Resorcinol Congeners of Dopamine Derived from Benzocycloheptene and Indan

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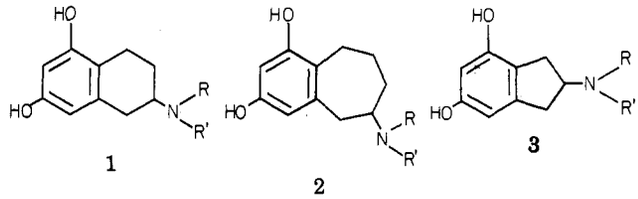
Series of N-alkylated derivatives of 2-amino-4,6-dihydroxyindan **3** and 6-amino-1,3-dihydroxybenzocycloheptene **2** were prepared for pharmacological testing as congeners of 2-amino-5,7-dihydroxytetralin, which elicits dopaminergic effects in a variety of assays. All of the subject compounds demonstrated a lower order of dopamine-like activity than the tetralin derivatives. Some of the subject compounds showed weak interactions with α_1- and β_1-adrenoceptors, but the major determinant of activity seemed to be the nature of the *N*-alkyl substituent rather than ring size.

2-Aminotetralin derivatives **1** bearing phenolic hydroxyl groups in a resorcinol pattern elicit dopamine-like effects in the cat cardioaccelerator nerve assay.[1] Derivatives of **1** where R = R′ = H or n-C_3H_7 potentiated dopamine-



1 **2** **3**

R, R′ = combinations of H, CH_3, C_2H_5, n-C_3H_7, and 2-C_3H_7

sensitive adenylate cyclase and displaced [^{3}H]dopamine from calf caudate homogenate.[2] In all of these assays, derivatives of **1** were less potent than their corresponding catechol-derived isomers (5,6-dihydroxy and 6,7-dihydroxy).[1,2] Certain derivatives of **1** demonstrated α- and β_1-adrenoceptor-activating properties.[1]

The present work addresses the synthesis and pharmacological evaluation of congeners of **1** in which the saturated ring contains seven (**2**) or five (**3**) carbons, with the object of evaluating structure–activity correlations in these resorcinol-derived ring systems and comparing them with their catechol congeners, some of which (especially, 2-aminoindans[3]) demonstrate prominent dopamine-like effects.

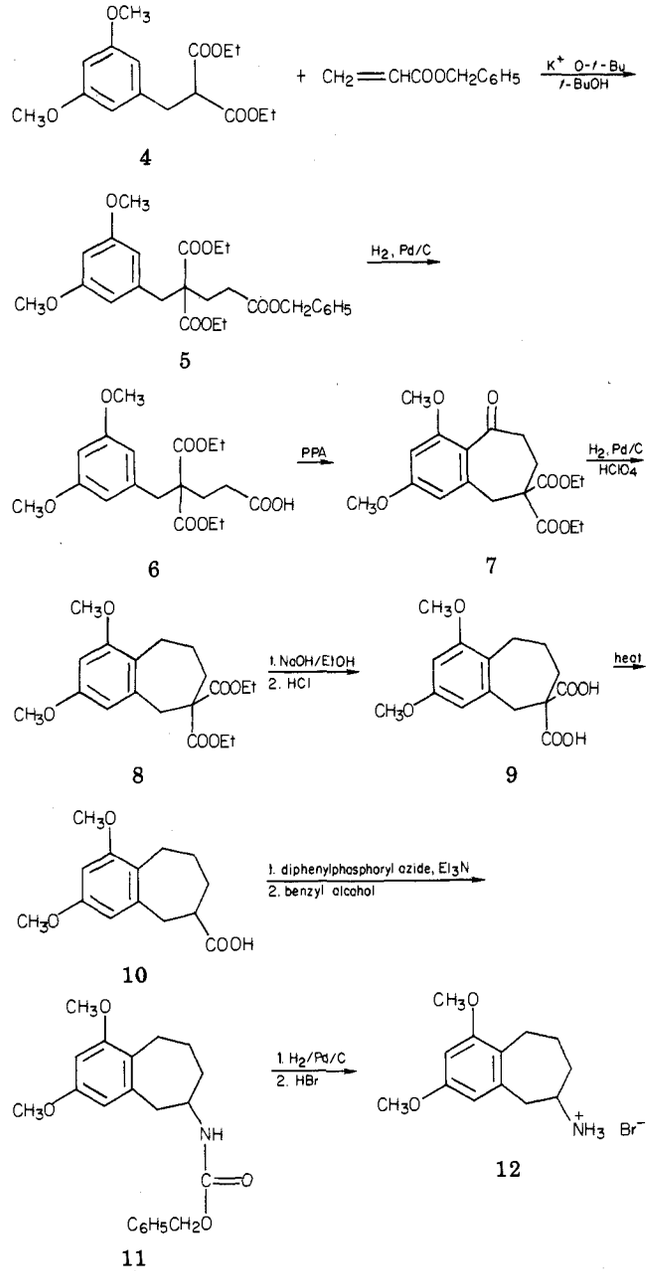
Chemistry. The approach to the target 6-aminobenzocycloheptene system **2** is shown in Scheme I. In conversion of **4** to **5**, conventional Michael reaction conditions (e.g., sodium ethoxide in ethanol) could not be used, due to likelihood of transesterification reactions.[4] However, *tert*-butoxide anion in *tert*-butyl alcohol is a sufficiently strong base to effect Michael condensation, but it is too weak a nucleophile to cause transesterification.[5,6] The preparation of the 2-aminoindan ring system **3** is shown in Scheme II. .

Alkylation of the primary amine products was effected by literature methods, [10,11] and the ether groups were cleaved under acid catalysis (see Table I). Spectral (IR and NMR) data on all intermediates and final compounds were consistent with the proposed structures.

Pharmacological Results and Discussion

Resorcinol derivatives of 2-aminotetralin systems **1** interact with dopamine receptors and with α_1- and β_1-andrenoceptors.[1] These derivatives are less active but their biological activity is of a longer duration than for the corresponding catechol-derived 2-aminotetralins.[1] These compounds would not be expected to be substrates for catechol *O*-methyltransferase. In contrast, the resorcinol derivatives of benzocycloheptene **2** and of indan **3** demonstrated limited interaction with dopamine receptors. Compound **3d** (Table I) at a 4 μM concentration inhibited

Scheme I. Preparation of 1,3-Dimethoxy-6-aminobenzocycloheptene Hydrobromide



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(1) Cannon, J. G.; Brubaker, A. N.; Long, J. P.; Flynn, J. R.; Verimer, T.; Harnirattisai, P.; Costall, B.; Naylor, R. J.; Nohria, V. *J. Med. Chem.* **1981**, *24*, 149.

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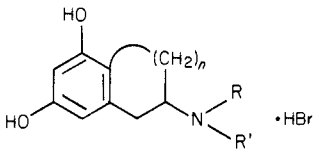
Table I. Resorcinol Congeners of Dopamine Derived from Benzocycloheptene and Indan



compd	R	R'	*n*	mp, °C	yield, %	formula	anal.
2a	H	H	3	229-231[a]	67	$C_{11}H_{16}BrNO_2$	C, H, N
2b	H	2-C_3H_7	3	253-254[b]	97	$C_{14}H_{22}BrNO_2$	C, H, N
2c	C_2H_5	C_2H_5	3	275-276[c]	91	$C_{15}H_{24}BrNO_2$	C, H, N
2d	*n*-C_3H_7	*n*-C_3H_7	3	260-263[c]	91	$C_{17}H_{28}BrNO_2$	C, H, N
3a	H	H	1	217-219[c]	86	$C_9H_{12}BrNO_2$	C, H, N
3b	H	2-C_3H_7	1	220-223[c]	56	$C_{12}H_{18}BrNO_2$	C, H, N
3c	C_2H_5	C_2H_5	1	249-251[c]	85	$C_{13}H_{20}BrNO_2$	C, H, N
3d	*n*-C_3H_7	*n*-C_3H_7	1	234-236[c]	95	$C_{15}H_{24}BrNO_2$	C, H, N

[a] From absolute EtOH-Me_2CO-Et_2O. [b] From *n*-PrOH-EtOH-Et_2O. [c] From 2-PrOH-Et_2O.

Scheme II. Preparation of 2-Amino-4,6-dimethoxyindan

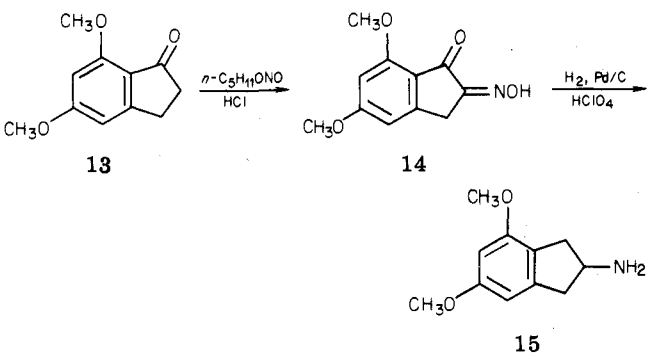


Table II. Influence of Derivatives of Indan and Benzocycloheptene on Arterial Pressure and Heart Rate in Anesthetized Cats

compd	dose, μg/kg, iv	rise, mmHg ± SE, in mean arterial pressure[a]	increase, beats/min ± SE, in heart rate[b]
2a	30	25.3 ± 3.8	4.3 ± 2.3
	100	40.0 ± 4.6	11.7 ± 3.0
	300	78.7 ± 6.7	42.0 ± 3.5
3a	100	13.3 ± 6.7	0.0
	1000	70.3 ± 8.4	7.3 ± 1.9
3d	100	10.0 ± 2.0	0.0
	1000	22.8 ± 3.4	21.7 ± 14.3
epinephrine	1.0	23.8 ± 8.7	47.4 ± 9.1
	2.0	50.4 ± 12.2	57.0 ± 9.8

[a] Responses inhibited by pretreatment with phentolamine (1.0 mg/kg). [b] Responses inhibited by pretreatment with propranolol (0.5 mg/kg).

tachycardia induced in isolated cat atria. The remaining compounds were inactive (<10% inhibition). With in vivo cat cardioaccelerator nerve preparations, only **3d** demonstrated any inhibition of neuronal stimulation (22% at 4 μmol/kg). As shown in Table II, three compounds activated α_1- and β_1-receptors, resulting in elevation of arterial pressure and heart rate. The remaining compounds were inactive in these assays. Compound **3d** was the only agent to produce contralateral rotations in rats with unilateral denervation of the caudate nucleus. The minimal effective dose was 1 mg/kg (subcutaneously). The potency ratio when compared with apomorphine, for total turns induced (4.5 h), was 0.035. Rotations induced by both compounds were prevented by pretreatment with haloperidol (1 mg/kg, sc). Binding studies indicated that all of the indan derivatives were quite inactive in their ability to displace [^{3}H]dopamine from rat caudate. Compound **3a** was the most active, with an IC_{50} of 3.0 μM. The IC_{50} for apomorphine is 10^{-4} μM.

Experimental Section

Pharmacology. Methods. Cats were anesthetized with pentobarbital sodium (35 mg/kg), administered into the thorax. Tracheotomy was performed, and ventilation was supported by a Harvard respiratory pump. The arterial blood pressure was measured from the femoral artery with a Statham P-23AA transducer and was recorded with a Beckman RS dynograph. The heart rate was recorded with a cardiotachometer. All injections were made into the cannulated left femoral vein. The thorax was opened by a midline incision, and the right cardioaccelerator nerves were exposed. Silver bipolar electrodes were placed on the postganglionic fibers. Increased heart rate was induced with a Grass Model 5 stimulator. The parameters of stimulation were a frequency of 2 or 10 Hz, pulse duration of 5 ms, stimulation for 15–30 s, and supramaximal voltage. After the positive chronotropic responses became consistent following stimulation, the experimental compounds were administered in increasing doses at 0.48 log intervals. Responses to nerve stimulation were allowed to return to control levels before additional doses were administered. Five animals were used to assay each compound. The dose required to produce 50% inhibition of the tachycardia induced by nerve stimulation was calculated from the regression line.

For the in vitro atrial experiments, cats were anesthetized as described above. The chest was opened by midsternal incision. The hearts were quickly removed and placed in Feigen's solution. Ventricular muscle, connective tissue, fat, blood vessels, and the left atrium were excised from the right atrium. Preparations were appropriately dissected in oxygenated nutrient solution. The right atrium was placed in an isolated organ bath (100 mL) between a pair of platinum electrodes. The right atrium was suspended in Feigen's solution of the following composition (millimolar concentration): NaCl, 153.6; KCl, 5.6; $NaHCO_3$, 6.0; $CaCl_2$, 216; glucose, 11.1. The solution was gassed with 95% O_2–5% CO_2 and maintained at 36 °C. Resting tension was adjusted to 1 g. During the equilibration period (20 min), the bathing medium was replaced at intervals of 5 min with fresh solution. The atrial rate was measured with a Statham strain gauge (GlOB) and a Beckman cardiotachometer. Stimuli were applied for 10 s at the following parameters: 5 ms duration, supramaximal voltage (60–80 V), and 2 Hz. The atrial rate was allowed to return to control values, and 10 min was allowed before additional stimulations.

In circling experiments, rats were subjected to unilateral denervation of the nigrostriatal projection (lateral hypothalamic

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(4) Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 453.
(5) Ames, D. E.; Bowman, R. D. *J. Chem. Soc.* **1950**, 329.
(6) Ginsburg, D.; Pappo, R. *J. Chem. Soc.* **1953**, 1524.

injection of 8 μg of 6-hydroxydopamine) and were used 14 days after surgery. Circling behavior was measured as the number of rotations performed by the animal after drug treatment, following its placement in a circular cage 40 cm in diameter. The animals were observed for at least 1 h.

Dopamine receptor agonist ligand binding studies were carried out with [^{3}H]dopamine as the ligand on the striatal tissue of rat brain as described by Bacopoulos,[7] with some minor modifications. The striata from adult, male, Sprague–Dawley rats were dissected and frozen on *dry ice* and stored at −80 °C until used. The tissue was homogenized with a *Teflon* pestle in a glass homogenizer in 50 vol (w:v) of ice-cold 50 mM Tris-HCl buffer of pH 7 (room temperature) containing 3 mM $CaCl_2$, and this mixture was incubated at 37 °C for 30 min. The homogenate was then centrifuged at 43500 *g* for 20 min, and the pellet was washed by resuspending it in the homogenizing buffer followed by centrifugation. This washing was repeated twice, except that the final resuspension was done in calcium-free 50 mM Tris-HCl incubation buffer of pH 7.1 (room temperature) containing 15 μM pargyline and 5 mM NaEDTA. Tissue was resuspended with a Polytron for 15 s at setting 7. All drugs were dissolved in the incubation buffer.

Binding Assay. Triplicate tubes received 100 μL of varying concentrations of competing drug, 200 μL of [1,1-^{3}H]dopamine (sp act. 41.5 Ci/mmol, New England Nuclear Corp., Boston, Ma) in a final concentration of 2.5 nM, and 200 μL of tissue suspension (0.2–0.3 mg of protein), all prepared in the incubation buffer. A parallel set of triplicate tubes received 100 mL of incubation buffer instead of drug, to estimate total binding. Another set of triplicate tubes received 100 μL of *d*-butaclamol to yield a final concentration of 1 μM. The samples were incubated at room temperature for 30 min with gentle shaking, and 0.4-mL aliquots were vacuum filtered through prewashed Whatman GF/B filters, followed by two 5-mL rinses with the incubation buffer. The filters were placed in counting vials, allowed to stand in 10 mL of aquasol II overnight, and then were counted by liquid scintillation spectrometry. The difference between total binding of [^{3}H]-dopamine and binding in the presence of 1 μM *d*-butaclamol represented specific binding. The K_d of [^{3}H]dopamine binding was 2.5 nM when 10 μM *d*-butaclamol was used to determine the specific binding. In the present studies, however, 1 μM *d*-butaclamol was used for determination of specific binding. [^{3}H]-Dopamine binding in the presence of varying concentrations of the competing drug as a percent of specific binding was calculated by the following formula: (binding in the presence of competing drug − binding in the presence of 1 μM *d*-butaclamol)/(total binding − binding in the presence of 1 μM *d*-butaclamol). Binding was plotted against log concentrations of the competing drug. The IC_{50} values of the competing drug on radioactive ligand binding were calculated. Similar experiments were repeated at least once on a different day, and the average of at least two IC50 values was used for comparison.

Chemistry. Melting points were determined in open glass capillaries with a Thomas-Hoover Uni-Melt apparatus and 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. Mass spectra were obtained on Finnigan 3200 and Ribermag 10/10 mass spectrometers.

4,4-Dicarbethoxy-5-(3,5-dimethoxyphenyl)pentanoic Acid (6). Diethyl 2-(3,5-dimethoxybenzyl)malonate (4;[8] 10.0 g, 0.0322 mol), benzyl acrylate (5.49 g, 0.0338 mol), and dry *t*-BuOH (5.2 g, 0.070 mol) were stirred in dry benzene at room temperature, and a small chip (ca. 0.05 g, 0.0013 mol) of potassium was added. When dissolution of this was complete, the reaction mixture was brought to 50 °C for 3 h, and then it was stirred overnight at room temperature. The reaction was quenched with 15 mL of 2 M HCl and 30 g of crushed ice. Et_2O (50 mL) was added, and the reaction mixture was transferred to a separatory funnel. The organic layer was washed with H_2O until the washings were neutral (pH paper); then the organic layer was dried ($MgSO_4$) and filtered, and the volatiles were removed from the filtrate to leave a pale yellow oil (compound 5).

This oil was hydrogenated in 170 mL of EtOAc over 0.70 g of 10% Pd/C at an initial pressure of 50 psig. After 1 equiv. of H_2 was consumed, the reduction mixture was filtered, and volatiles were removed from the filtrate to leave a viscous yellow oil, which soon crystallized. Recrystallization from Et_2O–pentane gave 8.93 g (73%) of colorless needles, mp 82–84 °C. Anal. ($C_{19}H_{26}O_8$) C, H, N.

6,6-Dicarbethoxy-1,3-dimethoxy-9-oxo-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (7). Compound 6 (4.00 g, 0.011 mol) was sprinkled over 20 min into 60 g of polyphosphoric acid at 65 °C, with efficient manual stirring. When the addition was complete, stirring was continued for 30 min, and the reaction mixture became light yellow. The reaction was quenched with crushed ice. The resulting mixture was stirred until the yellow color was discharged and a gummy white paste was deposited. The paste/H_2O mixture was transferred to a separatory funnel and extracted with three 75-mL portions of Et_2O. The combined organic extracts were washed with three 50-mL portions of H_2O, two 50-mL portions of 5% $NaHCO_3$, one 50-mL portion of 1 M HCl, and two 50-mL portions of H_2O. The organic layer was dried ($MgSO_4$) and filtered, and the volatiles were removed from the colorless filtrate to leave a colorless oil. This material crystallized on standing, and it was recrystallized from Et_2O–pentane to give 3.40 g (88%) of colorless needles, mp 93–95 °C (lit.[9] mp 94–95.5 °C.

6,6-Dicarbethoxy-1,3-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (8). Compound 7 (8.0 g, 0.022 mol) was hydrogenolyzed in 150 mL of AcOH and 0.5 mL of 70% $HClO_4$ over 0.5 g of 10% Pd/C at an initial pressure of 50 psig. After consumption of 1 equiv of H_2, the reduction mixture was filtered, and volatiles were removed from the filtrate under reduced pressure to leave a yellow oil. The was taken up in 100 mL of Et_2O, and the solution was washed with four 50-mL portions of 5% $NaHCO_3$ and then with two 30-mL portions of H_2O. The organic layer was dried ($MgSO_4$) and filtered, and volatiles were removed from the filtrate under reduced pressure. The resulting pale yellow oil was chromatographed on SiO_2 and eluted with Et_2O. Removal of the Et_2O left a pale yellow oil, which soon crystallized. Trituration of this with a small volume of cold EtOH yielded 7.18 g (94%) of a white powder, mp 57.5–59.5 °C. Anal. ($C_{19}H_{26}O_6$) C, H.

1,3-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6,6-dicarboxylic Acid (9). Compound 8 (8.10 g, 0.023 mol) was heated overnight at 70 °C in 40 mL of 70% EtOH and 2.80 g (0.075 mol) of NaOH. The cooled reaction mixture was brought to pH 4 (pH paper) by the addition of 12 M HCl. The volume of the mixture was reduced to 0.25 the original under reduced pressure, and the resulting slurry was filtered. The solid on the filter was washed with two 25-mL portions of cold H_2O, and the insoluble residue was dried under reduced pressure at 50 °C to give 6.52 g (97%) of a white powder: mp (with effervescence) 172 °C; MS, *m/e* 294 (M^+), 250 ($M^+ - CO_2$).

1,3-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6-carboxylic Acid (10). Compound 9 (5.00 g, 0.017 mol) was heated for 30 min at 185 °C at slightly reduced pressure (600 mm). Effervescence occurred as the solid melted. Upon cooling, the yellow glass slowly crystallized. Recrystallization from benzene–petroleum ether (bp 30–60 °C) gave 4.02 g (95%) of colorless needles, mp 132–134 °C. Anal. ($C_{14}H_{18}O_4$) C, H.

6-[(Carbobenzyloxy)amino]-1,3-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (11). Compound 10 (5.79 g, 0.023 mol), Et_3N (2.34 g, 0.023 mol) and diphenylphosphoryl azide (6.37 g, 0.023 mol) were stirred in 50 mL of dry benzene for 2 h at 40 °C and then at 75 °C for 2 h. At the end of this period, evolution of N_2 had ceased. Benzyl alcohol (10.0 g, 0.093 mol) was added, and the reaction mixture was stirred overnight at 75 °C. The cooled reaction mixture was diluted with 50 mL of benzene, and this solution was washed with three 25-mL portions of H_2O, two 15-mL portions of 5% $NaHCO_3$, and two 25-mL portions of H_2O. The organic layer was dried (Na_2SO_4) and filtered. Volatiles were removed from the filtrate under reduced pressure, and the residue

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(8) Yagi, K. *Nippon Nogei Kagaku Kaishi* **1955**, *29*, 198; *Chem. Abstr.* **1959**, *53*, 303*b*.
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was distilled at 1 mm to remove unreacted benzyl alcohol. The gummy pale yellow residue in the distilling pot was triturated with cold Et_2O, and the resulting slurry was filtered to give 7.85 g (96%) of an off-white powder: mp 112–114 °C; MS, *m/e* 355 (M^+). Anal. ($C_{21}H_{25}NO_4$) C, H, N.

6-Amino-1,3-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (12). A slurry of 6.00 g (0.017 mol) of **11** in 160 mL of AcOH and 20 mL of EtOH was hydrogenated over 0.60 g of 10% Pd/C at an initial pressure of 45 psig. After the consumption of 1 equiv of H_2, the reduction mixture was filtered, 3.75 mL of 9 M HBr was added to the filtrate, and volatiles were removed under reduced pressure. Recrystallization of the pale yellow solid residue from *n*-PrOH–Et_2O gave 4.54 g (90%) of colorless needles: mp 245.5–247 °C; MS, *m/e* 221 (M^+ – HBr). Anal. ($C_{13}H_{20}BrNO_2$) C, H, N.

6-(2-Propylamino)-1,3-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (16). A procedure of Sugihara et al.[10] was employed. A mixture of 0.800 g (0.00265 mol) of **12**, 0.207 g (0.0033 mol) of $NaCNBH_3$, 0.61 g (0.0066 mol) of dioxane, 32 mL of Me_2CO, and 40 mL of EtOH was stirred at 5–15 °C for 2 h and then at 25 °C overnight. The reaction mixture was brought to pH 4 (pH paper) with 1 M HCl, and the volatiles were removed under reduced pressure. The residual solid was taken up in 75 mL of H_2O, and this solution was brought to pH 10 (pH paper) with 5% NaOH, and extracted with three 30-mL portions of CH_2Cl_2. The pooled organic extracts were made acidic with a solution of 0.3 mL of 48% HBr in 5 mL of *n*-PrOH, and volatiles were removed from this mixture under reduced pressure. Recrystallization of the off-white solid residue from *n*-PrOH–Et_2O gave 0.852 g (93%) of fluffy white crystals, mp 258.5–259.5 °C; MS, *m/e* 235 (M^+ – HBr). Anal. ($C_{16}H_{26}BrNO_2$) C, H, N.

6-(Diethylamino)-1,3-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (17). To a complex formed from 0.938 g (0.0248 mol) of $NaBH_4$ and 4.97 g (0.0827 mol) of AcOH in 60 mL of benzene, generated according to a procedure of Marchini et al.,[11] was added dropwise, with stirring, the free base of **12** (0.50 g, 0.00165 mol) in 25 mL of CH_2Cl_2. The reaction mixture was heated under reflux overnight; then it was cooled to room temperature and stirred for 30 min with 20 mL of 1.5 M NaOH. The resulting mixture was transferred to a separatory funnel. The aqueous layer was removed, and the organic layer was washed twice with 25-mL portions of H_2O and dried (Na_2SO_4). The combined aqueous layer and washings were extracted with two 20-mL portions of Et_2O, and these extracts were added to the organic layer. This combined solution was treated with 0.4 mL of 48% HBr in 5 mL of *n*-PrOH, and volatiles were removed from the mixture under reduced pressure. The solid residue was recrystallized from *n*-PrOH–Et_2O to give 0.436 g (74%) of white crystals: mp 180–181 °C; MS, *m/e* 277 (M^+ – HBr). Anal. ($C_{17}H_{28}BrNO_2$) C, H, N.

6-(Di-*n*-propylamino)-1,3-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (18). To a complex formed from 0.938 g (0.0248 mol) of $NaBH_4$ and 6.12 g (0.0827 mol) of propionic acid in 30 mL of benzene, generated according to a procedure of Marchini et al.,[11] was added dropwise, with stirring, 0.50 g (0.00165 mol) of the free base of **12** in 25 mL of CH_2Cl_2. The reaction mixture was heated under reflux overnight; then it was cooled to room temperature and stirred with 20 mL of 1.5 M NaOH for 30 min. The resulting mixture was worked up as described for **17**. Recrystallization from EtOH–Et_2O gave 0.580 g (96%) of small white needles: mp 191.5–193 °C; MS, *m/e* 305 (M^+ – HBr). Anal. ($C_{19}H_{32}BrNO_2$) C, H, N.

5,7-Dimethoxy-2-oximido-1-indanone (14). By the procedure of Perkin and Robinson,[12] a solution of 2.5 g (0.013 mol) of 5,7-dimethoxy-1-indanone (**13**)[13] in 13 mL of MeOH was mixed with a solution of 1.6 g (0.013 mol) of *n*-pentyl nitrite in 12 mL of MeOH, followed by 2 drops of concentrated HCl. The pale yellow solution turned deep red. It was heated under gentle reflux for 5 min; then it was cooled to 0 °C for 30 min. The yellow solid that separated was washed with two 10-mL portions of cold MeOH to give 2.6 g (91%) of pale yellow crystals: mp 235–236 °C; MS, *m/e* 221 (M^+). Anal. ($C_{11}H_{11}NO_4$) C, H, N.

4,6-Dimethoxy-2-aminoindan Hydrochloride (15). A slurry of 4.2 g (0.019 mol) of **14** in 100 mL of AcOH and 5 mL of 60% $HClO_4$ was hydrogenated at 60 °C over 5 g of 5% Pd/C at an initial pressure of 45 psig, until 3 equiv of H_2 was absorbed. The reaction mixture was stirred for 5 min with 3 g of potassium acetate and then filtered, and the volatiles were removed from the filtrate under reduced pressure. The residue was basified with 1 N NaOH, and then it was extracted with three 50-mL portions of CH_2Cl_2. The pooled organic extracts were washed with 50 mL of H_2O, dried (Na_2SO_4), and evaporated. The solid residue was treated with 50 mL of ethereal HCl, and the resulting white powder was recrystallized from 2-PrOH–Et_2O to give 3.4 g (78%) of white crystals: mp 280–281.5 °C; MS, *m/e* 193 (M^+ – HCl). Anal. ($C_{11}H_{16}ClNO_2$) C, H, N.

4,6-Dimethoxy-2-(di-*n*-propylamino)indan Hydrobromide (19). The method described for **17** was followed, using 2.95 g (0.080 mol) of $NaBH_4$, 19 g (0.0258 mol) of propionic acid, 60 mL of benzene, and 1.0 g (0.00517 mol) of the free base of **15** in 40 mL of CH_2Cl_2. The cooled reaction mixture was quenched with 20 mL of 1.5 N NaOH, extracted with three 50-mL portions of CH_2Cl_2, dried (Na_2SO_4), and evaporated under reduced pressure. The residual oil was taken up in 50 mL of benzene and treated with 0.5 mL of 48% HBr in 10 mL of *n*-PrOH, and the resulting mixture was evaporated under reduced pressure. The residue was recrystallized from *n*-PrOH–Et_2O to give 1.6 g (86%) of a white powder: mp 178–180.5 °C; MS, *m/e* 277 (M^+ – HBr). Anal. ($C_{17}H_{28}BrNO_2$) C, H, N.

4,6-Dimethoxy-2-(diethylamino)indan Hydrobromide (20). The method described for **17** was followed, using 2.95 g (0.080 mol) of $NaBH_4$, 15.5 g (0.0258 mol) of glacial AcOH, 60 mL of benzene, and 1.0 g (0.00517 mol) of the free base of **15** in 40 mL of CH_2Cl_2. The reaction mixture was treated as described for **19** to yield 1.1 g (64%) of small white needles: mp 168–170 °C; MS, *m/e* 249 (M^+ – HBr). Anal. ($C_{15}H_{24}BrNO_2$) C, H, N.

4,6-Dimethoxy-2-(2-propylamino)indan Hydrobromide (21). The procedure described for **16** was followed, using 0.80 g (0.00348 mol) of **15**, 32 mL of Me_2CO, 0.27 g (0.00435 mol) of $NaCNBH_3$, and 40 mL of absolute EtOH. The product was recrystallized from 2-PrOH–Et_2O and then from MeOH to give 0.88 g (80%) of white needles: mp 222–223 °C; MS, *m/e* 235 (M^+ – HBr). Anal. ($C_{14}H_{22}BrNO_2$) C, H, N.

Ether Cleavage Reactions. The amine salt (0.001 mol) in 10 mL of 48% HBr and 1.0 mL of glacial AcOH was heated under reflux under N_2 for 2 h. Volatiles were removed under reduced pressure, and the residue was recrystallized. See Table I.

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Registry No. 2a, 87615-44-9; **2b**, 87615-45-0; **2c**, 87615-46-1; **2d**, 87615-47-2; **3a**, 87615-48-3; **3b**, 87615-49-4; **3c**, 87615-50-7; **3d**, 87615-51-8; **4**, 5859-68-7; **5**, 87615-52-9; **6**, 87615-53-0; **7**, 71978-63-7; **8**, 87615-54-1; **9**, 87615-55-2; **10**, 87615-56-3; **11**, 87615-57-4; **12**, 87615-58-5; **12** (free base), 87615-59-6; **13**, 880-87-5; **14**, 18110-61-7; **15**, 87615-60-9; **15** (free base), 87615-61-0; **16**, 87615-62-1; **17**, 87615-63-2; **18**, 87615-64-3; **19**, 87615-65-4; **20**, 87615-66-5; **21**, 87615-67-6; benzyl acrylate, 2495-35-4; diphenylphosphoryl azide, 26386-88-9.

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