Conformationally Restricted Congeners of Dopamine Derived from 2-Aminoindan

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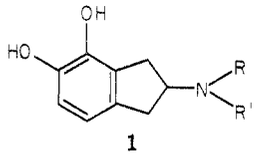
Two series of N-substituted 2-aminoindan systems have been prepared: 4,5-dihydroxy-2-aminoindan (1) has a hydroxylation pattern analogous to the α conformer of dopamine, and 5,6-dihydroxy-2-aminoindan (2) has a hydroxylation pattern of the β conformer of dopamine. All members of both series demonstrated only extremely weak binding to calf caudate homogenate. Certain N-alkylated 4,5-dihydroxyindans were violent emetics in the dog and were potent in blockade of the effect of stimulation of the cardioaccelerator nerve of the cat. In contrast, the 5,6-dihydroxy series displayed low or no activity/potency in these assays. Conformational analysis of the 2-aminoindan system is described and discussed.

Prior communications[1-3] have addressed a short series of 4,5-dihydroxy-2-aminoindans 1 (R, R′ = combinations



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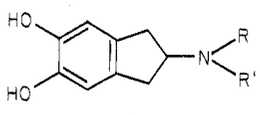

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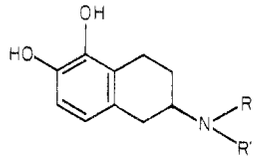

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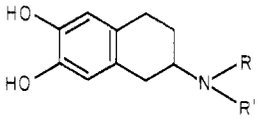

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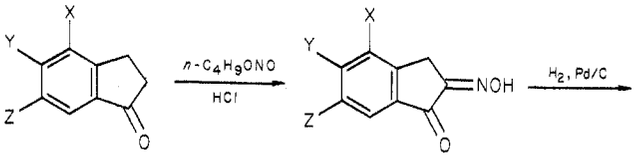
of H and CH_3), which display some prominent and selective dopamine-like effects and show animal species selectivity. The *N,N*-dimethyl derivative of 1 was approximately four times as potent an emetic as apomorphine in the pigeon, but in the dog emetic model it was 0.008 times as potent as apomorphine. The present work extends the nitrogen substituents of 1 (R, R′ = combinations of H, CH_3, C_2H_5, *n*-C_3H_7, and 2-C_3H_7) and describes a series (2) of hydroxy group positional isomers. Series 1 has a hydroxylation pattern analogous to the α conformer of dopamine[4] [also seen in apomorphine and in 5,6-dihydroxy-2-aminotetralin (3)], and series 2 has the hydroxylation pattern of the β conformer of dopamine[4] [illustrated here by 6,7-dihydroxy-2-aminotetralin (4)]. The two aminotetralin hydroxy group positional isomers (3 and 4) display qualitatively and quantitatively different spectra of dopaminergic effects, but extremely potent and highly active dopamine agonists are found in both series of aminotetralin derivatives.[5]

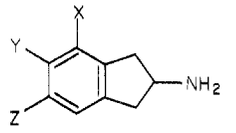
The aminoindan series (1 and 2) were prepared as illustrated in Scheme I. Appropriate alkyl substituents were placed on the amino groups, and ether linkages (R, R′, R″) were cleaved by literature methods. Spectral (IR, NMR, MS) data on all intermediates and final compounds were consistent with the proposed structures.

Pharmacology. Test data were obtained for the dimethyl ethers (**9a–g** and **10a–g**) and for the free catechol systems (**1a–h** and **2a–g**). (See Table I.) Binding studies using calf caudate homogenate, against spiperone (an index of postsynaptic binding activity) and against A-6, 7-DTN (an index of presynaptic binding activity), revealed only extremely weak binding activity for all of the methyl ethers and the free catechol systems tested, compared to dopamine, apomorphine, and lergotrile. The compounds were evaluated for their ability to inhibit the positive chronotropic effect of stimulation of the cardioaccelerator nerve in the anesthetized cat, which is an index of peripheral presynaptic dopamine receptor activity. In this assay, only the *N,N*-diethyl- and *N,N*-di-*n*-propyl-4,5-dihydroxy derivatives (**1g,h**) demonstrated significant effect. The action of these two compounds was blocked by haloperidol (100 μg/kg). In the case of the hydroxy group positional isomers (**2a–g**), only the di-*n*-propyl homologue **2f** displayed even weak inhibitory activity (ID_{50} > 3.0 μmol/kg). The remaining members of the series (**2a–e,g**) caused an *increase* in heart rate in the cardioaccelerator nerve assay, as did the primary amine and mono- and dimethylamines **1a,b,f**. It is noteworthy that there was no correlation between CNS binding data and the peripheral cardioaccelerator nerve effects of **1g** and **1h**.

Scheme I. Preparation of 2-Aminoindan Systems



5, X = Y = OCH_3; Z = H
6, X = H; Y = Z = OCH_3
7, X = Y = OCH_3; Z = H
8, X = H; Y = Z = OCH_3



9, X = Y = OCH_3; Z = H
10, X = H; Y = Z = OCH_3

A few selected compounds were evaluated for emetic activity in dogs (Table II). The two compounds that were potent in the cardioaccelerator nerve assay are also violent emetics (**1g,h**).

Hacksell et al.[6] have reported that 2-(di-*n*-propylamino)-4-hydroxyindan (11) is much more potent and active in a series of CNS dopamine assays than is the isomeric 2-(di-*n*-propylamino)-5-hydroxyindan (12). These findings seem to be consistent with the results in the present study of dihydroxyindans, and they demonstrate

[†] College of Pharmacy.
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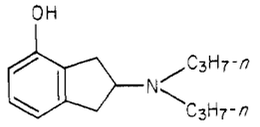

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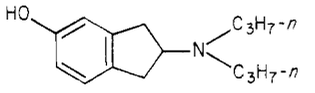

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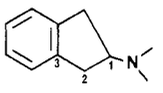
the importance of the "meta" OH group in the α conformer of dopamine.

It might be inferred from the biological data cited heretofore that the indan ring can hold the catecholethylamine moiety in the 2-amino derivative 1 conformationally discrete and in a manner that approximates the steric disposition presented by the catecholethylamine portion of the 2-aminotetralin system **3**. NMR studies have led to the conclusion[7,8] that the cyclopentene ring of 2-substituted indan systems is not planar and that the 2-substituent adopts a pseudoequatorial disposition, possibly in an attempt of the molecule to relieve the extensive eclipsing of bonds extant in the all-planar conformation of the molecule. Dreiding models suggest that the τ_2 (N–C_1–C_2–C_3) (structure **13**) could approach 140–150°. The



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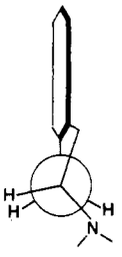

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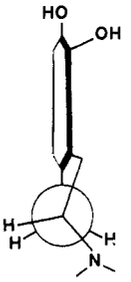

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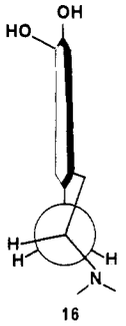

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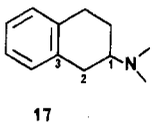
Newman projection **14** shows that in the 2-aminoindan system (where τ_2 = 140–150°) the dopamine moiety approaches the antiperiplanar disposition and the benzene ring is approximately coplanar with the ethylamine side chain, which steric dispositions have been proposed[4] to be required for interaction with dopamine receptor(s). Thus, the dopamine moieties of the two hydroxy group positional isomer indan systems (**1** and **2**), as illustrated in the Newman projections **15** and **16**, respectively, approximate the α and β conformers of dopamine, although the degree of correspondence of the indans is not as close as is the case with the 2-aminotetralins whose τ_2 (N–C_1–C_2–C_3) is 180° (structures **17** and **18**). It must be emphasized that this conformational analysis of the 2-aminoindan system is based solely upon a study of molecular models. X-ray data for these systems have not been found in the literature. Use of NMR data for stereochemical studies of indan derivatives leading to quantitative conclusions is unreliable, due to the erratic variation of vicinal coupling constants



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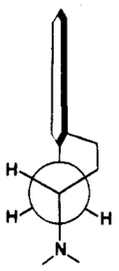

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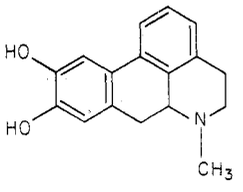
with substituent changes.[9,10] Some quantitative data (out of plane bending, relative amounts of axial vs. equatorial substituent) have been reported and discussed for 4-substituted cyclopentene systems. However, it is difficult to assess the extent to which the information obtained from unsaturated five-membered rings can be applied to the indan system.

The biological inactivity of the 5,6-dihydroxyindan series **2** contrasts with the high activity and potency mentioned previously for the analogous OH-position isomer 2-aminotetralins **4**, but it is consistent with the reported[11,12] dopaminergic inactivity of "isoapomorphine" **19**. It is



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difficult to rationalize dopaminergic inactivity of the 5,6-dihydroxy-2-aminoindans (and of "isoapomorphine") on a chemical structural basis.

Experimental Section

Melting points were determined in open glass capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Pharmacology. Cardioaccelerator Nerve Stimulation. Experiments were performed on cats (2–4 kg) of either sex. Cats were anesthetized with an intraperitoneal (ip) injection of pentobarbital sodium, 30 mg/kg. All animals were artificially respired with a Harvard respirator. The arterial blood pressure was measured from the femoral artery by a Statham P23AA transducer, and heart rate was monitored with a Beckman cardiotachometer. All injections were made via a catheter placed in the femoral vein. A Beckman R511A recorder was used to monitor physiological changes in these experiments. After bilateral vagotomy, the right postganglionic cardioaccelerator nerves were isolated and placed on bipolar electrodes. Right cardioaccelerator nerves were stimulated for 30 s with a Grass S48 or SD9 stimulator with the following parameters: 2 Hz, 5-ms pulse duration, and supramaximal voltage usually 20–25 V. All animals were pretreated with atropine sulfate, 0.2 mg/kg.

Emesis Experiments. Three adult mongrel dogs of either sex were housed individually with standard laboratory diet supplied ad libitum. Drug solutions were administered subcutaneously (sc), and the frequency of vomiting and retching was observed for 1 h. The dogs were tested on different days following at least

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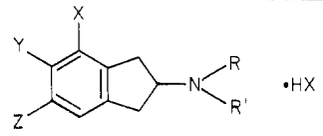
Table I. Binding Data and Cardioaccelerator Nerve Assay Data on 2-Aminoindans



compd	X	Y	Z	R	R′	binding data: IC_{50}, nM spiroperidol	ADTN	cardioaccelerator nerve: ID_{50}, μmol/kg
9a	OCH_3	OCH_3	H	H	H			inact[d]
9b	OCH_3	OCH_3	H	H	CH_3[b]			inact[d]
9c	OCH_3	OCH_3	H	H	C_2H_5			inact[d]
9d	OCH_3	OCH_3	H	H	n-C_3H_7	105 000	51 000 000	inact[d]
9e	OCH_3	OCH_3	H	H	2-C_3H_7			inact[d]
9f	OCH_3	OCH_3	H	CH_3	CH_3	100 000	2 300 000	inact[d]
9g	OCH_3	OCH_3	H	C_2H_5	C_2H_5	29 000	1 660 000	inact[d]
1a	OH	OH	H	H	H			↑ HR[c]
1b	OH	OH	H	H	CH_3			↑ HR[c]
1c	OH	OH	H	H	C_2H_5			>1.0
1d	OH	OH	H	H	n-C_3H_7			inact[d]
1e	OH	OH	H	H	2-C_3H_7			inact[d]
1f	OH	OH	H	CH_3	CH_3[b]	91 000	10 000	↑ HR[c]
1g	OH	OH	H	C_2H_5	C_2H_5	220 000	39 000	0.05
1h	OH	OH	H	n-C_3H_7	n-C_3H_7	53 860	10 000	0.02
10a	H	OCH_3	OCH_3	H	H			inact[d]
10b	H	OCH_3	OCH_3	H	CH_3			inact[d]
10c	H	OCH_3	OCH_3	H	2-C_3H_7			inact[d]
10d	H	OCH_3	OCH_3	CH_3	CH_3	50 000	400 000	inact[d]
10e	H	OCH_3	OCH_3	C_2H_5	C_2H_5			inact[d]
10f	H	OCH_3	OCH_3	n-C_3H_7	n-C_3H_7	10 400	147 000 000	inact[d]
10g	H	OCH_3	OCH_3	CH_3	2-C_3H_7			
2a	H	OH	OH	H	H			↑ HR[c]
2b	H	OH	OH	H	CH_3			↑ HR[c]
2c	H	OH	OH	H	2-C_3H_7			↑ HR[c]
2d	H	OH	OH	CH_3	CH_3	104 000	6 000	↑ HR[c]
2e	H	OH	OH	C_2H_5	C_2H_5	246 000		↑ HR[c]
2f	H	OH	OH	n-C_3H_7	n-C_3H_7	17 600	412 000	>3.0
2g	H	OH	OH	CH_3	2-C_3H_7			↑ HR[c]
apomorphine						8 700	830	0.022
dopamine						150 000	510	0.105[a]
lergotrile						23 700	4 500	0.27

[a] In the presence of cocaine, 5 mg/kg. [b] Preparation: see ref 1. [c] Increased heart rate, at 3 μmol/kg. [d] Inactive, at 3 μmol/kg.

Table II. Emetic Activity in Dogs

compd	potency ratio (95% CL)[a]
apomorphine	1.0[b]
2e	inactive[c]
1g	0.26 (0.19–0.32)
1h	1.24 (0.75–2.61)

[a] Subcutaneous administration. [b] ED_{50} = 70 μg/kg. [c] At 1 mg/kg.

a 2-day resting period. The frequency of emesis induced by different doses of the compounds was compared with that of apomorphine.

Binding Studies. Dopamine receptor binding studies were carried out on the striatal tissue of calf brain (pel-Freez Biologicals, Rogers, AR). The crude membrane preparation for ligand binding studies was essentially according to Seeman et al.[13] Triplicate tubes received 100 μL of varying concentrations of competing drug, 200 μL of radioactive ligand, and 200 μL of tissue suspension (0.3–0.6 mg of protein). A parallel set of triplicate tubes received 100 μL of 15 mM Tris-HCl, pH 7.4, containing 5 mM Na_2EDTA, 1.1 mM ascorbic acid, and 12.5 mM nialamide. The samples were incubated at 20–22 °C for 30 min, and 0.4-mL aliquots were vacuum filtered through Whatman GF/B filters, followed by two 5-mL rinses with 15 mM Tris-HCl buffer, pH 7.4. The filters were placed in counting vials, allowed to stand in 10 mL of Aquasol overnight, and then counted by liquid scintillation spectrometry. The differences between two sets of triplicate tubes represented the displacement of the radioactive ligand by the competing drug. IC_{50} values on radioactive ligand were calculated. Similar experiments were repeated on a different day, and the average of two IC_{50} values was used for comparison. [^{3}H]Spiperone (43.9 Ci/mmol, New England Nuclear, Boston, MA) was used as an antagonist ligand in a final concentration of 1 nM, and [^{3}H]ADTN (35.5 Ci/mmol, New England Nuclear) was used as an agonist ligand in a final concentration of 2.5 nM.

Statistical Analysis. The ED_{50} values were determined by probit analysis. A 3 × 3 parallel line bioassay was used to determine relative potencies.[14] Differences between means were compared by the Student's t test or the paired t test.

4,5-Dimethoxy-2-oximino-1-indanone (7). 4,5-Dimethoxy-1-indanone[15] (10.0 g, 0.052 mol) in 400 mL of MeOH was stirred and warmed to 40 °C. Dropwise addition of 5.8 g (0.057 mol) of n-butyl nitrite and then 5 mL of concentrated HCl resulted in the formation of a pale yellow mass. The reaction mixture was stirred for 0.5 h, and the solid product was collected on a filter to afford 9.3 g (80%) of a pale yellow solid, mp 241 °C dec (lit.[16] mp 244 °C dec).

5,6-Dimethoxy-2-oximino-1-indanone (8). Treatment of 20.0 g (0.104 mol) of 5,6-dimethoxy-1-indanone[17] with 12.0 g (0.116 mol) of n-butyl nitrite and 5 mL of concentrated HCl in 300 mL of MeOH, as described for **7**, gave 21.1 g (92%) of a yellow powder, mp 240 °C dec (lit.[17] mp 240 °C dec).

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4,5-Dimethoxy-2-aminoindan Hydrochloride (9a). Compound **7** (5.0 g, 0.022 mol) in 75 mL of glacial AcOH and 5 mL of concentrated H_2SO_4 was hydrogenated over 2.0 g of 5% Pd/C for 2 h at an initial pressure of 50 psig. The catalyst was removed and the solution was concentrated to 20 mL under reduced pressure. H_2O (40 mL) was added, and the pH was brought to 10 with 10% NaOH. This solution was extracted several times with $CHCl_3$, and the pooled extracts were dried ($MgSO_4$) and evaporated under reduced pressure. To the pale brown oily residue, diluted with 10 mL of Et_2O, was added ethereal HCl, and the resulting copious precipitate was recrystallized from 2-PrOH–Et_2O to give 4.8 g (92%) of white crystals, mp 205–208 °C (lit.[1] mp 205–206.5 °C).

5,6-Dimethoxy-2-aminoindan Hydrochloride (10a). Hydrogenation of 5.0 g (0.0226 mol) of **8** in 75 mL of glacial AcOH and 5 mL of concentrated H_2SO_4 over 2.0 g of 5% Pd/C at an initial pressure of 50 psig, as described for **9a**, gave 4.2 g of the free base of **10a** as a clear oil, which crystallized on standing, mp 75–81 °C. This material was converted to its HCl salt, which was recrystallized from 2-PrOH–Et_2O to give 4.0 g (77%) of white crystals, mp 288–290 °C (lit.[18] mp 289–290 °C).

4,5-Dimethoxy-2-(ethylamino)indan Hydrochloride (9c). The free base of **9a** (1.15 g, 0.0064 mol), 0.28 g (0.0064 mol) of acetaldehyde, 0.39 g (0.0064 mol) of glacial AcOH, and 0.1 g of PtO_2 in 80 mL of absolute EtOH were hydrogenated for 4 h at an initial pressure of 50 psig. The reduction mixture was filtered, and volatiles were removed from the filtrate under reduced pressure. The residue was treated with excess 10% NaOH, and the resulting mixture was extracted several times with Et_2O. The pooled extracts were dried ($MgSO_4$) and then treated with ethereal HCl. The resulting solid was recrystallized twice from 2-PrOH–Et_2O to give 0.9 g (54%) of white crystals, mp 188–192 °C. Anal. ($C_{13}H_{20}ClNO_2$) C, H, N.

4,5-Dimethoxy-2-(*n*-propylamino)indan Hydrochloride (9d). The reduction method described for **9c** was employed, using 2.0 g (0.0103 mol) of the free base of **9a**, 0.6 g (0.0103 mol) of propionaldehyde, 0.6 g (0.103 mol) of glacial AcOH, and 0.1 g of PtO_2 in 75 mL of absolute EtOH. The HCl salt was recrystallized twice from 2-PrOH–Et_2O to give 1.5 g (54%) of white crystals, mp 207–210 °C. Anal. ($C_{14}H_{22}ClNO_2$) C, H, N.

4,5-Dimethoxy-2-(2-propylamino)indan Hydrobromide (9e). A mixture of 2.0 g (0.0103 mol) of the free base of **9a** and 1.2 g (0.0206 mol) of Me_2CO in 80 mL of absolute EtOH was hydrogenated over 0.1 g of PtO_2 for 4 h at an initial pressure of 50 psig. The reduction mixture was filtered, and the filtrate was evaporated under reduced pressure. The clear oily residue was converted to its HBr salt, which was recrystallized from 2-PrOH–Et_2O to give 3.2 g (98%) of white needles, mp 239–241 °C. Anal. ($C_{14}H_{22}BrNO_2$) C, H, N.

4,5-Dimethoxy-2-(diethylamino)indan Hydrobromide (9g). To a solution of 1.0 g (0.005 mol) of the free base of **9a** in 100 mL of MeOH at 0 °C was added 1.4 g (0.032 mol) of acetaldehyde, and the resulting solution was stirred for 10 min. $NaCNBH_3$ (0.31 g, 0.005 mol) was added, and the resulting mixture was stirred for 12 h. The solvent was removed under reduced pressure, and excess concentrated HCl was added, followed by 100 mL of H_2O. This mixture was extracted with Et_2O, and the extracts were discarded. The aqueous layer was treated with excess 10% NaOH, and the resulting mixture was extracted several times with Et_2O. The pooled extracts were dried ($MgSO_4$), and volatiles were removed under reduced pressure to give 1.2 g of a clear oil. This was treated with 5 mL of phenyl isocyanate, and the resulting solution was allowed to stand at room temperature overnight. Excess MeOH was then added, the resulting mixture was brought to boiling, and then the volatiles were removed under reduced pressure. The yellow residue was treated with concentrated HCl until the pH was below 2. H_2O (100 mL) was added, and the heterogeneous mixture was extracted with 100 mL of Et_2O: then it was taken above pH 10 with NaOH pellets. A yellow oil separated, and this mixture was extracted with 200 mL of Et_2O in divided portions. The pooled extracts were dried ($MgSO_4$), and the solvent was evaporated to leave an oil, which was converted to its HBr salt with ethereal HBr. This salt was recrystallized from 2-PrOH–Et_2O to yield 1.2 g (73%) of white crystals, mp 132–135 °C. Anal. ($C_{15}H_{24}BrNO_2$) C, H, N.

4,5-Dimethoxy-2-(di-*n*-propylamino)indan Picrate (20). The free base of **9a** (2.0 g, 0.0103 mol) was dissolved with stirring in 100 mL of MeOH. Propionaldehyde (3.7 g, 0.064 mol) was added, and the solution was stirred for 10 min, then $NaCNBH_3$ (0.9 g, 0.0143 mol) was added, and the resulting solution was stirred for 18 h. The solvent was removed under reduced pressure, and the residue was brought below pH 2 with concentrated HCl. H_2O (100 mL) was added, and the mixture was extracted with Et_2O. The aqueous layer was basified with NaOH pellets. An oil separated, and the mixture was extracted several times with Et_2O. The pooled extracts were dried ($MgSO_4$), and the volatiles were removed under reduced pressure to give a clear brown oil, which was treated with phenyl isocyanate and further manipulated as described for **9g** to give 2.2 g (79%) of an oil, bp 138 °C (0.1 mm). Anal. ($C_{17}H_{27}NO_2$) C, H, N. Crystalline hydrohalide or fumarate salts could not be prepared, and the compound was further characterized as its picrate salt, mp 158–162 °C (from $CHCl_3$–pentane). Anal. ($C_{23}H_{30}N_4O_9$) C, H, N.

5,6-Dimethoxy-2-[(trifluoroacetyl)amino]indan (21). To 4.2 g (0.0217 mol) of the free base of **10a** in 50 mL of $CHCl_3$ was added 20.0 g (0.0952 mol) of trifluoroacetic anhydride, and this mixture was stirred at room temperature for 1 h. The volatiles were removed under reduced pressure, and the residual white solid was recrystallized from Me_2CO–pentane to give 5.9 g (94%) of white crystals, mp 149–154 °C. Anal. ($C_{13}H_{14}F_3NO_3$) C, H, N.

5,6-Dimethoxy-2-[[(trifluoroacetyl)methyl]amino]indan (22). A modification of a method of Oka[20] was used. A solution of 1.5 g (0.005 mol) of **21** and 3.0 g (0.02 mol) of MeI in 100 mL of dry Me_2CO was heated under reflux, and 1.1 g (0.02 mol) of KOH was added. This mixture was heated under reflux for 5 min, and then the volatiles were removed under reduced pressure. The gummy residue was washed several times with $CHCl_3$, and the volatiles were removed to leave 1.4 g of an oil, which was dissolved in 5 mL of $CHCl_3$. This solution was treated with 100 mL of pentane and was stored overnight in the cold to produce 1.3 g (87%) of white crystals, mp 88–92 °C. Anal. ($C_{14}H_{16}F_3NO_3$) C, H, N.

5,6-Dimethoxy-2-(methylamino)indan Hydrochloride (10b). A mixture of 1.3 g (0.0043 mol) of **22** and 2.0 g (0.0356 mol) of KOH in 20 mL of H_2O was heated under reflux for 30 min. The resulting mixture was cooled to room temperature and then extracted several times with Et_2O. The pooled extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to leave an oily residue. This was converted to its HCl salt with ethereal HCl, and the salt was recrystallized from MeOH–Et_2O to give 0.8 g (80%) of white crystals, mp 257 °C dec. Anal. ($C_{12}H_{18}ClNO_2$) C, H, N.

5,6-Dimethoxy-2-(2-propylamino)indan Hydrochloride (10c). A mixture of 2.0 g (0.0103 mol) of the free base of **10a** and 1.2 g (0.0206 mol) of Me_2CO in 80 mL of absolute EtOH was hydrogenated over 0.1 g of PtO_2 for 4 h at an initial pressure of 50 psig. The reduction mixture was filtered, and volatiles were removed from the filtrate under reduced pressure to give 2.2 g (91%) of crude oily amine, which solidified upon standing, mp 53–56 °C. This product was converted to its HCl salt, which was recrystallized from 2-PrOH–Et_2O to give 2.3 g (82%) of white crystals, mp 275–280 °C dec. Anal. ($C_{14}H_{22}ClNO_2$) C, H, N.

5,6-Dimethoxy-2-(dimethylamino)indan Hydrochloride (10d). A mixture of 1.0 g (0.0051 mol) of the free base of **10a** and 5 mL of 37% aqueous formaldehyde in 20 mL of MeOH was refluxed for 30 min. The mixture was cooled to room temperature, and 0.68 g (0.0178 mol) of $NaBH_4$ was added in portions with stirring. After stirring for an additional 1 h at room temperature, the volatiles were removed under reduced pressure, and excess 10% NaOH was added to the residue. The resulting mixture was extracted several times with Et_2O, and the pooled extracts were dried ($MgSO_4$). Addition of ethereal HCl to this solution gave a copious precipitate, which was recrystallized from MeOH–Et_2O

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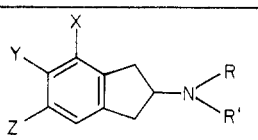
Table III. Dihydroxy-2-aminoindans



compd	X	Y	Z	R	R'	mp, °C	yield, %	formula	anal.
1a	OH	OH	H	H	H	215-220[a]	75		
1b	OH	OH	H	H	CH_3	244-247[b]	66		
1c	OH	OH	H	H	C_2H_5	217-222	84	$C_{11}H_{16}BrNO_2$	C, H, N
1d	OH	OH	H	H	n-C_3H_7	193-198	62	$C_{12}H_{18}BrNO_2$	C, H, N
1e	OH	OH	H	H	2-C_3H_7	225-230	91	$C_{12}H_{18}BrNO_2$	C, H, N
1f	OH	OH	H	CH_3	CH_3	220-227[c]	80	$C_{11}H_{16}BrNO_2$	C, H, N
1g	OH	OH	H	C_2H_5	C_2H_5	175-180	96	$C_{13}H_{20}BrNO_2$	C, H, N
1h	OH	OH	H	n-C_3H_7	n-C_3H_7	157-162	90	$C_{15}H_{24}BrNO_2$	C, H, N
2a	H	OH	OH	H	H	295 dec	74	$C_9H_{12}BrNO_2$	C, H, N
2b	H	OH	OH	H	CH_3	241-246	85	$C_{10}H_{14}BrNO_2$	C, H, N
2c	H	OH	OH	H	2-C_3H_7	205-210	94	$C_{12}H_{18}BrNO_2$	C, H, N
2d	H	OH	OH	CH_3	CH_3	246-250	38	$C_{11}H_{16}BrNO_2$	C, H, N
2e	H	OH	OH	C_2H_5	C_2H_5	220-230	83	$C_{13}H_{20}BrNO_2$	C, H, N
2f	H	OH	OH	n-C_3H_7	n-C_3H_7	278 dec	66	$C_{15}H_{24}BrNO_2$	C, H, N
2g	H	OH	OH	CH_3	2-C_3H_7	215-220	69	$C_{13}H_{20}BrNO_2$	C, H, N

[a] Literature[1] mp 214-219 °C. [b] Literature[1] mp 246.5-249.5 °C. [c] Literature[1] mp 216-219.5 °C.

to afford 1.1 g (78%) of white crystals, mp 255 °C dec. Anal. ($C_{13}H_{20}ClNO_2$) C, H, N.

5,6-Dimethoxy-2-(diethylamino)indan Hydrochloride (10e). The method of Marchini et al.[21] was utilized. To a stirred solution of 40.8 g (0.68 mol) of AcOH in 100 mL of benzene at 10 °C was slowly added 7.8 g (0.206 mol) of $NaBH_4$, with the temperature maintained below 20 °C by immersion in an ice bath. When H_2 evolution ceased, the free base of **10a** (2.0 g, 0.0103 mol) in 10 mL of benzene was added, and the reaction mixture was heated under reflux for 20 h. To the cooled mixture, NaOH pellets were added to bring the pH above 10. The resulting solution was extracted with 100 mL of H_2O, the organic layer was dried ($MgSO_4$), and the solvent was evaporated to give a yellow oil. This was treated with phenyl isocyanate and further manipulated as described for **9g**, and the free base was converted to its HCl salt. This was recrystallized from 2-PrOH–Et_2O to yield 2.2 g (75%) of white crystals, mp 190–191 °C. Anal. ($C_{15}H_{24}ClNO_2$) C, H, N.

5,6-Dimethoxy-2-(di-*n*-propylamino)indan Hydrochloride (10f). The method of Marchini et al.,[21] as described for **10e**, was utilized, employing 50 g (0.675 mol) of propionic acid, 7.7 g (0.203 mol) of $NaBH_4$, and the free base obtained from 1.9 g (0.0098 mol) of **10a**. The crude free base product was treated with phenyl isocyanate and further manipulated as described for **9g**, and the free base product was converted to its HCl salt with ethereal HCl. This salt was recrystallized from 2-PrCH–Et_2O to give 1.6 g (53%) of white crystals, mp 210–214 °C. Anal. ($C_{17}H_{28}ClNO_2$) C, H, N.

5,6-Dimethoxy-2-[*N*-methyl-*N*-(2-propyl)amino]indan Hydrochloride (10g). A mixture of the free base of **10c** (1.0 g, 0.0042 mol), 3 mL of 37% aqueous formaldehyde, and 0.05 g of PtO_2 in 80 mL of anhydrous EtOH was hydrogenated for 4 h at an initial pressure of 50 psig. The reduction mixture was filtered, and the filtrate was evaporated under reduced pressure to leave a clear oil, which was converted to its HCl salt. This was recrystallized from MeOH–Et_2O to give 1.1 g (91%) of white crystals, mp 195–201 °C. Anal. ($C_{15}H_{24}ClNO_2$) C, H, N.

Ether Cleavage Reactions. The amine hydrohalide salt (0.4 g) in 4 mL of 48% HBr was heated under reflux under N_2 for 3 h. Removal of the volatiles under reduced pressure left a solid residue, which was recrystallized from EtOH–Et_2O. See Table III.

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