Catechol Derivatives of 6-Aminobenzocycloheptene: Assessment of Dopaminergic Effects

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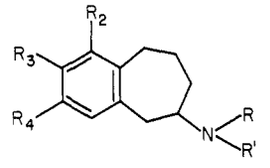
The title compounds were prepared as congeners of the dopaminergically potent 2-amino-5,6-dihydroxytetralin series ("A-5,6-DTN"). None of the variously nitrogen-substituted benzocycloheptenes demonstrated any dopamine-like effects in a variety of assays. The primary amine had α_1-adrenoceptor stimulant effects. This lack of dopaminergic effect parallels the inactivity found in 6-aminobenzocycloheptenes bearing no oxygen substitutents, those bearing a single phenolic group, and those bearing a resorcinol 1,3-diphenolic substitution pattern.

Literature descriptions of the evaluation of dopamine-like effects of 6-aminobenzocycloheptenes bearing no oxygen functions on the benzene ring (1, $R_2 = R_3 = R_4 = H$),[1]



1a, $R = R' = R_4 = H$; $R_2 = R_3 = OH$
b, $R = R_4 = H$; $R' = 2\text{-}C_3H_7$; $R_2 = R_3 = OH$
c, $R = R' = n\text{-}C_3H_7$; $R_2 = R_3 = OH$; $R_4 = H$

a single hydroxyl group (1, $R_2 = OH$; $R_3 = R_4 = H$),[2] and a resorcinol dihydroxy pattern (1, $R_2 = R_4 = OH$; $R_3 = h$)[3] prompted us to communicate the results of our evaluation of a short series of catechol-derived compounds, 1, where $R_2 = R_3 = OH$ and $R_4 = H$. The derivatives for which pharmacological data are reported are **1a–c**. The preparation of these compounds, beginning with 1,2-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one, followed literature strategies.[1,3] Spectral (IR and NMR) data on all intermediates and final compounds are consistent with the proposed structures.

Results and Discussion

Pharmacology. Only compound **1a** demonstrated significant biological activity; it was quite active as a pressor agent in anesthetized cats. The doses (μg/kg) and pressure (mmHg) increases (±SE) are as follows: 10, +15 ± 8; 20, +38 ± 21; 40, +70 ± 30. There was no tachycardia at these doses, but at higher doses, the compound induced an increase in heart rate. The pressor responses were significantly antagonized by phentolamine (200 μ/kg), thus suggesting α_1-adrenoceptor stimulation for **1a**.

None of the compounds, at doses up to 300 μg/kg, antagonized tachycardia induced by cardioaccelerator nerve stimulation in the cat. Thus, there was no evidence for dopamine receptor stimulant activity.

The compounds did not increase renal blood flow in dogs with intraarterial doses up to 300 μg/kg. There was a slight decrease in blood flow with compounds **1a** and **1c**.

The compounds were screened for dopamine-like activity (at 4 mg/kg dose level) in the rat with unilateral denervation of the caudate nucleus; in the dog emesis assay; and in the spontaneous locomotor activity assay in the mouse. There was no indication of biological activity in any of these assays. Thus, as has been described in some detail for other 6-aminobenzocycloheptene derivatives,[1,3] it appears that the structural constraints of the ring system in **1a–c** that maintain the aryl ring of the dopamine moiety in a steric disposition approaching perpendicularity with the ethylamine side chain are detrimental to dopamine-like activity.

Experimental Section

Pharmacology. Methods. Cat Cardioaccelerator Nerve Preparation. This assay was used to determine the activity of various agents at presynaptic dopamine receptors on the sympathetic nerve terminal. Cats were anesthetized with pentobarbital sodium (30 mg/kg, ip) and intubated. Respiration was maintained with a Harvard respirator. Systemic arterial pressure was monitored with a Statham P23A pressure transducer from a cannula positioned in the femoral artery. Mean heart rate was obtained from phasic arterial blood pressure pulses with a Beckman Type 9857 cardiotachometer. A femoral vein also was cannulated for drug administration. After bilateral vagotomy and systemic administration of atropine sulfate (200 μg/kg), the postganglionic right cardioaccelerator nerve trunk was exposed via a midsternal incision. The nerve trunk was placed on a bipolar electrode for stimulation. It was stimulated with a Grass 48 stimulator by using the following parameters: 2 Hz, 5-ms pulse duration, 20 V. These parameters produced reproducible chronotropic responses that were sensitive to β-adrenoceptor antagonism. Blood pressure and heart rate were continuously recorded on a Beckman R511A recorder.

Dog Renal Blood Flow. The influence of each compound on renal blood flow was evaluated in three dogs as previously described.[4]

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. NMR spectra were recorded on a Varian Associates T60 instrument with tetramethylsilane as the internal standard. Mass spectra were recorded on a Finnigan 3200 mass spectrometer.

6-Oximino-1,2-dimethoxy-6,7,8,9-5*H*-benzocyclohepten-5-one (2). A procedure of Lal et al.[5] was utilized. 1,2-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one[6] (2.84 g, 12.9 mmol) and 1.65 g (16 mmol) of *n*-butyl nitrite in 25 mL of dry Et_2O were added dropwise over 1 h to an ice–H_2O chilled suspension of 1.75 g (15.6 mmol) of KO-*t*-Bu in 25 mL of dry Et_2O, under N_2. The resulting mixture was stirred for an additional 1 h at 0–5 °C, and then it was permitted to come to room temperature over 3.5 h. The reaction mixture was filtered, and the filter cake was washed on the filter with dry Et_2O. The deep red filter cake was added in portions with stirring to 50 mL of 1 M HCl. A yellow syrup separated, which, upon continued manip-

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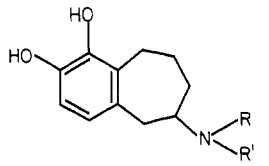
Table I. Catechol Derivatives of 6-Aminobenzocycloheptenes



no.	R	R′	yield, %	mp, °C	formula	anal.
1a	H	H	65	194–196[a]	$C_{11}H_{16}BrNO_2$	C, H, N
1b	H	2-C_3H_7	73	239.5–241[b]	$C_{14}H_{22}BrNO_2$	C, H, N
1c	n-C_3H_7	n-C_3H_7	74	259–261[c]	$C_{17}H_{28}BrNO_2$	C, H, N

[a] From n-PrOH–Et_2O. [b] From absolute EtOH–Et_2O. [c] From H_2O.

ulation with a stirring rod, congealed to a buff solid. This was collected on a filter, washed with H_2O, and air-dried to give 2.20 g (68%) of a buff solid: mp 80 °C dec; mp (sealed tube) 162–165 °C. All attempts to purify this material resulted in extensive decomposition, and it was employed in the subsequent step without purification: MS, m/e 249 (M^+); NMR ($CDCl_3$) δ 1.97–2.27 (m, 2H, aliphatic H), 2.59–2.97 (m, 4 H, aliphatic H), 3.87 and 3.97 (2 s, 6 H, OCH_3), 6.81–7.71 (m, 2 H, arom H).

6-Amino-1,2-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (3). Compound **2** (1.0 g, 4 mmol) in 100 mL of glacial AcOH was hydrogenated over 0.08 g of 10% Pd/C at an initial pressure of 45 psig. When 2 molar equiv of H_2 was taken up, 3.75 mL of 70% $HClO_4$ was added, and hydrogenation was continued until uptake of H_2 ceased. The reduction mixture was treated with 4.5 g of KOAc in 20 mL of AcOH, and the resulting mixture was filtered. The filtrate was treated with 25 mL of 1 M HCl, and this solution was evaporated under reduced pressure. The syrupy residue was taken up in H_2O, and this solution was washed with Et_2O and then basified with 1 M NaOH. The resulting mixture was extracted with Et_2O. The dried (Na_2SO_4) ethereal extract was treated with ethereal HBr, and the resulting solid was recrystallized from n-PrOH–Et_2O to give 0.75 g (62%) of white microcrystals: mp 210.5–212.5 °C; MS, m/e 221 (M^+ – HBr); NMR ($CDCl_3$) δ 0.84–2.20 (m, 5 H, aliphatic H), 2.96 (s, 4 H, aliphatic H), 3.56 and 3.70, (2 s, 6 H, OCH_3), 6.70 (s, 2 H, arom H). Anal. ($C_{13}H_{20}BrNO_2$) C, H, N.

6-(Isopropylamino)-1,2-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (4). Compound **3** (0.165 g, 0.545 mmol) in 6.6 mL of dry Me_2CO and 10.9 mL of 99% EtOH was stirred at 0 °C, and 0.038 g (0.6 mmol) of $NaCNBH_3$ in 0.11 mL of dry dioxane and 5 mL of 99% EtOH was added dropwise. The reaction mixture was stirred for 4 h at 0–10 °C; then it was permitted to come to room temperature over 2 h. The mixture was adjusted to pH 2 (pH paper) with 1 M HCl. Volatiles were removed under reduced pressure. The residue was taken up in H_2O and made basic with 5% NaOH. This mixture was extracted with Et_2O. The ethereal extract was dried (Na_2SO_4) and filtered, and the filtrate was treated with 0.3 mL of 48% HBr in 0.6 mL of EtOH. The white solid that separated was recrystallized from n-PrOH–Et_2O to afford 0.104 g (56%) of product: mp 244.5–246 °C; MS, m/e 263 (M^3 – HBr); NMR (Me_2SO-d_6) δ 1.20 and 1.30 (2 s, 6 H, CCH_3), 3.60 and 3.73 (2 s, 6 H, OCH_3), 6.63–6.87 (m, 2 H, arom H). Anal. ($C_{16}H_{26}BrNO_2$) C, H, N.

6-(Di-*n*-propylamino)-1,2-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrobromide (5). An N-alkylation method of Marchini et al.[7] was used. To 3.06 g (41.3 mmol) of propionic acid in 10 mL of dry benzene was added with stirring 0.469 g (12.4 mmol) of $NaBH_4$ in small portions, maintaining the temperature between 10 and 15 °C. When this mixture ceased evolving H_2, 0.183 g (0.83 mmol) of the free base of **3** in 5 mL of CH_2Cl_2 was added in one portion, and the resulting mixture was stirred and heated under reflux overnight. The cooled reaction mixture was treated with 20 mL of 3 M NaOH. The organic phase of this mixture was separated. The aqueous phase was extracted several times with Et_2O, and these extracts were added to the original organic layer. This combined solution was treated with 1 mL of 48% HBr, and the resulting mixture was evaporated under reduced pressure. The solid residue was recrystallized from n-PrOH–Et_2O to give 0.140 g (43%) of small clusters of crystals, mp 231–232 °C; MS, m/e 305 (M^+ – HBr); NMR ($CDCl_3$) δ 0.81–1.11 (m, 6 H, CCH_3), 1.59–3.43 (m, 17 H, aliphatic H), 3.66 and 3.73 (2 s, 6 H, OCH_3), 6.43–7.03 (m, 2 H, arom H). Anal. ($C_{19}H_{32}BrNO_2$) C, H, N.

Ether Cleavage Reactions. The HBr salt (0.3 mmol) of the appropriate dimethyl ether was heated under N_2 with 6 mL of 48% HBr at 125–128 °C for 4 h. The reaction mixture was evaporated under reduced pressure, and H_2O was removed by successive azeotroping with n-BuOH, heptane, and EtOH. The resulting brown oil was crystallized. (See Table I.)

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Registry No. **1a**, 9019-12-9; **1a**·HBr, 90109-11-8; **1b**, 90109-14-1; **1b**·HBr, 9019-13-0; **1c**, 90109-16-3; **1c**·HBr, 90109-15-2; **2**, 60054-89-9; **3**, 90109-09-4; **3**·HBr, 90109-07-2; **4**·HBr, 90109-08-3; **5**·HBr, 90109-10-7; 1,2-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one, 54130-94-8.

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