,4-dimethoxy phenyl succinic acid (5) (16 Gm.) and polyphosphoric acid (740 Gm.) was heated at 100° for 3 hr. under stirring. The keto acid thus formed was extracted with chloroform. The yield was 80%, m.p. 190–191° dec. The keto acid was then subjected to Clemmensen reduction and the 1-carboxy 5:6-dimethoxy indan distilled at 176–180°/0.7 mm., crystallized from benzene, mp. 114–116°.

Anal.—Calcd. for $C_{12}H_{14}O_4$: C, 65.86; H, 6.30. Found: C, 64.82; H, 6.28. The acid chloride was prepared by reacting with thionyl chloride but it was not distilled as it decomposed on distillation.

1-N-Dialkyl Carboxy Amido Indans (IIa)—The 1-chlorocarboxy indan or 1-chlorocarboxy 5:6-dimethoxy indan (1 mole) was added dropwise to a mixture of an appropriate amine (1.5 mole) and sodium hydroxide solution (10%; 1 mole) cooled in an ice bath. The amide was extracted with a suitable solvent and either distilled under reduced pressure or crystallized from a suitable solvent. The physical properties and analyses of the amides are listed in Table I.

1-N-Dialkyl Aminomethyl Indans (II)—The amide (1 mole) so prepared was reduced with $LiAlH_4$ (2 mole) in dry ether under reflux for 8–12 hr. in the usual manner. In some cases, the secondary amines, thus prepared, were methylated by heating a mixture of amine, formic acid, and formaldehyde on an oil bath in the usual manner (8). The bases were characterized as their hydrochlorides and other physical properties and hypoglycemic activities were listed in Table I.

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Keyphrases

Pyrroles—synthesis
Indan amines—synthesis
Hypoglycemic activity—pyrroles, indan amines
Structure–activity relationship