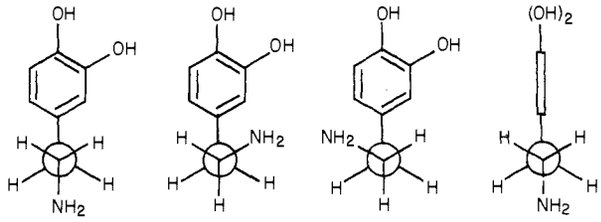
Synthesis and Dopaminergic Properties of Some *exo*- and *endo*-2-Aminobenzonorbornenes Designed as Rigid Analogues of Dopamine

Peter Burn,† Peter A. Crooks,*† Frank Heatley,‡ Brenda Costall,§ Robert J. Naylor,§ and Virinder Nohria§

Departments of Pharmacy and Chemistry, University of Manchester, Manchester, M13 9PL, United Kingdom, and School of Studies in Pharmacology, University of Bradford, Bradford, West Yorkshire, United Kingdom. *Received March 23, 1981*

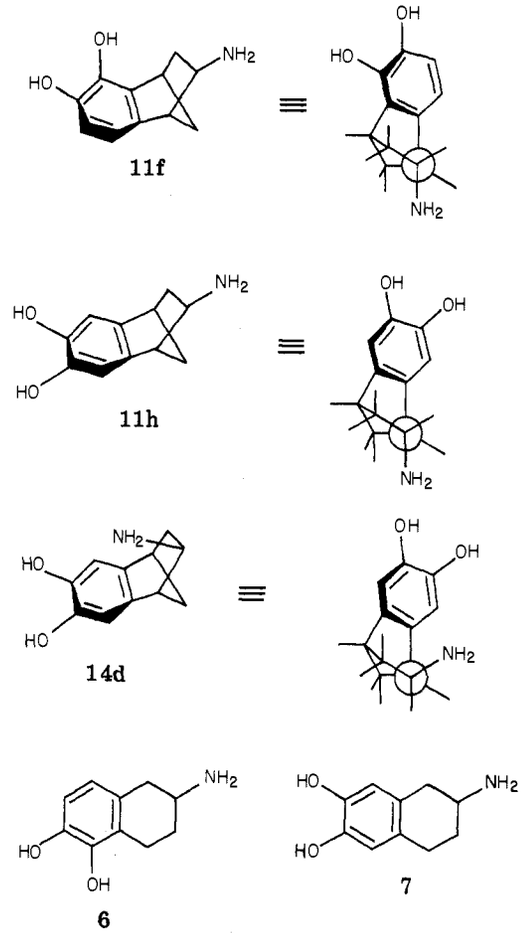
Stereospecific syntheses of *exo*-2-amino-5,6-dihydroxybenzonorbornene (**11f**), *exo*-2-amino-6,7-dihydroxybenzonorbornene (**11h**), *exo*-2-amino-7,8-dihydroxybenzonorbornene (**11g**), and *endo*-2-amino-6,7-dihydroxybenzonorbornene (**14d**), rigid analogues of dopamine, are described. Compounds **11h** and **14d**, their *N*-methyl (**11i** and **11j**) and *N,N*-dimethyl (**14i** and **14j**) derivatives, and compounds **11f** and **11g** were inactive as dopamine agonists when evaluated for dopaminergic activity by their ability to induce stereotyped behavior in mice after subcutaneous injection and by their ability to cause hyperactivity in rats after bilateral injection into the nucleus accumbens. However, compounds **11f**, **11g**, **11h**, and the *N*-methyl derivatives **11i** and **14d** were all effective in displacing [^{3}H]-2-amino-6,7-dihydroxytetralin ([^{3}H]ADTN) and [^{3}H]-*N*-*n*-propylnorapomorphine ([^{3}H]NPA) from rat striatal membranes.

The neurotransmitter molecule dopamine can exist in either a trans (**1**) or two gauche forms[1] (**2** and **3**). Previous



1 **2** **3** **4**

communications have attempted to determine the active conformation of dopamine at its receptor, and evidence from both physical measurements[2-5] and structure–activity studies[6-9] have indicated that the trans conformer is the active species. Examination of the trans conformer shows that it can exist in two extreme forms: form **1**, where the plane of the catechol ring is perpendicular with a plane through $CH_2CH_2NH_2$, and form **4**, where the ring is coplanar with it. Furthermore, rotation of the catechol ring about 180° in **1** gives rise to two additional and distinct rotameric forms. The question of whether the active conformation of dopamine is **1** or **4** has been the subject of recent comment.[1] Physical measurements of the dopamine molecule in both the crystal form[10] and in solution[11] indicate that the preferred form is **1**, while extensive structure–activity studies with aporphine[12,13] and 2-aminotetrahydronaphthalene[14-18] derivatives point to form **4** as the pharmacologically active species. Surprisingly, no completely rigid analogues of conformer **1** of dopamine have been examined for dopaminergic activity. We now report the synthesis and dopaminergic properties of the 5,6- and 6,7-dihydroxy derivatives of *exo*-2-aminobenzonorbornene, **11f** and **11h**, respectively, which may be regarded as rigidly fixed, extreme conformations of the 5,6- and 6,7-dihydroxy derivatives of 2-aminotetrahydronaphthalene, **6** and **7**, respectively, and which are stereochemically related to conformer **1** of dopamine. In addition, the isomeric endo compound **14d** has been prepared, a rigid analogue related to conformer **2** of dopamine. The *N*-methyl and *N,N*-dimethyl derivatives of both **11h** and **14d** have also been synthesized. All the above compounds were evaluated for dopaminergic activity by their ability to induce stereotyped behavior in mice after subcutaneous injection, by their ability to cause hyperactivity in rats after bilateral injection into the nucleus accumbens, and by their



11f ≡

11h ≡

14d ≡

6 **7**

* Address correspondence to The College of Pharmacy, University of Kentucky, Lexington, Kentucky 40506.
† Department of Pharmacy, University of Manchester.
‡ Department of Chemistry, University of Manchester.
§ University of Bradford.

(1) A. S. Horn and J. R. Rodgers, *J. Pharm. Pharmacol.*, **32**, 521 (1980).
(2) B. Pullman, H. Berthod, and Ph. Courriere, *Int. J. Quant. Chem.*, 1, 93 (1974).
(3) L. B. Kier, *J. Theor. Biol.*, **40**, 211 (1973).
(4) R. Katz, S. R. Heller, and A. E. Jacobson, *Mol. Pharmacol.*, **9**, 486 (1973).
(5) C. J. Grol and H. Rollema, *J. Pharm. Pharmacol.*, **29**, 153 (1977).
(6) R. J. Miller, A. S. Horn, L. L. Iversen, and R. Pinder, *Nature (London)*, **250**, 238 (1974).
(7) R. Costall, R. J. Naylor, and R. Pinder, *J. Pharm. Pharmacol.*, **26**, 753 (1974).
(8) H. L. Komiskey, J. F. Bossart, D. D. Miller, and P. N. Patil, *Proc. Natl. Acad. Sci. U.S.A.*, **75**, 2641 (1978).
(9) D. D. Miller, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2392 (1978).

0022-2623/82/1825-0363$01.25/0

Table I. Chemical Shifts, Coupling Constants and Spin-Lattice Relaxation Times for 11f in CD_3OD

proton	T_1,[a] s	chem shift,[b] τ	coupling constant, Hz (coupling proton)
C-1		~6.60	1 (C-2), 2 × 1.5 (C-9)
C-2	2.7	6.81	1 (C-1), 4 (exo C-3), 8 (endo C-3)
exo C-3	0.61	8.18	4 (C-2), 13 (endo C-3), 4 (C-4)
endo C-3	0.63	8.05	8 (C-2), 13 (exo C-3), 1 (C-4)
C-4	2.3	6.23	1 (exo C-3), 1 (endo C-3), 2 × 1.5 (C-9)
C-7	3.6	3.39	7.5 (C-8)
C-8	2.7	3.31	7.5 (C-7)
C-9	0.60	7.96	1.5 (C-1), 1.5 (C-4), 10 (geminal)
	0.63	8.06	

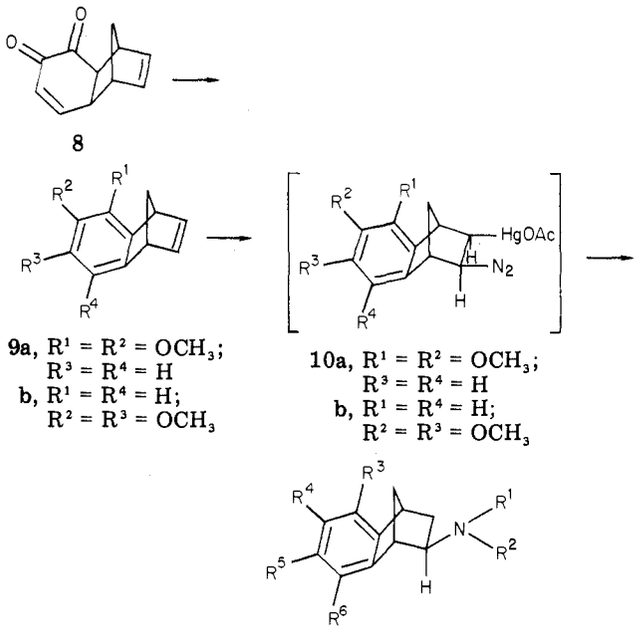
[a] ±5%. [b] Calculated assuming CHD_2OD at τ 6.6.

ability to displace [^{3}H]ADTN and [^{3}H]NPA from rat striatal membranes.

Results

Chemistry. Compound **11f** was prepared as outlined in Scheme I. A modification of the existing literature method[19] for the preparation of the quinone–cyclopentadiene adduct, 8, almost doubled the yield of this compound, which could be converted directly into **9a** by treatment with alkaline dimethyl sulfate. Amination of **9a** (via the mercuric acetate–azide complex **10**[20]) afforded only the exo-isomeric product. However, due to the nonregiospecifity of the addition to the C2–C3 double bond in this reaction, the two possible exo isomers, **11a** and **11b**, were obtained in a 2:1 ratio, respectively. No attempt was made to separate **11a** and **11b** at this stage, and the isomeric mixture was O-demethylated in 47% HBr to give a mixture of the hydrobromide salts of **11f** and **11g**. Fractional crystallization of the above mixture afforded a chromatographically pure compound (**11f**). The isomeric **11g** was obtained impure from the mother liquors. Compounds **11f** and **11g** give very similar ^{1}H NMR spectra and cannot be identified unequivocally from the spectra alone. The compound crystallized was identified absolutely as **11f** by measurements of proton spin–lattice relaxation times (T_1) and nuclear Overhauser enhancements (NOE).[21] At the frequency of 300 MHz used for those experiments, all protons are clearly resolved. Table I gives the chemical shifts, coupling constants, and T_1 values. (Note that these data are for a CD_3OD solution; therefore, the shifts may differ from those reported above for D_2O solutions at 60 MHz). Most of the assignments in Table I were made from spin-decoupling experiments, starting with the unequivocal assignment of H-2 to the signal at τ 6.81. H-1 was found to be obscured by the solvent residual CHD_2 signal. The coupling constants are consistent with those expected from the Karplus relationship[22] for the dihedral angles estimated from a Dreiding model. The assignment of H-7 and H-8 was made on the basis of the T_1 data: the H-8 proton is expected to have a shorter T_1 because of the adjacent bridgehead proton (290 ppm). The distinction between structures **11f** and **11g** was made from a comparison of NOE's of H-2 and H-8 when the two bridgehead signals were separately irradiated. Saturation of the lower-field bridgehead resonance produced no measureable enhancement of either H-2 or H-8, whereas saturation of the higher-field bridgehead proton produced enhancements of both H-2 (9%) and H-8 (6%). Thus, one bridgehead proton is proximate to both H-8 and H-2, identifying the compound as **11f**. Compound **11h** was prepared from the previously reported 6,7-dimethoxybenzonorbornadiene

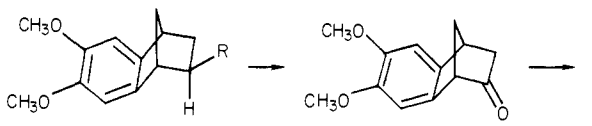
Scheme I



11a, $R^1 = R^2 = R^5 = R^6 = H$; $R^3 = R^4 = OCH_3$
b, $R^1 = R^2 = R^3 = R^4 = H$; $R^5 = R^6 = OCH_3$
c, $R^1 = R^2 = R^3 = R^6 = H$; $R^4 = R^5 = OCH_3$
d, $R^1 = CH_3$; $R^2 = R^3 = R^6 = H$; $R^4 = R^5 = OCH_3$
e, $R^1 = R^2 = CH_3$; $R^3 = R^6 = H$; $R^4 = R^5 = OCH_3$
f, $R^1 = R^2 = R^5 = R^6 = H$; $R^3 = R^4 = OH$
g, $R^1 = R^2 = R^3 = R^4 = H$; $R^5 = R^6 = OH$
h, $R^1 = R^2 = R^3 = R^6 = H$; $R^4 = R^5 = OH$
i, $R^1 = CH_3$; $R^2 = R^3 = R^6 = H$; $R^4 = R^5 = OH$
j, $R^1 = R^2 = CH_3$; $R^3 = R^6 = H$; $R^4 = R^5 = OH$

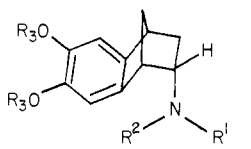
(10) R. Bergin and D. Carlström, *Acta Crystallogr., Sect. B*, **24**, 1506 (1968).
(11) C. Gussner-Prettre and B. Pullman, *J. Magn. Reson.*, 18, 564 (1975).
(12) J. L. Neumeyer, W. P. Dafeldecker, B. Costall, and R. S. Naylor, *J. Med. Chem.*, **20**, 190 (1977).
(13) J. L. Neumeyer, J. F. Reinhard, W. P. Dafeldecker, J. Guarino, D. S. Kosersky, K. Fuxe, and L. Agnati, *J. Med. Chem.*, **19**, 25 (1976).
(14) J. G. Cannon, J. A. Perez, J. P. Pease, J. P. Long, J. R. Flynn, D. B. Rusterholz, and S. E. Dryer, *J. Med. Chem.*, **23**, 745 (1980).
(15) H. C. Cheng, J. P. Long, L. S. Van Orden III, J. G. Cannon, and J. P. O'Donnell, *Res. Commun. Chem. Pathol. Pharmacol.*, **15**, 89 (1976).
(16) M. K. Menon, W. G. Clark, and J. G. Cannon, *J. Pharm. Pharmacol.*, **28**, 778 (1976).
(17) J. G. Cannon, T. Lee, F. Hsu, J. P. Long, and J. R. Flynn, *J. Med. Chem.*, **23**, 502 (1980).
(18) J. G. Cannon, D. L. Koble, J. P. Long, and T. Verimer, *J. Med. Chem.*, **23**, 750 (1980).
(19) W. M. Horspool, J. M. Tedder, and Zia ud Din, *J. Chem. Soc., C*, 1597 (1968).
(20) S. J. Dominianni and P. V. Demarco, *J. Org. Chem.*, **36**, 2534 (1971).
(21) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York, 1971.
(22) A. A. Bothner-By, *Adv. Magn. Reson.*, 1, 195 (1965).

Scheme II



12a, R = OCHO
b, R = OH

13



14a, $R^1 = R^2 = H$; $R^3 = CH_3$
b $R^1 = R^3 = CH_3$; $R^2 = H$
c, $R^1 = R^2 = R^3 = CH_3$
d, $R^1 = R^2 = R^3 = H$
e, $R^1 = CH_3$; $R^2 = R^3 = H$
f, $R^1 = R^2 = CH_3$; $R^3 = H$

(**9b**)[23] via the route shown in Scheme I. Compound **11c** was converted into its *N*-methyl derivative (**11d**) by lithium aluminum hydride reduction of the intermediate *N*-formyl derivative and into its *N,N*-dimethyl derivative (**11e**) by reaction with a formaldehyde–formic acid mixture.

The endo-isomer **14a** was prepared from 6,7-dimethoxybenzonorbornen-2-one (**13**)[24] via the Leuckart reaction with formamide and formic acid.[25] This reaction is known to afford selectively *endo*-aminobenzonorbornenes.[26,27] Compounds **16b** and **16c** were prepared similarly, utilizing *N*-methylformamide and *N,N*-dimethylformamide respectively, in place of formamide in this reaction (see Scheme II).

The dimethoxy compounds **11c–e** and **14a–c** were all O-demethylated in refluxing 47% HBr to their corresponding dihydroxy derivatives.

Pharmacology. Induction of Stereotyped and Climbing Behavior in the Mouse. The characteristic behavioral responses of the mouse to the dopamine agonist apomorphine, stereotyped sniffing or biting (1.5–5.0 mg/kg sc) and climbing behavior (0.5–1.5 mg/kg sc), were not induced by any of the test compounds in doses up to and including 10 mg/kg sc. Some repetitive head movements were recorded at the highest doses of compounds **11f**, **11h**, **14d**, and **14e**, but these persisted for only a few minutes. The only other manifestations of drug action were observed using 10 mg/kg sc compound **11e**, i.e., muscular rigidity, poor motor coordination, analgesia (lack of response to tail pinch), and periodic myoclonus and convulsions, onset 5–7 min, duration 40–60 min.

Induction of Hyperactivity/Stereotypy Following Intra-accumbens Injection. The characteristic development of a dose-related hyperactivity to intra-accumbens dopamine (6.25–50 μg bilateral, 8–76 counts/5 min) was not mimicked by any of the benzonorbornene derivatives. At the largest dose used, 50 μg, **11f**, **11g**, **14d**, and **11h** caused a very inconsistent, low intensity hyperactivity of 1–15 counts/min, frequently accompanied by irregular repetitive head movements and, using **11g**, a head tremor.

Displacement of [^{3}H]ADTN and [^{3}H]NPA from rat striatal membranes. The dimethoxybenzonorbornene derivatives at concentrations up to and including 10^{-5} M failed to displace [^{3}H]ADTN and [^{3}H]NPA binding. The ability of the remaining agents to displace [^{3}H]ADTN and [^{3}H]NPA is shown in Table II.

Table II. Abilities of Some 2-Aminobenzonorbornene Derivatives to Displace [^{3}H]ADTN and [^{3}H]NPA in Radioligand Binding Assays

displacing drug	IC_{50},[a] M	
	[^{3}H]NPA	[^{3}H]ADTN
11f	5.4×10^{-7}	8.1×10^{-8}
11g	3.0×10^{-7}	3.3×10^{-8}
11h	4.2×10^{-7}	7.8×10^{-9}
11i	8.0×10^{-6}	8.4×10^{-8}
11j	$>10^{-5}$	$>10^{-5}$
14d	1.1×10^{-7}	3.4×10^{-7}
14e	6.1×10^{-7}	7.5×10^{-6}
14f	$>10^{-5}$	$>10^{-5}$
ADTN	3.0×10^{-9}	1.7×10^{-9}
apomorphine	1.8×10^{-9}	1.4×10^{-9}
dopamine	2.0×10^{-9}	2.1×10^{-9}

[a] IC_{50} values are assessed as the concentration of drug causing a half-maximal displacement of 1.0 nM [^{3}H]-ADTN and 1.0 nM [^{3}H]NPA specific binding, assessed using 10^{-5} sulpiride and (±)-ADTN, respectively. Each value is the mean value of two experiments performed in quadruplicate.

Discussion

In the present behavioral study we have shown an absence of dopamine-like potential (stereotypy, climbing induction) in a series of *exo*- and *endo*-2-amino-6,7-dihydroxybenzonorbornenes, their respective *N*-methyl and *N,N*-dimethyl derivatives, and the related isomeric *exo*-2-amino-5,6-dihydroxy- and *exo*-2-amino-7,8-dihydroxybenzonorbornenes. The inactivity of the peripherally administered benzonorbornene derivatives to facilitate motor function is unlikely to reflect an inadequate brain penetration, for on direct injection into the nucleus accumbens of the rat, a locomotor hyperactivity–stereotypy response, characteristic of dopamine agonist action,[28] was absent. The behavioral inactivity of the *exo*-2-amino-5,6- and -6,7-dihydroxybenzonorbornenes directly contrasts with the potent dopamine-like actions of 2-amino-5,6- and -6,7-dihydroxytetrahydronaphthalenes.[29] It is apparent that the inclusion of a methylene bridge between the 1 and 4 positions in the tetralin structure imposes a degree of rigidity that precludes an effective receptor interaction. This may be due to steric hindrance brought about by the additional methylene grouping and/or may reflect the imposition of a conformation approaching 1 between the catechol ring and the CH_2–NH_2 bond. While the general consensus has been that the tetralin, aporphine, and octahydrobenzoquinoline data may favor conformation 4, much of the rationale for this consensus has been based upon conformationally loose or flexible structural models, and it has been assumed that the most energetically favorable conformers in these compounds are the ones responsible for mediating the agonist response.[1] This present study, using 2-aminotetrahydronaphthalene analogues rigidly fixed in a conformation approaching that of 1, with the minimum addition of steric bulk to the molecule, and which are pharmacologically inactive as dopamine agonists, offers the most direct comment on the potential importance of the trans conformations 1 and 4 in dopamine–receptor interaction. The increased perspective afforded

(23) H. L. Goering, A. C. Backus, C. S. Chang, and D. Masilamani, *J. Org. Chem.*, 40, 1553 (1975).
(24) H. L. Goering, D. C. K. Change, and W.-S. Chang, *J. Org. Chem.*, 42, 1145 (1977).
(25) M. L. Moor, *Org. React.*, 5, 301 (1949).
(26) P. Burn, P. A. Crooks, and O. Meth-Cohn, *Org. Magn. Reson.*, 11, 370 (1978).
(27) P. Burn, P. A. Crooks, B. L. Ratcliffe, and J. M. H. Rees, *J. Pharm. Pharmacol.*, 32, 87 (1980).
(28) B. Costall and R. J. Naylor, *Eur. J. Pharmacol.*, 35, 161 (1976).
(29) B. Costall, R. J. Naylor, J. G. Cannon, and T. Lee, *Eur. J. Pharmacol.*, 41, 307 (1977).

by the present negative behavioral data would seem to support conformer 4 as the "active" form of dopamine.

In the receptor-labeling assay, *exo*-2-amino-6,7-dihydroxybenzonorbornene (**11h**) was ten times more potent in displacing [^{3}H]ADTN than any of the other agents, which were inactive at 10^{-5} M (methoxy derivatives) or had rather similar orders of potency, i.e., 10^{-8} to 10^{-7} M (compounds **11f**, **11g**, **11i**, and **14d**). In the [^{3}H]NPA assay, the three primary *exo*-amines, **11f**, **11g**, and **11h**, had very similar displacing potencies and, surprisingly, the endo-isomer **14d** was at least as potent. While one can make the general comment that the methoxy derivatives were also inactive in the assay and that *N*-methyl substitution also reduced displacing potency, in the absence of pharmacological data it is difficult to comment on the biochemical findings. One offers a cautious comment that of the agents tested, the primary amines may have some affinity for a "dopamine" receptor mechanism, but whether this affinity presents agonist or partial agonist–antagonist potential is not decided.

Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Manchester. Analytical results obtained for all compounds were within ±0.4% of the theoretical values unless otherwise stated. ^{1}H NMR spectra were recorded on a Bruker HX-90 spectrometer; tetramethylsilane was used as internal standard. Proton spin–lattice relaxation times and nuclear Overhauser enhancements were measured on a Varian Associates SC-300 spectrometer operating at 300 MHz. In order to reduce the complexity of the intramolecular relaxation contributions, the OH and NH_2 protons were deuterated by freeze–drying from D_2O solution. Intermolecular contributions were eliminated by making measurements on a solution of approximately 10 mg mL^{-1} in CD_3OD, degassed, and sealed in vacuo. The ambient temperature was 25 °C. High-pressure liquid-chromatographic (HPLC) analyses were carried out on a modular unit consisting of a Milton Roy minipump and an Altex Model 153 analytical optical unit operating at 254 nm. Elutions were carried out on a 25 × 0.46 cm Partisil-10 SCX cation exchange column (Whatman) at a column inlet pressure of 1100 psig and a flow rate of 0.5 mL/min at ambient temperature, using 0.05 M sodium phosphate, pH 4.6, as the mobile phase. Samples were introduced using a 100-μL Hamilton syringe, Model HP 1810. IR spectra were recorded on a Perkin-Elmer 235 grating spectrophotometer, and mass spectra were recorded on an AEI MS 12 spectrometer operating at a probe temperature of 200 °C.

4a,5,8,8a-Tetrahydro-5,8-methano-1,2-naphthoquinone (8). Utilizing a modified procedure described by Horspool,[19] a solution of iodic acid (28.8 g, 0.164 mol) in aqueous ethanol (80% v/v, 600 mL) was added to a stirred solution of pyrocatechol (44.0 g, 0.1 mol) and cyclopentadiene (26.4 g, 0.4 mol) in aqueous ethanol (80% v/v, 1.2 L) over a period of 30 min. The resulting red solution was stirred vigorously for 1 h and then left to stand at 0 °C for 48 h. The mixture was filtered, and the filtrate was evaporated to low volume and decolorized by the addition of a saturated sodium thiosulfate solution. The resulting solution was extracted with carbon tetrachloride (5 × 300 mL), the combined organic extracts were evaporated to low volume, and ether was added to give a yellow crystalline precipitate. The crystals were filtered at the pump and air-dried to give 8 in 75% yield (53.0 g), mp 88–91 °C (lit.[19] 89–91 °C).

5,6-Dimethoxybenzonorbornadiene (9a). The quinone–cyclopentadiene adduct 8 (53.0 g, 0.3 mol) was dissolved in aqueous NaOH (10% w/v, 500 mL), and the solution was stirred vigorously under nitrogen. The solution was cooled to 0 °C, and dimethyl sulfate (118.0 mL, 0.94 mol) was added dropwise over a period of 30 min. The resulting solution was allowed to warm to ambient temperature and stirred for 10 h. An additional volume of aqueous NaOH (10% w/v, 250 mL) was then added, followed by the dropwise addition of dimethyl sulfate (50 mL, 0.4 mol), and the solution was left to stir overnight. The solution was then extracted with ether (3 × 500 mL); the combined ether liquors were washed with aqueous NaOH (10% w/v, 1 × 300 mL) and water (1 × 500 mL) and dried over $MgSO_4$. The filtered ethereal extract was evaporated to dryness under reduced pressure to give a light-yellow oil, which was distilled in vacuo to afford **9a** as a clear oil: yield 46.0 g (74.0%); bp 138–140 °C (74.5 mmHg); ^{1}H NMR ($CDCl_3$) τ 3.15 (1 H, d, C-7 H, $J_{7,8}$ = 8 Hz), 3.40 (2 H, m, C-2 H and C-3 H), 3.65 (1 H, d, C-8 H, $J_{8,7}$ = 8 Hz), 5.86 (1 H, m, C-4 H), 6.20 (3 H, s, OCH_3), 6.29 (3 H, s, OCH_3), 6.20–6.29 (1 H, m, C-1 H), 7.83 (2 H, m, C-9 H's).

***exo*-2-Amino-5,6-dimethoxybenzonorbornene (11a) and *exo*-2-Amino-7,8-dimethoxybenzonorbornene (11b).** To a stirred solution of mercuric acetate (12.62 g, 0.04 mol) in water (40 mL) was added tetrahydrofuran (40 mL), sodium azide (7.8 g, 0.12 mol), and 5,6-dimethoxybenzonorbornadiene (**9a**; 8.0 g, 0.04 mol). The mixture was stirred at 50–55 °C for 18 h and cooled, and aqueous KOH (15% w/v, 40 mL) was added, followed by a solution of sodium borohydride (0.8 g, 0.02 mol) in KOH (15% w/v, 40 mL). The resulting gray-colored mixture was cooled to 0 °C (ice bath) with stirring, and NaCl (15 g) was added. The mixture was extracted with ether (3 × 100 mL) and the combined ethereal extracts were washed with ice–water (2 × 100 mL) and dried over $MgSO_4$ at 0 °C. The filtered solution was added dropwise to a suspension of lithium aluminium hydride in anhydrous ether (10.0 g in 300 mL, 0.26 mol), and the mixture was refluxed for 1 h and then left to stir at ambient temperature for 12 h. The excess lithium aluminium hydride was destroyed by the dropwise addition of water (18.0 mL), aqueous NaOH (20% w/v, 12.0 mL), and then water (56.0 mL). The clear ethereal supernatant was decanted, and the residue was washed with ether (2 × 100 mL). The combined ethereal liquors were dried ($MgSO_4$), filtered, and evaporated to dryness to give a yellow oil, which was dissolved in dilute HCl solution (30 mL). The acidic solution was washed with ether (2 × 20 mL), the ether was discarded, and the aqueous layer was basified and extracted with ether (2 × 20 mL). Evaporation of the combined ether liquors afforded a 2:1 mixture of **11a** and **11b**: yield 5.9 g (68%); t_R = 33.75 and 44.6 min, respectively; bp 118–126 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) (an asterisk indicates chemical shifts given by isomer **11b**) τ 3.34 (4 H, 2 d of d, C-7 H, C-8 H, C-5* H and C-6* H), 6.16 (3 H, s, 1 OCH_3), 6.18 (3 H, s, 1 OCH_3), 6.25 (6 H, s, 2 OCH_3), 6.20–7.15 (6 H, m, C-1 H, C-2 H, C-4 H, C-1* H, C-2* H, and C-4* H), 7.95–8.80 (8 H, m, C-9 H, C-3 H, C-9* H, and C-3* H), 8.40 (2 H, s, exchangeable with D_2O, NH_2), ^{13}C NMR ($CDCl_3$) (* indicates chemical shift given by isomer **11b**) δ 150.77 and 150.58 (C-5 and C-8*), 143.76 and 142.58 (C-6 and C-7*), 140.43 and 140.04 (C-4a and C-8a*), 137.98 (C-8a and C-4a*), 116.21 and 115.71 (C-7 and C-6*), 109.67 and 109.44 (C-8 and C-5*), 60.76 (C-5 OCH_3 and C-8* OCH_3), 55.97 (C-6 OCH_3 and C-7* OCH_3), 53.90 and 52.44 (C-4 and C-4*), 53.42 and 49.90 (C-1* and C-1), 45.02 (C-9 and C-9*), 43.06 and 40.52 (C-2* and C-2), 39.95 and 33.55 (C-3 and C-3*).

***exo*-2-Amino-5,6-dihydroxybenzonorbornene Hydrobromide (11f).** The isomeric mixture of **11a** and **11b** (6.9 g, 0.0315 mol) was treated with 48% v/v HBr (140 mL) at 140 °C for 2 h under nitrogen, and the solution was left to stand overnight. On concentrating the solution under reduced pressure to about one-third its original volume, a crystalline material was slowly deposited, which was filtered at the pump and recrystallized four times from an ethanol/ether solution to afford pure **11f**: yield 1.90 g (31.4%); mp 141–147 °C; ^{1}H NMR (D_2O) τ 3.07 (2 H, d of d, 2 aromatic H), 6.08 (1 H, m, C-4 H), 6.30 (1 H, m, C-1 H), 6.55 (1 H, m, C-2 H), 7.91 (4 H, m, C-3 H and C-9 H); ^{13}C NMR δ (D_2O) 144.39, 138.68, 138.16, 135.38 (C-5, C-6, C-4a, and C-8a), 115.41 and 114.24 (C-7 and C-8), 53.58 (C-2), 48.02 (C-1), 45.83 (C-3), 40.41 (C-4), 34.78 (C-9). HPLC analysis showed a single component: t_R = 13.25 min. Anal. ($C_{11}H_{13}NO_2HBr$) C, H, N.

***exo*-2-Amino-7,8-dihydroxybenzonorbornene Hydrobromide (11g).** The mother liquors, after the separation of **11f**, were evaporated to dryness to give a crude sample of **11g**, which was obtained as an amorphous solid: yield 1.68 g (28.0%); ^{1}H NMR (D_2O) τ 3.16 (2 H, "s", 2 aromatic H), 6.08 (1 H, m, C-4 H), 6.46 (1 H, m, C-1 H), 6.27–6.77 (1 H, m, C-2 H), 7.95 (4 H, m, C-3 H and C-9 H); t_R = 16.57 min contaminated with a small amount (~5–8%) of **11f**. Attempts to crystallize this product were unsuccessful.

***exo*-2-Amino-6,7-dimethoxybenzonorbornene (11c).** Treatment of **9b**[23,30] with mercuric acetate–sodium azide–sodium borohydride, followed by lithium aluminium hydride reduction of the resulting azide as described for the preparation of *exo*-2-amino-5,6- and -7,8-dimethoxybenzonorbornenes, afforded **11c** as a light-yellow oil: yield 6.2 g (71.5%). The half-fumarate salt showed mp 182–186 °C; ^{1}H NMR (D_2O) τ 2.93 and 3.02 (2 H, 2 s, 2 aromatic H), 3.52 (1 H, s, $0.5C_4H_4O_4$), 6.22 (6 H, s, 2 OCH_3), 6.42–6.69 (2 H, m, C-1 H and C-2 H), 6.73–6.98 (1 H, m, C-4 H), 7.93–8.39 (4 H, m, C-9 H and C-3 H). Anal. ($C_{13}H_{17}NO_2 \cdot 0.5C_4H_4O_4$) C, H, N.

***exo*-6,7-Dimethoxy-2-(methylamino)benzonorbornene (11d).** A solution of 11c (3.7 g, 0.017 mol) in formic acid (4.88 g, 98%, 0.1 mol) was heated at 180–190 °C in an open flask for 2 h. The cooled reaction mixture was diluted with water and extracted with ether (3 × 25 mL). The combined ether extracts containing the intermediate *N*-formyl derivative were washed with dilute hydrochloric acid and water, dried, and added dropwise to a suspension of lithium aluminium hydride in dry ether (9.0 g in 75 mL, 0.024 mol). After complete addition, the mixture was heated under reflux for 6 h. Excess lithium aluminium hydride was decomposed by the addition of water (15.0 mL), aqueous NaOH (20% w/v, 10.0 mL), and then water (45.0 mL). The clear ethereal supernatant was decanted, and the residue was washed with ether (2 × 50 mL). The combined ether solutions were dried, filtered, and evaporated to dryness to give **11d** as an oil: yield 3.72 g (94%). The fumarate salt had mp 172–175 °C; ^{1}H NMR (D_2O) τ 2.88–3.15 (2 H, 2 s at τ 2.99 and 3.08, 2 aromatic H), 3.40 (2 H, s, $C_4H_4O_4$), 6.25 (6 H, s, 2 OCH_3), 6.35–6.54 (1 H, m, C-1 H), 6.47–6.70 (1 H, m, C-4 H), 6.80–7.40 (1 H, m, C-2 H), 7.26 (3 H, s, NCH_3), 8.00–8.35 (4 H, m, C-9 H and C-3 H). Anal. ($C_{14}H_{19}NO_2 \cdot C_4H_4O_4$) C, H, N.

***exo*-6,7-Dimethoxy-2-(dimethylamino)benzonorbornene (11e).** To a solution of 11c (3.2 g, 0.015 mol) in formic acid (6.9 g, 98%, 0.015 mol) was added formaldehyde solution (4.72 g, 37%, 0.06 mol). The mixture was stirred and heated at 120 °C for 18 h. The cooled reaction mixture was diluted with water (15.0 mL), washed with ether, basified, and extracted with ether (2 × 25 mL). The combined ether extracts were dried, filtered, and evaporated to dryness to give 11e: yield 3.05 g (85%). The fumarate salt showed mp 179–184 °C; ^{1}H NMR (D_2O) τ 2.99–3.20 (2 H, 2 s at τ 3.05 and 3.16, 2 aromatic H), 3.42 (2 H, s, $C_4H_4O_4$), 6.26 (3 H, s, OCH_3), 6.30 (3 H, s, OCH_3), 6.20–6.45 (1 H, m, C-1 H), 6.55–6.80 (1 H, m, C-4 H), 6.94–7.28 (1 H, m, C-2 H), 7.02 (3 H, s, NCH_3), 7.18 (3 H, s, NCH_3), 8.05–8.38 (4 H, m, C-3 H and C-9 H). Anal. ($C_{15}H_{21}NO_2 \cdot C_4H_4O_4$) C, H, N.

***exo*-2-Amino-6,7-dihydroxybenzonorbornene Hydrobromide (11h).** Compound 11c (1.5 g, 0.007 mol) was dissolved in aqueous HBr (48% v/v, 30 mL), and the solution was heated at 125–130 °C under nitrogen for 1.25 h. The resulting solution was evaporated under vacuum to one-third its original volume and allowed to stand at ambient temperature for 8 h. During this time, a crystalline deposit formed, which was filtered at the pump and recrystallized from an ethanol–ether solution to give the hydrobromide salt of **11h** (1.25 g, 66.8%): mp 233–238 °C dec; ^{1}H NMR (D_2O) τ 3.05–3.25 (2 H, 2 s at τ 3.11 and 3.20, 2 aromatic H), 6.52–6.73 (2 H, m, C-1 H and C-2 H), 6.75–7.00 (1 H, m, C-4 H), 8.12–8.29 (4 H, m, C-9 H and C-3 H); ^{13}C NMR δ (D_2O) 143.36, 142.56, 141.54 and 137.14 (C-6, C-7, C-4a, and C-8a), 111.83, 110.96 (C-5 and C-8), 53.66 (C-2), 48.10 (C-1), 46.05 (C-3), 43.63 (C-4), 35.73 (C-9). Anal. ($C_{11}H_{13}NO_2 \cdot HBr$) C, H, N.

***exo*-6,7-Dihydroxy-2-(methylamino)benzonorbornene Hydrobromide (11i).** Compound **11d** was treated as described previously for the O-demethylation of 11c to give **11i**: 81% yield; mp 156–161 °C dec; ^{1}H NMR (D_2O) τ 2.98–3.23 (2 H, 2 s at 3.08 and 3.15, 2 aromatic H), 6.38–6.57 (1 H, m, C-1 H), 6.55–6.86 (1 H, m, C-4 H), 6.89–7.40 (1 H, m, C-2 H), 7.20 (1 H, s, NCH_3), 8.00–8.45 (4 H, m, C-9 H and C-3 H). Anal. ($C_{12}H_{15}NO_2 \cdot HBr$) C, H, N.

***exo*-6,7-Dihydroxy-2-(dimethylamino)benzonorbornene Hydrobromide (11j).** Compound 11e was treated as described previously for the O-demethylation of 11c to give **11j**: 86% yield; mp 175–192 °C dec; ^{1}H NMR (D_2O) τ 3.00–3.16 (2 H, 2 s at τ 3.05 and 3.13, 2 aromatic H), 6.23–6.36 (1 H, m, C-1 H), 6.48–6.66 (1 H, m, C-4 H), 6.81–7.25 (1 H, m, C-2 H), 6.96 (3 H, s, NCH_3), 7.10 (3 H, s, NCH_3), 7.97–8.30 (4 H, m, C-3 H and C-9 H). Anal. ($C_{13}H_{17}NO_2 \cdot HBr$) C, H, N.

***exo*-2-Hydroxy-6,7-dimethoxybenzonorbornene Formyl Ester (12a).** A solution of 6,7-dimethoxybenzonorbornadiene (**9b**;[23] 30.0 g, 0.15 mol) in formic acid (98%, 26.8 g, 0.57 mol) was heated under reflux for 5 h. The cooled reaction mixture was diluted with water (200 mL) and extracted with diethyl ether (2 × 100 mL). The combined ether extracts were washed with dilute sodium bicarbonate (4 × 50.0 mL), dried, filtered, and evaporated to dryness. Recrystallization of the residue from petroleum ether (bp 30–40 °C) afforded **12a**: yield 34.3 g (92.2%); mp 85–87 °C; IR ν_{max} (Nujol) 1710 (s) cm^{-1}; ^{1}H NMR (carbon tetrachloride) τ 1.95 (1 H, s, OCOH), 3.13 and 3.22 (2 H, 2 s, C-5 H and C-8 H), 5.07–5.48 (1 H, m, C-2 H), 6.20 (3 H, s, OCH_3), 6.23 (3 H, s, OCH_3), 6.56–6.90 (2 H, m, C-1 H and C-4 H), 7.95–8.46 (4 H, m, C-3 H and C-9 H); mass spectrum, *m/e* 248 (M^+) and 109 (base). Anal. ($C_{14}H_{16}O_4$) C, H.

***exo*-2-Hydroxy-6,7-dimethoxybenzonorbornene (12b).** A solution of *exo*-2-hydroxy-6,7-dimethoxybenzonorbornene formyl ester (**12a**; 23.7 g, 0.096 mol) in dry diethyl ether (75.0 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (30.0 g, 0.79 mol) in dry diethyl ether (300 mL). After complete addition the mixture was heated under reflux for 2 h and stirred at room temperature overnight. Excess lithium aluminium hydride was decomposed by the dropwise addition of water (30.0 mL), NaOH solution (20% w/v, 22.0 mL), and water (30.0 mL). The ethereal supernatant was decanted, and the residue was washed with diethyl ether (2 × 50.0 mL). The combined ether solutions were dried, filtered, and evaporated to dryness, and recrystallization of the residue from diethyl ether–/hexane afforded **12b**: yield 19.5 g (88.6%); mp 87–89 °C (lit.[24] 88–89 °C); IR ν_{max} (Nujol) 3660–3880 (br s) cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 3.20 and 3.26 (2 H, 2 s, C-5 H and C-8 H), 6.22 (6 H, s, 2 OCH_3), 5.98–6.25 (1 H, m, C-2 H), 6.70–6.95 (2 H, m, C-1 H and C-4 H), 7.60–7.90 (1 H, m, OH, D_2O replaceable), 7.92–8.49 (4 H, m, C-3 H and C-9 H); mass spectrum, *m/e* 220 (M^+ and base).

6,7-Dimethoxybenzonorbornen-2-one (13). A solution of *exo*-2-hydroxy-6,7-dimethoxybenzonorbornene (**12b**; 25.0 g, 0.114 mol), *p*-benzoquinone (14.4 g, 0.133 mol), and aluminium *tert*-butoxide (55.1 g, 0.224 mol) in anhydrous benzene (1.0 L) was stirred and heated under reflux for 2 days. The cooled reaction mixture was washed with dilute H_2SO_4 (2 × 200 mL) and then dilute NaOH solution (5 × 200 mL). The benzene solution was dried, filtered, and evaporated to dryness, and the residue was recrystallized from diethyl ether/hexane to afford **13**: yield 18.9 g (76.0%); mp 106–111 °C (lit.[23] 106–107 °C); IR ν_{max} (Nujol) 1740 (s) cm^{-1}; ^{1}H NMR (carbon tetrachloride) τ 3.25 (2 H, s, C-5 H and C-8 H), 6.28 (6 H, s, 2 OCH_3), 6.44–6.78 (2 H, m, C-1 H and C-4 H), 7.63–7.88 (2 H, m, C-9 H's), 8.00 and 8.15 (2 H, 2 d, C-3 H's, J = 4.5 Hz); mass spectrum, *m/e* 218 (M^+), 190 (base).

***endo*-2-Amino-6,7-dimethoxybenzonorbornene (14a).** A solution of **13**[24] (4.36 g, 0.018 mol) in formamide (6.0 g, 0.133 mol) was added dropwise to a stirred mixture of formamide (6.0 g, 0.133 mol) and formic acid (98%, 3.75 g, 0.08 mol) preheated to 120 °C. The mixture was heated under reflux for 17 h. The cooled reaction mixture was stripped of excess formamide and formic acid on a rotary evaporator, aqueous HCl was added (50.0 mL, 20% w/v), and heating under reflux was continued for 7 h. The cooled mixture was washed with ether (2 × 15 mL), basified with dilute NaOH solution, and extracted with ether (3 × 20 mL). Evaporation of the ether extracts afforded **14a** as an oil: yield 2.1 g (48.2%). The half-fumarate salt showed mp 174–177 °C; ^{1}H NMR (D_2O) τ 2.80 (2 H, s, C-5 and C-8 H), 3.35 (1 H, s, half-fumarate H), 5.70–6.20 (1 H, m, C-2 H), 6.10 (6 H, s, 2 OCH_3), 6.35 (1 H, m, C-1 H), 6.55 (1 H, m, C-4 H), 7.51 (1 H, m, C-3 exo H), 8.22 (2 H, m, C-9 H's), 8.82 (1 H, m, C-3 endo H). Anal. ($C_{13}H_{17}NO_2 \cdot 0.5C_4H_4O_4$) C, H, N.

***endo*-6,7-Dimethoxy-2-(methylamino)benzonorbornene (14b).** Using the method described for the preparation of **14a**, but substituting *N*-methylformamide for formamide, gave **14b** as an oil: 64.3% yield. The fumarate salt had mp 141–145 °C; ^{1}H NMR (D_2O) τ 2.95 and 3.00 (2 H, 2 s, 2 aromatic H), 3.45 (2 H, s, fumarate H's), 5.92–6.52 (1 H, m, C-2 H), 6.22 (6 H, s, 2 OCH_3), 6.38 (1 H, m, C-1 H), 6.70 (1 H, m, C-4 H), 7.38 (3 H, s,

(30) H. L. Goering, personal communication.

NCH_3), 7.58 (1 H, m, C-3 exo H), 8.25 (2 H, m, C-9 H's), 8.95 (1 H, m, C-3 endo H). Anal. ($C_{14}H_{19}NO_2 \cdot C_4H_4O_4$) C, H, N.

***endo*-6,7-Dimethoxy-2-(dimethylamino)benzonorbornene (14c).** A solution of 13 (3.27 g, 0.013 mol) in *N,N*-dimethylformamide (7.3 g, 0.1 mol) was added dropwise to a stirred mixture of formic acid (98%, 2.8 g, 0.06 mol) and *N,N*-dimethylformamide (7.3 g, 0.1 mol) preheated to 120 °C. The mixture was heated under reflux for 17 h, cooled, acidified with aqueous HCl (10% v/v), and washed with ether (1 × 15 mL) and ethyl acetate (1 × 15 mL). The mixture was basified and extracted with ether (2 × 15 mL), and the ether solution was evaporated to give 14c as an oil: yield 3.55 g (95.9%). The fumarate salt gave mp 178–180 °C; ^{1}H NMR (D_2O) τ 2.81 and 2.90 (2 H, 2 s, 2 aromatic H), 3.32 (2 H, s, fumarate H's), 6.00–6.45 (2 H, m, C-2 H and C-1 H), 6.15 (6 H, s, 2 OCH_3), 6.45–6.80 (1 H, m, C-4 H), 7.03 and 7.25 [6 H, 2 s, $N(CH_3)_2$], 7.20–7.75 (1 H, m, C-3 exo H), 8.15 (2 H, m, C-9 H's), 8.81 (1 H, m, C-3 endo H). Anal. ($C_{15}H_{21}NO_2 \cdot C_4H_4O_4$) C, H, N.

***endo*-2-Amino-6,7-dihydroxybenzonorbornene Hydrobromide (14d).** O-Demethylation of the amine 14a according to the method described for 11c gave 14d: 78% yield; mp 230 °C dec; ^{1}H NMR (D_2O) τ 3.02 (2 H, s, 2 aromatic H), 5.73–6.30 (1 H, m, C-2 H), 6.41 (1 H, m, C-1 H), 6.60 (1 H, m, C-4 H), 7.10–7.81 (1 H, m, C-3 exo H), 8.13 (2 H, m, C-9 H), 8.77 and 9.00 (1 H, pair of m, C-3 endo H). Anal. ($C_{11}H_{13}NO_2 \cdot HBr$) C, H, N.

***endo*-6,7-Dihydroxy-2-(methylamino)benzonorbornene Hydrobromide (14e).** *O*-Demethylation of the amine 14b according to the method described for 11c gave 14e: 73% yield; mp 204–208 °C dec; ^{1}H NMR (D_2O) τ 3.5 and 3.9 (2 H, 2 s, 2 aromatic H), 6.22–6.70 (1 H, m, C-2 exo H), 6.71 (1 H, m, C-1 H), 7.00 (1 H, m, C-4 H), 7.75 (3 H, s, NCH_3), 7.89 (1 H, m, C-3 exo H), 8.52 (2 H, m, C-9 H's), 9.21 (1 H, m, C-3 endo H). Anal. ($C_{12}H_{15}NO_2 \cdot HBr$) C, H, N.

***endo*-6,7-Dihydroxy-2-(dimethylamino)benzonorbornene Hydrobromide (14f).** O-Demethylation of the amine 14c according to the method described for 11c gave 14f: 69% yield; mp 215–225 °C dec; ^{1}H NMR (D_2O) τ 2.85 and 2.95 (2 H, 2 s, 2 aromatic H), 5.81–6.41 (2 H, m, C-2 H and C-1 H), 6.40–6.71 (1 H, m, C-4 H), 7.01 and 7.20 [6 H, 2 s, $N(CH_3)_2$], 7.44 (1 H, m, C-3 exo H), 8.13 (2 H, m, C-9 H's), 8.80 (1 H, m, C-3 endo H). Anal. ($C_{13}H_{17}NO_2 \cdot HBr$) C, H, N.

Pharmacology. Behavioral studies were carried out using male Sprague–Dawley rats, 250–300 g, and male albino B.K.W. mice 20–25 g. The potential to cause a locomotor hyperactivity and/or stereotyped behavior was assessed in the rat following bilateral injections of the test compound or reference agent (dopamine) into the nucleus accumbens.[28] Hyperactivity was measured in photocell cages, light beam interruptions being recorded every 5 min for at least 5 h. The presence of stereotyped sniffing, head and/or limb movements, gnawing, biting, or licking was noted.[29] Nialamide (Sigma Chemical Co.), 100 mg/kg, was given intraperitoneally 2 h before the intra-accumbens injection. All compounds were prepared for intra-accumbens injection in distilled water containing 0.1% sodium metabisulfite, with the addition of minimum quantities of *N,N*-dimethylformamide. In all experiments, control animals received intra-accumbens solvent. At least six rats were used per treatment and were used on one occasion only. A subsequent histological examination confirmed that all injections were made into the area of the nucleus accumbens. Climbing behavior in mice, measured in cages lined with wire mesh, was assessed using a "climbing index".[31] All compounds were prepared for subcutaneous administration by dissolving in the minimal quantity of hydrochloric acid and making up to volume with a 0.1% solution of sodium metabisulfite.

For the receptor-labeling experiments, rats were killed by cervical dislocation, and their brains were rapidly removed. The striata were dissected out over ice, homogenzied (Polytron PT-10, setting 5 for 10 s) in 100 volumes of ice-cold 15 mM Tris-HCl buffer (pH 7.4), and centrifuged twice at 50000*g* for 10 min with resuspension in fresh buffer for incubation at 37 °C for 12 min. The homogenate was centrifuged twice and prepared to give a final tissue suspension of 10 mg/mL. Binding was determined by incubating (25 °C, 20 min) 500 μL of tissue suspension (containing approximately 250 μg of protein) with 1.0 nM [^{3}H]ADTN (2-amino-6,7-dihydroxytetralin; 35 Ci/mmol, N.E.N.) or [^{3}H]NPA (*N*-*n*-propylnorapomorphine; 68 Ci/mmol, N.E.N.), 200 μL, in the presence of varying concentrations of cold ADTN, dopamine, or benzonorbornene derivatives, the total incubate volume being 1.1 mL. Samples were rapidly filtered under vacuum through Whatman GF/B filters and washed with two 5-mL rinses of ice-cold buffer. Radioactivity was measured by liquid scintillation spectrometry, and protein was determined by the method of Lowry et al.[32]

Acknowledgment. We are grateful to the Pharmaceutical Society of Great Britain and the Wellcome Research Foundation for grants to P.B. and the Parkinson's Disease Society of the United Kingdom for support of V.N.

(31) B. Costall, R. J. Naylor, and V. Nohria, *Eur. J. Pharmacol.*, **50**, 39 (1978).

(32) D. J. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, *J. Biol. Chem.*, **193**, 265 (1951).