Synthesis and Dopamine Receptor Binding of *exo*- and *endo*-2-Amino-6,7-dihydroxybenzonorbornene, Rigid Analogues of 2-Amino-6,7-dihydroxytetrahydronaphthalene

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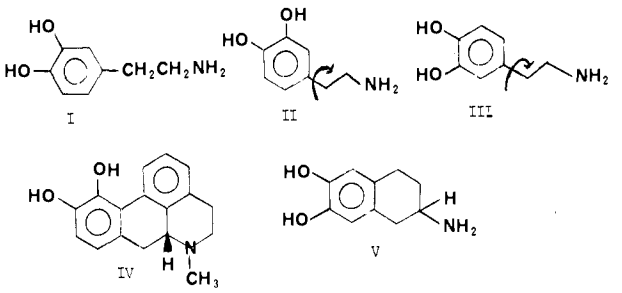
Two bridged tricyclic analogues of 2-amino-6,7-dihydroxytetrahydronaphthalene (ADTN) in which the amino group is held rigidly in an equatorial and axial conformation, respectively, and in which the catechol ring is twisted out of the plane of the ethylamine chain have been synthesized and assayed for their effects on the binding of [^{3}H]dopamine, [^{3}H]apomorphine, and [^{3}H]spiperone to calf and rat striatal homogenates. Up to concentrations of 2000 nM, these *exo*- and *endo*-2-amino-6,7-dihydroxybenzonorbornenes displayed no ability to displace any of the radioligands from their receptor sites in the calf and rat brain homogenates, in contrast to measured IC_{50} values of 6 and 3.1 nM for racemic ADTN vs. [^{3}H]dopamine in the two preparations, respectively. The enantiomers of the exo amine showed no specific activity vs. [^{3}H]dopamine. Although negative, these data are informative in molecular modeling of dopaminergic receptor interactions.

The molecular interactions which take place at receptor sites on dopaminergic neurons in the central nervous system are of vital significance because such receptors have been identified as sites of action of neuroleptic drugs,[1-8] indicating they play a role in schizophrenia, at least at the stage of symptom expression. In addition, degeneration of the nigrostriatal dopaminergic pathway has been shown to lead to neuromotor abnormalities as expressed in Parkinson's disease and other syndromes.[4,9,10]

A number of studies have addressed the question of the precise molecular shape (i.e., conformation) of dopamine (DA) and DA agonists required for effective interaction with its various receptors in the central nervous system as well as the periphery.[11-22] The structural requirements for effective binding of DA agonists to their receptors in the brain have been reviewed and analyzed by Seeman,[23] using data obtained with a variety of rigid and semirigid analogues of dopamine. Dopamine (I) itself is conformationally flexible and can assume a number of low-energy trans-anti and gauche conformations separated by small rotational potential barriers.[24-27] The α- and β-rotameric forms (II and III, respectively) of the extended or trans-anti DA conformation ($\theta = 180°$, Figure 1a) are represented by the potent DA agonists apomorphine (APO, IV) and 2-amino-6,7-dihydroxytetrahydronaphthalene (ADTN, V), respectively.[28-33] Although ADTN is structurally constrained relative to DA itself, it has some conformational mobility, since the nonaromatic ring can exist in either boat or half-chair conformations and the amino group can assume either an axial or equatorial orientation.[15,34] In what is generally agreed to be the preferred conformation of ADTN with an equatorial amino group attached to a half-chair tetralin ring, the catechol ring is nearly coplanar ($\phi \sim 10°$; see Figure 1b) with the ethylamine side chain of the DA moiety contained within ADTN. A similar relationship exists in APO.[35]



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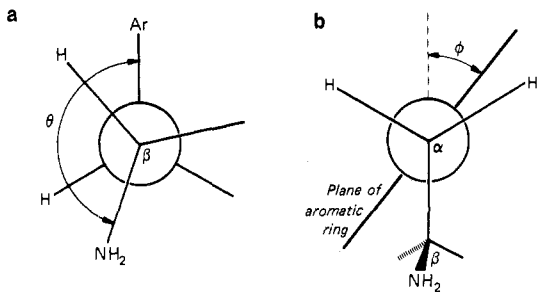
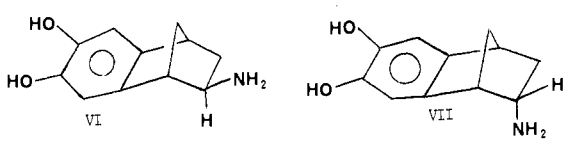


Figure 1. Definitions of dihedral angles θ and ϕ in dopamine analogues: (a) View along the C_α–C_β bond; (b) view along the bond between C_α and the ring carbon, where ϕ is the angle between the plane of the aromatic ring and the plane defined by C_α, C_β, and N.

In order to define more precisely the conformational limitations on dopaminergic activity of molecules related to ADTN,[23] we have prepared the completely rigid bridged tricyclic analogues VI and VII in which the nonaromatic

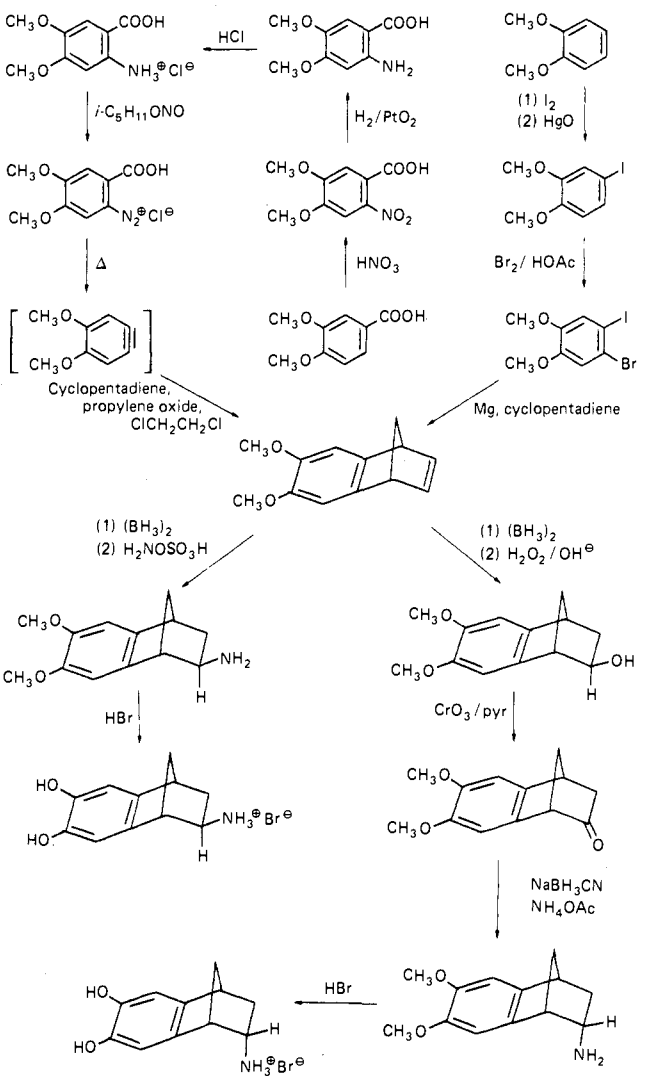


ring is forced into a boat conformation, and amino groups are constrained to pseudoequatorial and pseudoaxial orientations, respectively. In VI, the DA moiety still retains an extended anti conformation with $\theta = 180°$ (Figure 1a), but the dihedral angle ϕ between the catechol ring and the ethylamine side chain is fixed at about 60° (Figure 1b), according to molecular models. In VII, the DA moiety assumes an overall gauche conformation, with ϕ now approaching 90°.

Results and Discussion

The route used for synthesis of the dopamine and ADTN analogues VI and VII is depicted in Scheme I. The key step was the formation of 6,7-dimethoxybenzonorbornadiene by cycloaddition of cyclopentadiene and 4,5-dimethoxybenzyne,[41] which could be conveniently generated either by heating the appropriate diazonium carboxylate or by reaction of 3-bromo-4-iodoveratrole with magnesium. Conversion of this alkene stereospecifically to either the *exo*- or *endo*-6,7-dimethoxybenzonorbornenylamines (VI or VII) was readily achieved by reactions modeled on that of norbornene itself, involving (a) hydroboration followed by reaction with hydroxylamine-*O*-sulfonic acid[36] or (b) conversion to the exo alcohol by standard hydroboration, oxidation to the corresponding ketone, and finally reaction with sodium cyanoborohydride.[37] The spectral data for these two amines are

Scheme I. Synthetic Route to *exo*- and *endo*-2-Amino-6,7-dihydroxybenzonorbornenes



consistent with the configurations assigned by the methods of synthesis, based on the chemical shifts of the protons at C-2.[38] In the course of the synthetic phase of this study, the exo amine was resolved into its (+) and (−) enantiomers using optically active tartaric acid as the resolving agent, but attempts to resolve the endo amine were unsuccessful.

Both amines VI and VII are stable when kept in the refrigerator under nitrogen, as determined by TLC as well as by spectral analysis. On exposure to the atmosphere at room temperature for a prolonged period of time, both amines formed tarry materials, characteristic of catechol oxidation. The stability of the exo amine VI in TEAN buffer at concentrations down to 10^{-5} M was checked by monitoring its UV absorbance at 287 nm (λ_{max}, ϵ 2980), where the buffer did not absorb significantly. No change in the absorbance at 287 nm nor in the overall appearance of the UV spectrum was noted during the 2-day period in which the spectrum was monitored.

The binding of freshly prepared samples of (±)-VI, (+)-VI, (−)-VI, and (±)-VII to calf and rat striatal homogenates in TEAN buffer was studied at amine concentrations from 1 to 2000 nM. No reproducible trends indicative of specific binding of any of these amines to dopaminergic

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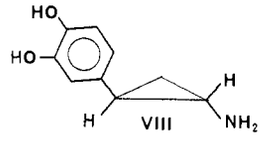
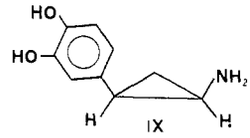
receptor sites in calf caudate were observed in a number of runs, as indicated by DA receptor binding assays using [^{3}H]DA, [^{3}H]APO, and [^{3}H]spiperone. The IC_{50} for binding of racemic exo amine VI vs. [^{3}H]DA in the rat preparation was found to be >2000 nM. In our hands, the IC_{50} for displacement of [^{3}H]DA by (±)-ADTN was 6 nM in the calf striatal homogenate, comparable to a literature value of 10 nM,[31] while in the rat preparation it was 3.1 nM (lit.[31] 1.5 nM).

In a recent study of the DA analogues VIII and IX, in



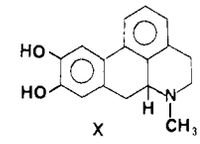
VIII



IX

which the aryl rings are theoretically free to rotate with respect to the cyclopropane rings but where a conformation with $\phi \approx 90°$ (Figure 1b) is presumed to be preferred, it was found that both compounds lacked dopaminergic activity.[17] The inactivity of IX is readily attributed to the nearly eclipsed conformation of the DA moiety. The authors ascribed the inactivity of VIII to the presumed orthogonality of the aryl and ethylamine subunits, although the electronic effects of the cyclopropane ring could not be eliminated as playing an important role. Similar findings were reported for cyclobutyl analogues by other workers.[22] However, in cyclopropane and cyclobutane rings, the trans stereoisomers cannot assume a "pure" anti conformation with $\theta = 180°$ (as in APO and ADTN); that dihedral angle has been proposed to be 110–160° in the cyclobutyl analogue.[22] Thus, the deviation of θ from 180° may be more critical or at least as important a factor in reducing dopaminergic activity as the deviation of ϕ from 0°. Thus, important questions still remain from prior studies with respect to structural constraints on dopaminergic activity.

Since the DA subunit of VI more closely approximates a pure anti conformation, with $\theta = 180°$ as in ADTN itself, it represents a better system than those discussed above for investigating the effect on dopaminergic activity of deviations of ϕ from 0°. Since the resolution of VI had been accomplished prior to the bioassays, the enantiomers of VI were individually assayed as well, since ADTN itself shows moderate enantiospecificity in various assays.[39,40] The observed lack of activity in receptor binding vs. several test ligands for all these compounds in the range of concentrations typical of active DA agonists (i.e., up to 2000 nM) supports the view[17,35] that coplanarity of the catechol and ethylamine units, even in a molecule with a true anti conformation, may be essential for dopaminergic activity, although a wider range of biological testing of these materials seems appropriate to confirm this conclusion (see Note Added in Proof). An additional structural factor which must be considered, however, is that the methylene bridge introduced in order to attain structural rigidity in VI may directly interfere with the receptor topology, preventing an effective "fit" of VI into the dopaminergic receptor site. It is interesting to analyze these results in terms of the model for interaction of DA agonists at the D_2 receptor proposed recently by Seeman (see Figure 14 in ref 23). One of the enantiomers of VI would appear to interact unfavorably with the obstacle "P" proposed by Seeman[23] from studies of other dopamine-related congeners, while the other enantiomer would be displaced on the surface and might well interfere with obstacle "Q". The situation, in fact, strongly resembles that of the two enantiomers of isoapomorphine X and adds strength to Seeman's proposed model.[23] The lack of activity of the gauche DA analogue VI was not surprising based on literature precedents.[11-13,16,17,20,22,35]



X

We are currently investigating the effect on dopaminergic activity of bridge size (which will alter ϕ in a controlled manner), the incorporation of hetero atoms into the bridge in analogues of VI, as well as the effect on neurochemical activity of N-alkylation; we will report those results in due course.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Model 735 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Hitachi Perkin-Elmer R-20 and Varian EM 360 60-MHz spectrometers; ^{13}C NMR spectra were obtained on a Varian XL-100 Fourier transform spectrometer. Proton chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. Mass spectra were taken on a DuPont 21-492 double-focusing mass spectrometer. Specific rotations were measured on a Perkin-Elmer Model 141 digital polarimeter.

Preparation of 6,7-Dimethoxybenzonorbornadiene. This compound was made according to the procedure of Goering et al.[41] The yield was 25% and the mp 81–82 °C (lit.[41] yield 35%; mp 82 °C). Spectral data agreed with those reported.

An alternative method for the preparation of the title compound was followed according to the general procedure given by Tanida et al.[42] To a three-necked flask equipped with a magnetic stirrer and a dropping funnel was placed magnesium (1.51 g, 62 mmol), and the system was flushed with nitrogen for 45 min. A solution of 3-bromo-4-iodoveratrole[43] (20.6 g, 60 mmol) and freshly generated cyclopentadiene (7.9 g, 120 mmol) in 90 mL of dry tetrahydrofuran (THF) was placed in the dropping funnel. A part of the solution from the funnel was added to cover the magnesium and then heated to boiling. After the reaction commenced, the rest of the solution was added dropwise over a period of 1 h. The system was then heated at reflux for an additional 0.5 h. The solvent was removed in vacuo, and the residue was poured into a mixture of diethyl ether and a saturated solution of ammonium chloride in water. The organic layer was separated, washed with a 5 M solution of sodium bisulfite, and dried over Na_2SO_4. Removal of the solvent gave a yellow-brown liquid, which was dissolved in a small amount of diethyl ether. The product crystallized out in an acetone–dry ice bath. The crude yield was 3.47 g (28.5%), mp 76–78 °C. After treatment with Norite and recrystallization from diethyl ether–pentane, 2.74 g (22.6%) of a white compound, mp 81–82 °C, was obtained. Spectral data were in agreement with those of Goering et al.[41]

***exo*-2-Hydroxy-6,7-dimethoxybenzonorbornene.** The procedure used was that followed by Goering,[41] which is a modification of the method of Brown et al.[45] for the synthesis of

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norborneol. In a typical run, 6,7-dimethoxybenzonorbornadiene (2.02 g, 10 mmol) was dissolved in 5 mL of dry tetrahydrofuran. To this solution was added 3.3 mL of 1.0 M diborane solution in tetrahydrofuran. After 3 h of stirring at room temperature, 1.6 mL of 3 N NaOH solution was added to the system, followed by 1.6 mL of 30% H_2O_2 solution. After 30 min of additional stirring, the reaction mixture was washed with water, the aqueous layers were extracted with diethyl ether, the organic layers were combined and dried over Na_2SO_4, and the solvent was removed in vacuo, yielding 1.81 g (82%) of crude product, mp 84–86 °C. Recrystallization from ether–pentane gave white crystals: mp 89–89.5 °C; IR 3600–3050, 1610, 1490, 1470, 1325, 1315, 1290, 1260, 1220, 1120, 1080, 990, 850, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.84 (s, 1), 6.77 (s, 1), 3.87 (s, 6), 4.07–3.77 (m, 1), 3.37–3.10 (m, 2), 2.27–1.83 (m, 3), 1.83–1.54 (m, 2); MS, *m/e* 220 (M^+).

6,7-Dimethoxy-2-benzonorbornenone.[44] A solution of oxalyl chloride (0.05 mL, 0.55 mmol) in 0.5 mL of methylene chloride was placed in a three-neck round-bottom flask equipped with a thermometer and a magnetic stirrer. The system was maintained under nitrogen throughout the experiment. A solution of dimethyl sulfoxide (0.085 mL, 1.1 mmol) in 0.25 mL of methylene chloride was injected into the flask at −50 to −60 °C. The reaction mixture was stirred for 2 min, and *exo*-2-hydroxy-6,7-dimethoxybenzonorbornene (110 mg, 0.5 mmol) in 1.25 mL of methylene chloride was added to the system, maintaining the low temperature. The mixture was stirred for 15 min, and triethylamine (0.3 mL, 2.3 mmol) was added. The resultant mixture was stirred for 2 min; it was then allowed to warm to room temperature. Water (2.5 mL) was added, the organic layer was separated, and the aqueous layer was saturated with methylene chloride. The organic layers were combined and washed sequentially with saturated aqueous NaCl, 1% HCl, saturated NaCl, 5% $NaHCO_3$, and saturated NaCl. The organic layer was dried over $MgSO_4$, and solvent was removed in vacuo to yield a yellowish solid, which was recrystallized from diethyl ether–pentane to give 90 mg (83%) of product: mp 106–108 °C (lit.[41] 106–107 °C). Repeated recrystallization resulted in formation of the pure product: mp 112–113 °C; IR 2840, 1725, 1600, 1580, 1490, 1310, 1220, 1120, 1065, 1000, 885, 850, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (s, 2), 3.80 and 3.86 (overlapping singlets, 6), 3.37–3.70 (m, 2), 1.60–2.60 (m, 4).

***endo*-2-Amino-6,7-dimethoxybenzonorbornene [VII-(OMe)$_2$].** This compound was prepared according to the procedure of Borch et al.[37] for the synthesis of *endo*-2-norbornylamine from norbornenone. A solution of 6,7-dimethoxybenzonorbornenone (780 mg, 3.6 mmol), ammonium acetate (2.8 g, 36 mmol), and sodium cyanoborohydride (158 mg, 2.5 mmol) in 20 mL of absolute CH_3OH was stirred for 36 h under nitrogen at 25 °C. Concentrated HCl was added until the pH was less than 2.0, and the solvent was removed in vacuo. The residue was taken up in water and washed twice with diethyl ether, and the resultant aqueous layer was made strongly alkaline with solid KOH. This was saturated with NaCl and extracted with diethyl ether. The combined ether extracts were dried over $MgSO_4$, and the solvent was removed in vacuo to yield 650 mg (82%) of a clear thick liquid. A small portion of this liquid was dissolved in diethyl ether, and upon addition of gaseous HCl, a white precipitate formed. This compound had mp 145–147 °C after recrystallization from methanol–diethyl ether. Spectral data for the amine: IR 3320, 3260, 3100, 2940, 2840, 2800, 1610, 1585, 1490, 1460, 1410, 1325, 1310, 1280, 1260, 1215, 1110, 1075, 1015, 850, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90–6.67 (m, 2), 4.00–3.70 (overlapping singlets, 6), 3.70–2.67 (br m, 3), 2.33–1.23 (m, 3), 0.77–0.20 (br d, 1); MS, *m/e* 219 (M^+). Absolute mass for $C_{13}H_{17}NO_2$: calcd, 219.1254; found, 219.1262. Anal. ($C_{13}H_{17}NO_2$) C, H; N: calcd, 6.39; found, 5.66. Spectral data for the amine hydrochloride: NMR (D_2O) δ 7.11–6.90 (m, 2), 3.90–3.60 (s, 6), 3.60–2.87 (m, 4), 1.97–1.54 (m, 3). In the neutral amine, ^{13}C NMR spectra indicated the presence of impurities. Comparison with the ^{13}C spectrum of the exo analogue showed that the endo amine was not contaminated with its epimer to any observable extent.

***exo*-2-Amino-6,7-dimethoxybenzonorbornene [VI(OMe)$_2$].** This compound was made according to the procedure given by Brown et al.[36] for the synthesis of *exo*-2-norbornylamine from norbornene. 6,7-Dimethoxybenzonorbornadiene (1.01 g, 5 mmol) was placed with 2 mL of dry tetrahydrofuran into a 25-mL, three-necked flask equipped with a reflux condenser. After flushing with nitrogen, hydroboration was accomplished by the addition of 1.7 mL of a 1.0 M solution of diborane solution in THF. After the solution was stirred for 6 h at room temperature, hydroxylamine-*O*-sulfonic acid (566 mg, 5.0 mmol) was added, and the system was heated under reflux for 3 h. The solution was then acidified with dilute aqueous HCl, washed with diethyl ether, made alkaline with solid KOH, and extracted with diethyl ether. The ether layer from the extraction was dried over $MgSO_4$, and the solvent was removed in vacuo to yield 549 mg (50.1%) of a yellowish liquid, which solidified when a stream of nitrogen was passed over the material. A small portion of this product, mp 74–76 °C, was dissolved in diethyl ether and was treated with gaseous HCl to give a white salt, which was recrystallized from methanol–ether, mp 264 °C.

This amine was also prepared by a general method described by Grunewald[46] for the amination of the benzonorbornene system, involving sodium borohydride reduction of the adduct of 6,7-dimethoxybenzonorbornadiene and mercuric azide, with subsequent reduction of the resultant azide with $LiAlH_4$. The product was obtained in 43% yield: mp 79–80 °C; IR 3290, 1600, 1585, 1485, 1205, 1120, 1060, 980, 780, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (s, 1), 6.77 (s, 1), 3.87 (s, 6), 3.30–3.10 (m, 1), 3.10–2.80 (m, 2), 1.90–1.60 (m, 2), 1.60–1.10 (m, 4); ^{13}C NMR ($CDCl_3$) 147.28, 147.01, 140.64, 138.27, 106.99, 106.30, 56.23, 53.54, 52.41, 45.49, 43.35, 39.47 ppm; MS, *m/e* 219 (M^+). Absolute mass for $C_{13}H_{17}NO_2$: calcd, 219.1254; found, 219.1267. Anal. for HCl salt ($C_{13}H_{18}NO_2Cl$) C, H, N.

***exo*-2-Amino-6,7-dihydroxybenzonorbornene Hydrobromide (VI·HBr).** *exo*-2-Amino-6,7-dimethoxybenzonorbornene (100 mg, 0.46 mmol) was placed in a 50-mL, round-bottom flask equipped with a reflux condenser. To the flask was added 14 mL of 48% aqueous HBr, and the solution was heated under reflux for 3 h under a nitrogen atmosphere. The solution was then distilled in vacuo to yield 118 mg (95%) of a gray-green solid. The most efficient purification method found was repeated recrystallization from absolute methanol–ether in a dry ice–acetone bath, which gave a brownish solid, mp 246–249 °C dec, in a yield of 52%: IR 3410, 3300, 2850, 1960, 1615, 1390, 1315, 1175, 1150, 1110, 885, 800 cm^{-1}; ^1H NMR (D_2O) δ 6.93 (s, 1), 6.87 (s, 1), 3.6–3.00 (m, 3), 2.00–1.67 (m, 4); ^{13}C NMR (D_2O) 141.79, 141.03, 140.01, 135.65, 110.29, 109.48, 52.25, 46.75, 44.68, 42.33, 34.35 ppm; MS, *m/e* 191 (M^+ − HBr). Absolute mass for $C_{11}H_{13}NO_2$: calcd, 191.0943; found, 191.0996. Anal. for HBr salt ($C_{11}H_{14}NO_2Br$) H, N; C: calcd, 48.54; found, 47.72, 47.92.

***endo*-2-Amino-6,7-dihydroxybenzonorbornene Hydrobromide (VII·HBr).** The compound was prepared from *endo*-2-amino-6,7-dimethoxybenzonorbornene using the method described above for the preparation of the exo analogue. The yield of the crude product was 76%. Treatment with Norite-1 and recrystallization from methanol–diethyl ether in a dry ice–acetone bath gave white crystals of the product. The final yield was 50%. This material showed only one spot on TLC using silica gel G upon development with 1-butanol/acetic acid/water (15:3:5) and was utilized in the binding assays. This compound is extremely hygroscopic. The highest melting point observed was 198–200 °C. Some runs yielded impure product from which the desired endo amine could not be isolated in pure form by preparative TLC: IR 3600–3000, 1615, 1495, 1320, 1300, 1265, 1120, 1100, 1060, 1040, 810, 800 cm^{-1}; MS, *m/e* 191 (M^+ − HBr). Absolute mass: for $C_{11}H_{13}NO_2$: calcd, 191.0943; found, 191.0954. A satisfactory elemental analysis could not be obtained for the HBr salt, which is very hydroscopic and is unstable when completely dry.

Resolution of *exo*-2-Amino-6,7-dimethoxybenzonorbornene Using (+)- and (−)-Tartaric Acid.[47] To a stirred solution of the above amine (539 mg, 2.5 mmol) in 40 mL of absolute ethanol was added (+)-tartaric acid (369 mg, 2.5 mmol), dissolved in a mixture of 30 mL of ethanol and 10 mL of water,

(46) Grunewald, G. L.; Reitz, T. J.; Hallett, A.; Rutledge, C. O.; Vollmer, S.; Archuleta III, J. M.; Ruth, J. A. *J. Med. Chem.* **1980**, *23*, 614.
(47) Vaughan, W. R.; Perry, Jr. R. *J. Am. Chem. Soc.* **1953**, *75*, 3168. Collins, C. J.; Cheema, Z. K.; Werth, R. G.; Benjamin, B. M. *Ibid.* **1964**, *86*, 4913.
(48) Titeler, M.; Weinreich, P.; Sinclair, D.; Seeman, P. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 1153.

dropwise under nitrogen over a period of 1 h. The resulting clear solution was cooled at −20 °C for 36 h until precipitation occurred. Filtration gave 155 mg of the salt, mp 208–210 °C. This was recrystallized from 50 mL of absolute ethanol overnight to give 77.5 mg of material: mp 208–210 °C; $[\alpha]^{25}_D$ +28.8° (c 1, H_2O). It was dissolved in 10% NaOH, the solution was extracted with diethyl ether, and the organic extract was dried over $MgSO_4$ and then evaporated in vacuo to yield 40 mg of the corresponding amine: $[\alpha]^{25}_D$ +42° (c 2, EtOH). The first filtrate was evaporated in vacuo to give the tartarate salt, which was treated with Norite and then dissolved in a 10% NaOH solution, which when extracted with ether afforded 233 mg (1.06 mmol) of the recovered amine. This optically enriched amine was dissolved in 15 mL of absolute ethanol and was mixed with an equimolar amount of (−)-tartaric acid (159 mg, 1.06 mmol) dissolved in 10 mL of ethanol and 5 mL of water. After overnight crystallization at −20 °C, 111 mg of the salt precipitated: $[\alpha]^{25}_D$ −29.8° (c 1, H_2O); mp 207–208 °C. Treatment of the salt with base as above gave 59 mg of amine: $[\alpha]^{25}_D$ −42° (c 2, EtOH). Amine with lower optical purity was isolated from the other filtrates.

Binding assays were carried out on crude homogenates of calf and rat striatum. Calf brains were obtained from Max Insel Cohen, Inc. (Newark, NJ), and rat striata were obtained from male Sprague–Dawley rats, 200–250 g. Rat striata were obtained immediately after sacrifice by decapitation, and calf striata were obtained within 2 h of death. The striata were pooled, sliced, and homogenized in a Potter-Everjeim homogenizer using 5–10 up–down strokes at 500 rpm in cold TEAN buffer (15 mM Tris-HCl, 5 mM Na_2EDTA, 1.1 mM ascorbate, 12.5 μM nialamide, pH 7.4), at 4 °C. The pooled homogenate was treated with a high-speed homogenizer ("Tissuemizer", Tekmar, Inc.) at a setting of 45 for 10 s. The resultant homogenate was then sedimented at 69500*g* for 10 min in a Beckman L5-40 ultracentrifuge at 4 °C. The supernatant was discarded, and the pellet was resuspended in ice-cold TEAN buffer and rehomogenized with the high-speed homogenizer. The homogenizing and washing process was repeated a total of five times, and the final homogenate (resuspended at 200 mg wet weight/mL) was stored in 3-mL aliquots at −4 °C. This is subsequently referred to as "striatal homogenate".

[^{3}H]Apomorphine Assays.[31] In 12 × 74 mm glass test tubes was placed 800-μL aliquots of 4 nM [^{3}H]APO (New England Nuclear Corp., 30 Ci/mmol), along with 800 μL of TEAN buffer or a solution of control ligand, 800 μL of the test ligand in TEAN buffer, and 800 μL of striatal homogenate. The final concentration of [^{3}H]APO was 1 nM. The tubes were incubated at room temperature for 30 min and then at 0 °C for 15 min. Four 0.5-mL aliquots were taken from each tube and vacuum filtered using a Millipore suction apparatus on which were placed Whatman GF/B glass-fiber filters (2.4 cm diameter) which had been presoaked in 0.5% bovine serum albumin (Sigma Chemical Co.) solution. The filters were washed with 10 mL of cold TEAN buffer delivered at a constant flow rate from a peristaltic pump (Manostat, Inc.) and were then counted for tritium radioactivity on a Beckman LS 7500 liquid scintillation counter in plastic vials containing a standard scintillation cocktail [50 mL of toluene and 50 mL of Triton X-100 (v/v) with 4 g/L of Omniscint (98% PPO, 2% Bis-MSB] after equilibration at room temperature for approximately 18 h. Specific binding was operationally defined as the total [^{3}H]APO activity bound less the amount bound in the presence of 1 μM unlabeled apomorphine in the incubation medium.

[^{3}H]Dopamine (New England Nuclear Corp., 44.03 Ci/mmol) was utilized as described above for apomorphine but at a final concentration of 0.5 nM. Specific binding was defined as above.

[^{3}H]Spiperone (New England Nuclear Corp., 25.7 Ci/mmol) was used as described above at a final concentration of 0.5 nM. Specific binding was operationally defined as the total [^{3}H]SPIP bound minus that bound in the presence of 1.5 μM (+)-butaclamol.[47]

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Note Added in Proof: Another paper describing the synthesis and dopaminergic activity of the title compounds by P. Burn et al., submitted after the present paper, was recently published in this journal (*J. Med. Chem.* **1982**, *25*, 363–368). In that study, these and other related compounds were also concluded to be inactive as dopamine agonists when tested in vivo for their ability to induce stereotyped behavior and hyperactivity in rats. Radioligand binding assays were carried out using [^{3}H]ADTN and [^{3}H]NPA, ligands not used in the present study. Both amines VI and VII showed similar low activity in displacing [^{3}H]NPA, but the exo-amine VI had an IC_{50} of 7.8 nM vs. [^{3}H]ADTN, a surprising result in light of its low potency in animal models for dopaminergic activity and its low affinity (present study) for sites labeled by [^{3}H]DA and [^{3}H]APO. It should be noted that the binding assays in the study by Burn et al. were carried out in the absence of ascorbate, which could represent a serious omission in light of recent studies by Leff et al. (*Life Sci.* **1981**, *29*, 2081–2090) indicating that ascorbic acid is required for reversible and specific binding of [^{3}H]agonists to dopamine receptors. The interpretation by Burn et al. of their results in terms of structural requirements for effective interaction of DA agonists at DA receptors is very similar to that presented in the present paper.