

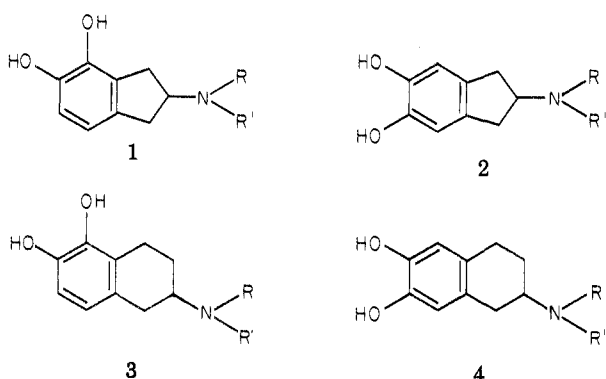
Conformationally Restricted Congeners of Dopamine Derived from 2-Aminoindan

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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 communications¹⁻³ have addressed a short series of 4,5-dihydroxy-2-aminoindans 1 (R, R' = combinations

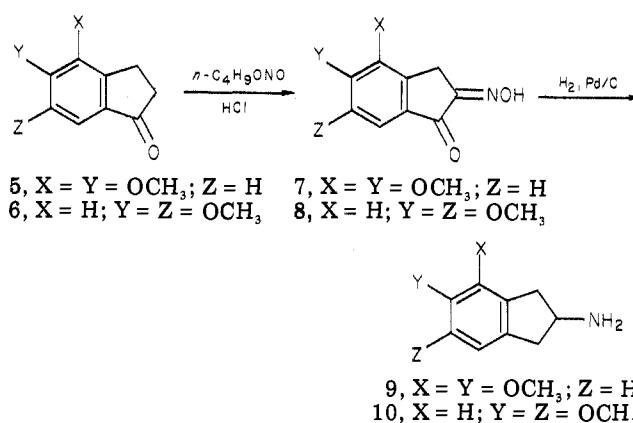


of H and CH₃), which display some prominent and selective dopamine-like effects and show animal species selectivity. The *N,N*-dimethyl derivative of 1 was approximately four times as potent an emetic as apomorphine in the pigeon, but in the dog emetic model it was 0.008 times as potent as apomorphine. The present work extends the nitrogen substituents of 1 (R, R' = combinations of H, CH₃, C₂H₅, *n*-C₃H₇, and 2-C₃H₇) and describes a series (2) of hydroxy group positional isomers. Series 1 has a hydroxylation pattern analogous to the α conformer of dopamine⁴ [also seen in apomorphine and in 5,6-dihydroxy-2-aminotetralin (3)], and series 2 has the hydroxylation pattern of the β conformer of dopamine⁴ [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 lergotriole. The compounds were evaluated for their ability to inhibit the positive chrono-

Scheme I. Preparation of 2-Aminoindan Systems



tropic 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 μ g/kg). In the case of the hydroxy group positional isomers (2a-g), only the di-*n*-propyl homologue 2f displayed even weak inhibitory activity (ID₅₀ > 3.0 μ mol/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.

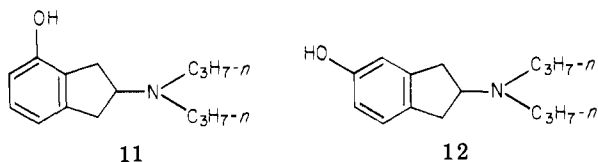
A few selected compounds were evaluated for emetic activity in dogs (Table II). The two compounds that were potent in the cardioaccelerator nerve assay are also violent emetics (1g,h).

Hacksell et al.⁶ have reported that 2-(di-*n*-propyl-amino)-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

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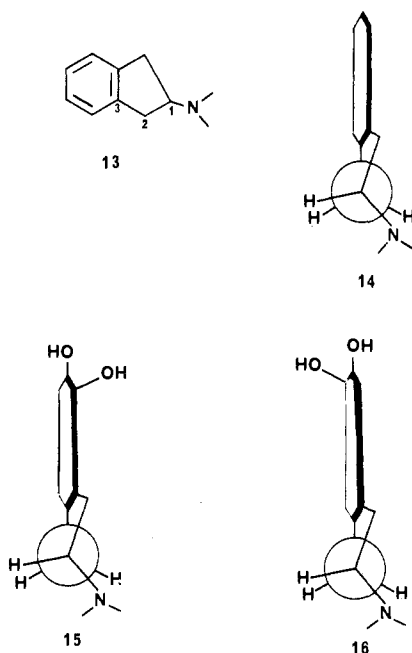
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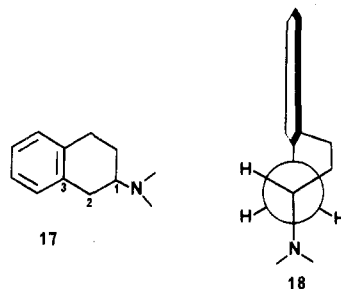


the importance of the "meta" OH group in the α conformer of dopamine.

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-C₁-C₂-C₃) (structure 13) could approach 140–150°. The

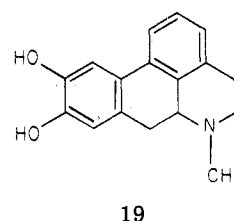


Newman projection 14 shows that in the 2-aminoindan system (where $\tau_2 = 140\text{--}150^\circ$) the dopamine moiety approaches the antiperiplanar disposition and the benzene ring is approximately coplanar with the ethylamine side chain, which steric dispositions have been proposed⁴ to be required 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-C₁-C₂-C₃) 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



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



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 $\pm 0.4\%$ 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 cardiachometer. 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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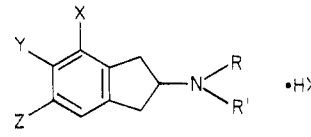
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Table I. Binding Data and Cardioaccelerator Nerve Assay Data on 2-Aminoindans



compd	X	Y	Z	R	R'	binding data: IC ₅₀ , nM		cardio- accelerator nerve:
						spiroperidol	ADTN	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 ₂ H ₅			inact ^d
9d	OCH ₃	OCH ₃	H	H	n-C ₃ H ₇	105 000	51 000 000	inact ^d
9e	OCH ₃	OCH ₃	H	H	2-C ₃ H 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 ₂ H ₅	C ₂ H 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 ₂ H ₅			>1.0
1d	OH	OH	H	H	n-C ₃ H ₇			inact ^d
1e	OH	OH	H	H	2-C ₃ H ₇			inact ^d
1f	OH	OH	H	CH ₃	CH ₃ ^b	91 000	10 000	↑ HR ^c
1g	OH	OH	H	C ₂ H ₅	C ₂ H ₅	220 000	39 000	0.05
1h	OH	OH	H	n-C ₃ H ₇	n-C ₃ H 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 ₃ H 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 ₂ H ₅	C ₂ H ₅			inact ^d
10f	H	OCH ₃	OCH ₃	n-C ₃ H ₇	n-C ₃ H ₇	10 400	147 000 000	inact ^d
10g	H	OCH ₃	OCH ₃	CH ₃	2-C ₃ H ₇			inact ^d
2a	H	OH	OH	H	H			↑ HR ^c
2b	H	OH	OH	H	CH ₃			↑ HR ^c
2c	H	OH	OH	H	2-C ₃ H ₇			↑ HR ^c
2d	H	OH	OH	CH ₃	CH ₃	104 000	6 000	↑ HR ^c
2e	H	OH	OH	C ₂ H ₅	C ₂ H ₅	246 000		↑ HR ^c
2f	H	OH	OH	n-C ₃ H ₇	n-C ₃ H ₇	17 600	412 000	>3.0
2g	H	OH	OH	CH ₃	2-C ₃ H ₇			↑ HR ^c
apomorphine						8 700	830	0.022
dopamine						150 000	510	0.105 ^a
lergotril						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 ED₅₀ = 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 Na₂EDTA, 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. IC₅₀ values on radioactive ligand were calculated. Similar experiments were repeated on a different day, and the average of two IC₅₀ values was used for comparison. [³H]Spiperone (43.9 Ci/mmol, New England Nuclear, Boston, MA) was used as an antagonist ligand in a final concentration of 1 nM, and [³H]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 ED₅₀ 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-indanone¹⁵ (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-indanone¹⁷ 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 H₂SO₄ 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. H₂O (40 mL) was added, and the pH was brought to 10 with 10% NaOH. This solution was extracted several times with CHCl₃, and the pooled extracts were dried (MgSO₄) and evaporated under reduced pressure. To the pale brown oily residue, diluted with 10 mL of Et₂O, was added ethereal HCl, and the resulting copious precipitate was recrystallized from 2-PrOH-Et₂O 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 H₂SO₄ 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-Et₂O 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 PtO₂ 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 Et₂O. The pooled extracts were dried (MgSO₄) and then treated with ethereal HCl. The resulting solid was recrystallized twice from 2-PrOH-Et₂O to give 0.9 g (54%) of white crystals, mp 188–192 °C. Anal. (C₁₃H₂₀ClNO₂) 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 PtO₂ in 75 mL of absolute EtOH. The HCl salt was recrystallized twice from 2-PrOH-Et₂O to give 1.5 g (54%) of white crystals, mp 207–210 °C. Anal. (C₁₄H₂₂ClNO₂) 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 Me₂CO in 80 mL of absolute EtOH was hydrogenated over 0.1 g of PtO₂ 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-Et₂O to give 3.2 g (98%) of white needles, mp 239–241 °C. Anal. (C₁₄H₂₂BrNO₂) 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. NaCNBH₃ (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 H₂O. This mixture was extracted with Et₂O, and the extracts were discarded. The aqueous layer was treated with excess 10% NaOH, and the resulting mixture was extracted several times with Et₂O. The pooled extracts were dried (MgSO₄), 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. H₂O (100 mL) was added, and the heterogeneous mixture was extracted with 100 mL of Et₂O: then it was taken above pH 10 with NaOH pellets. A yellow oil separated, and this mixture was extracted with 200 mL of Et₂O in divided portions. The pooled extracts were dried (MgSO₄), 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-Et₂O to yield 1.2 g (73%) of white crystals, mp 132–135 °C. Anal. (C₁₅H₂₄BrNO₂) 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 NaCNBH₃ (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. H₂O (100 mL) was added, and the mixture was extracted with Et₂O. The aqueous layer was basified with NaOH pellets. An oil separated, and the mixture was extracted several times with Et₂O. The pooled extracts were dried (MgSO₄), 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. (C₁₇H₂₇NO₂) 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 CHCl₃-pentane). Anal. (C₂₃H₃₀N₄O₉) 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 CHCl₃ 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 Me₂CO-pentane to give 5.9 g (94%) of white crystals, mp 149–154 °C. Anal. (C₁₃H₁₄F₃NO₃) C, H, N.

5,6-Dimethoxy-2-[(trifluoroacetyl)methylamino]indan (22). A modification of a method of Oka²⁰ 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 Me₂CO 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 CHCl₃, and the volatiles were removed to leave 1.4 g of an oil, which was dissolved in 5 mL of CHCl₃. 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. (C₁₄H₁₆F₃NO₃) 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 H₂O was heated under reflux for 30 min. The resulting mixture was cooled to room temperature and then extracted several times with Et₂O. The pooled extracts were dried (MgSO₄), 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-Et₂O to give 0.8 g (80%) of white crystals, mp 257 °C dec. Anal. (C₁₂H₁₈ClNO₂) 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 Me₂CO in 80 mL of absolute EtOH was hydrogenated over 0.1 g of PtO₂ 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-Et₂O to give 2.3 g (82%) of white crystals, mp 275–280 °C dec. Anal. (C₁₄H₂₂ClNO₂) C, H, N.

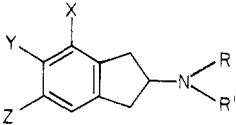
5,6-Dimethoxy-2-(dimethylamino)indan Hydrochloride (10d). A mixture of 1.0 g (0.0051 mol) of the free base of 10a and 5 mL of 37% aqueous formaldehyde in 20 mL of MeOH was refluxed for 30 min. The mixture was cooled to room temperature, and 0.68 g (0.0178 mol) of NaBH₄ was added in portions with stirring. 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 Et₂O, and the pooled extracts were dried (MgSO₄). Addition of ethereal HCl to this solution gave a copious precipitate, which was recrystallized from MeOH-Et₂O

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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 ₂ H ₅	217–222	84	C ₁₁ H ₁₆ BrNO ₂	C, H, N
1d	OH	OH	H	H	<i>n</i> -C ₃ H ₇	193–198	62	C ₁₂ H ₁₈ BrNO ₂	C, H, N
1e	OH	OH	H	H	2-C ₃ H 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 ₂ H ₅	C ₂ H ₅	175–180	96	C ₁₃ H ₂₀ BrNO ₂	C, H, N
1h	OH	OH	H	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	157–162	90	C ₁₅ H ₂₄ BrNO ₂	C, H, N
2a	H	OH	OH	H	H	295 dec	74	C ₉ H 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 ₃ H 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 ₂ H ₅	C ₂ H ₅	220–230	83	C ₁₃ H ₂₀ BrNO ₂	C, H, N
2f	H	OH	OH	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	278 dec	66	C ₁₅ H ₂₄ BrNO ₂	C, H, N
2g	H	OH	OH	CH ₃	2-C ₃ H ₇	215–220	69	C ₁₃ H ₂₀ BrNO ₂	C, H, N

^a Literature¹ mp 214–219 °C. ^b Literature¹ mp 246.5–249.5 °C. ^c Literature¹ mp 216–219.5 °C.

to afford 1.1 g (78%) of white crystals, mp 255 °C dec. Anal. (C₁₃H₂₀ClNO₂) 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 NaBH₄, with the temperature maintained below 20 °C by immersion in an ice bath. When H₂ 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 H₂O, the organic layer was dried (MgSO₄), 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–Et₂O to yield 2.2 g (75%) of white crystals, mp 190–191 °C. Anal. (C₁₅H₂₄ClNO₂) 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 NaBH₄, 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-PrOH–Et₂O to give 1.6 g (53%) of white crystals, mp 210–214 °C. Anal. (C₁₇H₂₈ClNO₂) 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 PtO₂ 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–Et₂O to give 1.1 g (91%) of white crystals, mp 195–201 °C. Anal. (C₁₅H₂₄ClNO₂) C, H, N.

Ether Cleavage Reactions. The amine hydrohalide salt (0.4 g) in 4 mL of 48% HBr was heated under reflux under N₂ for 3 h. Removal of the volatiles under reduced pressure left a solid residue, which was recrystallized from EtOH–Et₂O. See Table III.

Acknowledgment. This investigation was supported in part by Grant GM-22365 from the National Institute of General Medical Sciences. J.A.P. is a Fellow of the Consejo de Desarrollo Científico y Humanístico de la Universidad Central de Venezuela.

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