the crystal y axis). The list of contacts are given in Tables I and II. Table III lists meta contacts for an iodinated biphenyl system (numbered as in Chart I) calculated on the basis of the coordinates for the 2,2',4,4',6,6'-HCB.

Binding Assays. The thyroxine reference standard and all analogues were dissolved in methanol in the concentration range from 0.1 to 10 μM and were stored at 4 °C. The stock solution of TBPA contained 0.127 mg/mL of the protein in imidazole acetate buffer. The stock solution was further diluted to 200 nM prior to use. No change of the binding capacity of the TBPA stock solution due to storage was observed. However, the 200 nM solution quickly lost binding capacity and had to be prepared immediately prior to use. To characterize the affinity of L-T_4 for the high affinity binding site of TBPA, Scatchard analysis was carried out. In contrast to the procedure of the competitive binding assay, the amount of [^{125}I]-L-T_4 was varied together with the increasing concentration of unlabeled T_4 (1.9–940 nM) to achieve a constant specific activity (320 pCi/nmol). The TBPA concentration was 10 nM. Incubation was carried out at 25 °C. Nonspecific binding was measured by adding excess (940 nM) unlabeled L-T_4.

A binding assay using the gel filtration procedure described by Somack et al.[24] was used to measure the ability of various halogenated biphenyls and other analogues to displace [^{125}I]-L-T_4 from the high-affinity TBPA binding site. The assay mixture contained imidazole acetate buffer, 10 nM TBPA, 0.57 nM [^{125}I]-L-T_4 with a total activity of <0.25 μCi, and 1–5 μL of unlabeled compounds in methanol, which were added with a Hamilton syringe. The final concentration of the unlabeled compounds was in the range of 10^{-10} to 10^{-7} M. The final volume of the assay mixture was 0.5 mL. The methanol concentration was held at 1% for every assay mixture. A 20% decrease of the binding capacity of TBPA was observed with this concentration. After incubation at 25 °C for 1 h the mixtures were quickly cooled to 4 °C, and a 0.4-mL portion was filtered at 4 °C on Sephadex G-25 minicolumns (bed volume ≅2 mL). With an additional volume of 1.2 mL, the protein-bound [^{125}I]-L-T_4 and analogue compound respectively were removed from the column. Slight nitrogen pressure was applied to achieve an elution time for the first fraction of 40–60 s, minimizing the dissociation of the complex. The first fraction was followed by a 1.8-mL fraction that contained free radioactive iodide. Free hormone binds tightly to the gel matrix and does not elute in the volume used. Therefore the remaining gel that was saved contained the total amount of unbound [^{125}I]-L-T_4 (third fraction). The amount of radioactive L-T_4 in the different fractions was measured with a Packard Prias Auto Gamma Counter (60% efficiency).

The amount of total [^{125}I]-L-T_4 binding (referred to as total binding) was determined by incubation with [^{125}I]-L-T_4 alone (no unlabeled competitors added) and was used as reference standard. Two standards were run with each competitor tested. Competitive binding curves were obtained by plotting the percentage of total binding against increasing concentrations of competitor. The concentration of L-T_4 where 50% of total binding was achieved gave the binding potency of L-T_4 and was assigned a value of 100. The binding potency of each analogue relative to that of thyroxine was calculated as follows:

$$\text{analogue binding potency} = \frac{\text{concn of } T_4 \text{ at 50\% total binding}}{\text{concn of analogue at 50\% total binding}} \times 100$$

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Registry No. 1, 51-48-9; 2, 300-30-1; 3, 6893-02-3; 4, 5817-39-0; 5, 100837-36-3; 6, 91821-67-9; 7, 92-52-4; 8, 15968-05-5; 9, 33284-52-5; 10, 32774-16-6; 11, 1137-59-3; 12, 5335-24-0; 13, 14962-28-8; 14, 4400-06-0; 15, 67651-34-7; 16, 100702-98-5; 17, 13049-13-3; 18, 63527-88-8; thyroxine, 51-48-9.

Drug Design via Pharmacophore Identification. Dopaminergic Activity of 3*H*-Benz[*e*]indol-8-amines and Their Mode of Interaction with the Dopamine Receptor

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The design and synthesis of a series of 3*H*-benz[*e*]indol-8-amines are described. Two of the compounds are potent, orally active dopaminergic agents as established by their ability to induce contralateral turning in rats with unilateral 6-hydroxydopamine-induced lesions of the nigrostriatal pathway, to induce ambulation in rats rendered akinetic by bilateral injections of 6-hydroxydopamine into the anterolateral hypothalamus, and to antagonize reserpine-induced catalepsy in mice. The dopamine agonist activity of the 3*H*-benz[*e*]indol-8-amines establishes that a pyrrolo ring and a phenolic hydroxyl group can interact similarly with the dopamine receptor and provides evidence for the existence of a hydrogen-bond acceptor nucleus on the dopamine receptor macromolecule that is involved in the behavioral manifestations of dopamine agonists.

We demonstrated several years ago[1] that the dopamine (DA) agonist (−)-apomorphine (1) and conformer B of the DA antagonist (+)-butaclamol (2) possess a common pharmacophore, namely a phenyl ring with its centrum situated 5.1 Å from a nitrogen atom and lying ~1 Å above the plane in which the nitrogen is situated.

This pharmacophore has since been found, by modeling studies, to be present in a wide range of DA agonists and antagonists,[2] including bromocriptine. When the X-ray-derived structures of apomorphine and the bromocriptine nucleus 3 are compared via superpositioning of their common pharmacophores[3] (Figure 1), it is evident that the

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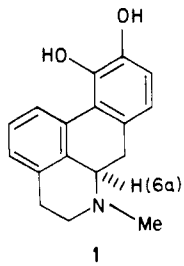

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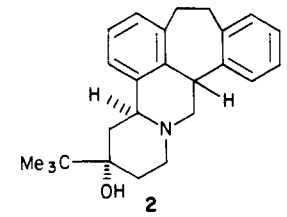

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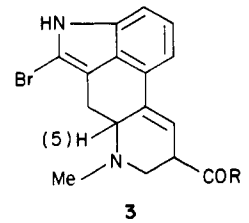


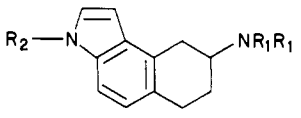
3

pyrrolo NH group of bromocriptine is nearly coincident with the phenolic hydroxyl group of apomorphine at position 11. This *m*-hydroxyl group is essential for DA agonist activity and, when present alone on the apomorphine skeleton, gives rise to a compound, 10-deshydroxyapomorphine, which has a high level of dopaminergic activity.[4,5]

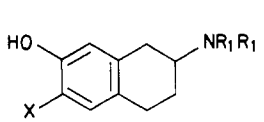
This observation suggests that bromocriptine's indolic NH serves as a surrogate for the *m*-hydroxyl of apomorphine. The same conclusion has been independently arrived at by Cannon et al.[6,7] and by Camerman and Camerman.[8] The common pharmacopohore identified in both bromocriptine and apomorphine is constrained within their phenylethylamine moieties (see Figure 1). This is in sharp contrast to the proposal of Nichols,[9] subsequently adopted by Bach et al.[10], that the pyrroloethylamine moiety of bromocriptine is the pharmacophore that permits recognition by the DA receptor.

To examine the hypothesis that at the DA receptor, a phenolic hydroxyl group, which is essential for agonist activity, can be replaced by a pyrrolo group, we have synthesized and evaluated, in vivo, the DA agonist properties of the 3*H*-benz[*e*]indol-8-amines **4–7**, the first representatives of this novel ring system.

Compound **4** is the pyrrolo analogue of the 7-hydroxy-(dipropylamino)tetralin **8**,, the 2*R* enantiomer of which possesses dopaminergic properties,[11-13] and **6** is a pyrrolo



4: R_1 = *n*-Pr, R_2 = H
5: R_1 = *n*-Pr, R_2 = Me
6: R_1 = Me, R_2 = H
7: R_1 = R_2 = Me



8: R_1 = *n*-Pr, X = H
9: R_1 = Me, X = OH

analogue of **9**, a presynaptic dopamine agonist.[14] The *N*-methylpyrroles **5** and **7** were prepared to investigate a possible role for the pyrrolo NH groups of **4** and **6** in hydrogen bonding to the DA receptor.

Chemistry

The strategy adopted for the synthesis of the hitherto unknown 3*H*-benz[*e*]indol-8-amine system required the preparation of the 7-methoxy-2-aminotetralins **10** and **11**. Replacement of the methoxy group by an amino group using known methods[15] would afford the 2,7-diaminotetralins **20** and **21**. The required 3*H*-benz[*e*]indol-8-amines could then be constructed by elaborating the 7-amino function into a pyrrolo ring. Discrete steps of the process are shown in Scheme I.

The di-*n*-propylamino intermediate **10** was obtained from 7-methoxy-2-tetralone by hydrogenation of the enamine formed with di-*n*-propylamine, while the dimethylamino derivative **11** was prepared by an Eschweiler–Clarke methylation of 7-methoxy-2-aminotetralin[16].

The methoxy groups of **10** and **11** were replaced by amino groups following the method elaborated by Wentland et al.[15] Thus, sodium in ammonia reductions of **10** and **11** gave the enol ethers **12** and **13**, which on acid hydrolysis afforded mixtures of conjugated and unconjugated ketones **14** and **15**. They were directly converted to the oximes **16** and **17**, which were obtained as mixtures of isomers. Semmler–Wolff dehydration of the oximes with acetyl chloride or acetic anhydride afforded the acetamido derivatives **18** and **19**, which were subjected to acid hydrolysis to give the anilines **20** and **21**.

The desired 3*H*-benz[*e*]indole derivatives **4** and **5** were obtained from the anilines **18** and **19** by using the Sandmeyer isatin synthesis,[17] via the isonitrosoacetanilides **22** and **23**, followed by lithium aluminum hydride reduction of the isatins **24** and **25**. The indolic nitrogens of **4** and **5** were methylated with methyl iodide and sodamide to afford the methyl analogues **6** and **7**.

Pharmacology

The indolamines were investigated in three animal models that reflect a compound's ability to exert DA agonist effects at central DA receptors and thus predict therapeutic potential as an antiparkinson drug. For the purpose of comparison, bromocriptine, a known DA agonist, was also evaluated.

In the first model the compounds were tested for their ability to induce contralateral rotations in unilaterally 6-hydroxydopamine- (6-OHDA-) lesioned rats. Such behavior results from the differential sensitivity of the

(3) A reviewer has suggested that conclusions derived from the superpositioning of apomorphine (1) and the ergoline nucleus (**3**) (Figure 1) are not valid because of opposite chiralities at the 6a and 5 positions, respectively. The superpositioning shown in Figure 1 is based upon the presence in each ligand, of the same pharmacophore, which is defined in terms of the relative positions of a phenyl ring and a nitrogen atom. The intervening carbon atms, with their unique chirality, are not a part of the pharmacophore but serve as essential structural elements in maintaining the relative positions of the phenyl rings and the nitrogen atoms.

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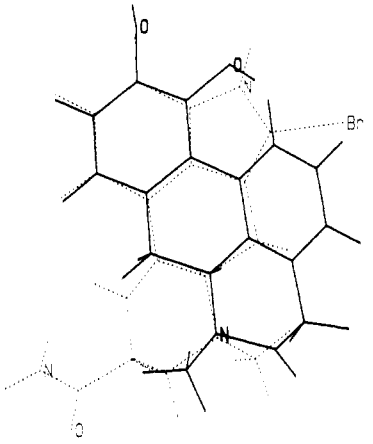

Figure 1. Superpositioning of the bromocriptine nucleus and apomorphine.

Scheme I

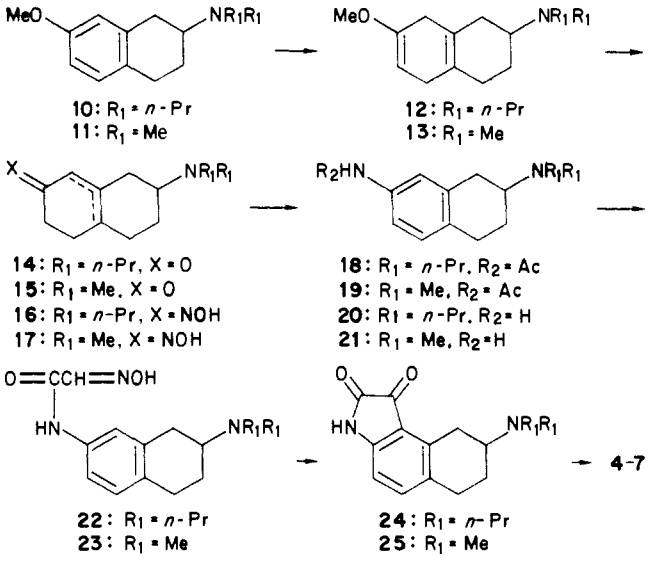

Table I. Rotational Behavior Induced by 3*H*-Benz[*e*]indol-8-amines in Rats with Unilateral 6-OHDA-Induced Lesions of the Nigrostriatal DA Pathway

compd	dose, mg/kg	total no. of contralateral turns: mean ± SEM
4	5 po	4843 ± 408
5	2.5 sc	<300
6	5 po	3256 ± 1117
	10 po	4947 ± 1657
	10 sc	4540 ± 1216
bromocriptine	5 po	1805 ± 232

postsynaptic dopamine receptors in the denervated and innervated striata.[18] Table I shows that compounds **4** and **6** produced vigorous contralateral turning characteristic of dopamine agonists. At the dose of 5 mg/kg po both **4** and **6** appeared more potent than bromocriptine, while at 2.5 mg/kg sc **5**, an analogue of **4** with the indolic nitrogen methylated, induced less than 10% of the number of turns elicited by **4**. At doses of 10 mg/kg, either orally or subcutaneously, compound **6** gave similar results, suggesting that it was well absorbed after oral administration.

In a subsequent experiment, stores of endogenous DA were depleted by prior treatment with α-methyl-*p*-tyrosine. Compound **4** still produced a vigorous turning behavior

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Table II. Effect of Pretreatment with α-Methyl-*p*-tyrosine on the Rotational Behavior Induced by **4** (5 mg/kg sc) in Rats with Unilateral 6-OHDA-Induced Lesions of the Nigrostriatal DA Pathway

pretreatment,[a] mg/kg, ip	total no. of contralateral turns: mean ± SEM	% dec
vehicle	4165 ± 670	0
α-MPT (2 × 50)	3460 ± 404	17

[a] Two injections of α-MPT were made at 4-h intervals, and compound **4** was injected 1 h after the second injection.

Table III. Comparative Ability of 3*H*-Benz[*e*]indol-8-amines to Antagonize 6-OHDA-Induced Akinesia in Rats

compd	dose, mg/kg sc	cumulative ambulation score:[a] mean ± SEM
4	2.5	287 ± 109
5	10	<100
6	2.5	378 ± 83
7	30	inactive
bromocriptine	10	112 ± 23

[a] The cumulative ambulation score represents mean ± SEM values, accumulated during six 2-min observation periods.

Table IV. Comparative Ability of 3*H*-Benz[*e*]indol-8-amines to Reverse Reserpine-Induced Catalepsy in Mice

compd	ED_{50}, mg/kg sc: mean ± SEM	compd	ED_{50}, mg/kg sc: mean ± SEM
4	2.3 ± 0.6	7	>30
5	5.0 ± 1.4	bromocryptine	2.3 ± 0.5
6	5.8 ± 1.0		

in such animals (Table II), indicating that it acted directly on DA receptors and did not produce an indirect effect via the release of endogenous DA from nerve endings. Previously we had used a similar experimental arrangement to demonstrate that ciladopa, another DA agonist from our laboratories, also exerted a direct effect on DA receptors.[19]

In the second model, the compounds were evaluated for their ability to induce locomotion in rats rendered akinetic by bilateral anterolateral hypothalmic injections of 6-OHDA.[20] The results displayed in Table III concur with those produced in the previous model, for compounds **4** and **6** produced locomotion exceeding that induced by bromocriptine. As in the first test, compounds **5** and **7** had little or no effect.

In the third model, compounds were compared for their ability to antagonize the catalepsy produced in mice by the prior injection of reserpine.[21] The results are summarized in Table IV. Compounds **4**–**6** all reversed the reserpine-induced catalepsy after subcutaneous administration, indicating their ability to act as agonists at central DA receptors. The activity of **4** and **6** lasted for several hours, while that of **5** was of short duration (results not shown). Compound **7** was inactive in this test.

Discussion

The results presented demonstrate that the 3*H*-benz[*e*]indoles **4** and **6** induced contralateral turns in rats with

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a unilaterally degenerated nigrostriatal pathway, induced ambulation in rats that were akinetic due to degeneration of dopaminergic pathways that maintain locomotion, and antagonized reserpine-induced catalepsy in mice. Such a profile is characteristic of DA agonists.[22,23]

The potent dopaminergic effects of these 3*H*-benz[*e*]-indoles suggest that the central DA receptor does not distinguish between a phenolic hydroxyl group and a pyrrolo ring. This finding is of both practical and theoretical value.

Thus, dopaminergic agents that contain phenolic hydroxyl groups frequently exert little pharmacological effect because they are poorly absorbed on oral administration, are incapable of crossing the blood–brain barrier, or have a short duration of action due to rapid metabolism via conjugation. The difference between a phenol and an indole in absorption from the gut, and in organ/tissue distribution, would be expected to be markedly affected by their lipophilicities. The partition coefficients of the 3*H*-benz[*e*]indole **4** and the phenol **8** have been determined in an 1-octanol buffer system at pH 7.4, and values of 109 and 43, respectively, were found. This difference in physicochemical properties provides a basis for the suggestion that the unfavorable pharmacokinetic properties associated with the presence of phenolic hydroxyl groups would not be expected to be manifested in the corresponding pyrrolo analogue.

The demonstrated equivalency of the pyrrolo ring and the phenolic hydroxyl group provides also an insight into the probable role that these groups have in the interaction of a dopaminergic agent with the DA receptor. A hydroxyl group can function equally well as a hydrogen-bond donor or acceptor. When it functions as a donor, because of free rotation about the C–O bond, the acceptor nucleus can lie (for a linear H bond) anywhere on the periphery of the base of a cone with the donor oxygen atom situated at the apex. The lone pair on the pyrrole nitrogen cannot participate in a H bond because of the aromaticity of the pyrrolo ring, and the relative inactivity of the *N*-methyl pyrroles **5** and **7** provides compelling evidence that the pyrrolo NH group acts as a H-bond donor in eliciting the receptor response. When the pyrrolo NH participates in H-bond formation, it acts, in effect, as the equivalent of a conformationally rigid hydroxyl group, with respect to the directional vector of its O–H bond.

Earlier, we described our approaches to mapping features of the DA receptor and identified an aromatic binding site, a nitrogen location site, and an accessory lipophilic binding site.[24,25] From this model and the ideas developed herewith (see below), it should be possible to gain some insight into the region of the receptor macromolecule where the acceptor nucleus (or nuclei) that participates in H-bond formation with dopaminergic ligands is located.

Figure 2 shows how the 2*R* enantiomer of the 3*H*-benz[*e*]indole **4** and the bromocriptine nucleus **3** fit the DA receptor model via their common pharmacophore. Both dopaminergic ligands possess pyrrolo NH groups as the sole H-bond donors. The choice of the 2*R* enantiomer for modeling studies was based on the observation (see below) that this is the enantiomer that can form an H bond with the same acceptor nucleus as bromocriptine. This

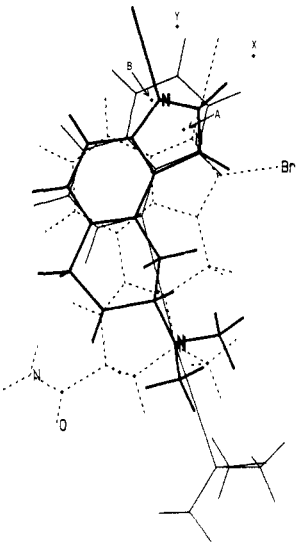

Figure 2. Fit of compound 4 (thick lines) and the bromocriptine nucleus (dashed lines) to the DA receptor model (thin lines).

observation also leads to the prediction that the activity of racemic **4** is due to the *R* enantiomer.

The 3*H*-benz[*e*]indoles **4** and **6** share the same aminotetralin moiety as does (2*R*)-7-hydroxy(dipropylamino)-tetralin (**8**), the nucleus of the latter being a fragment of apomorphine. However, the aminotetralin moiety in **8** is conformationally more mobile than it is when constrained within the apomorphine molecule, wherein it has two additional sp^2 carbon atoms. The conformation of the aminotetralin moiety in the 3*H*-benz[*e*]indole **4** that was used for fitting to the receptor model was chosen on the basis that it was a low-energy conformer that, when used for comparing the fit of the (+) and (−) enantiomers of 5- and 7-hydroxy(dipropylamino)tetralins to the receptor model, was in concordance with the enantiospecificity observed with these DA agonists.[26]

It is assumed that both ligands **3** and **4** in Figure 2 exhibit dopaminergic activity by virtue of their ability to participate in H-bond formation with an acceptor nucleus on the receptor macromolecule. The donor nuclei are not coincident, however; rather, they are separated by ~1.8 Å, and the directional vectors of their H bonds would diverge by almost 30°. It is not possible to define a unique locus for a common acceptor nucleus that could participate in H-bond formation with each of the ligands. For example, if an acceptor nucleus were situated at point X, the only point that is at optimum H-bonding distance (3.0 Å) from both pyrrolo nitrogens, it could form a quasi-linear H bond with the pyrrolo nitrogen of bromocriptine, but not with that of the 3*H*-benz[*e*]indole.

However, these two ligands could still form H bonds with the same acceptor nucleus if that nucleus were part of a conformationally mobile side chain of an amino acid moiety in a peptide chain. For example, if the CH_2 group of a serine side chain were centered at position Y (see Figure 2), the attached oxygen would be able to assume any position on the circle with center Y and a radius of 1.43 Å, equivalent to the C–O bond length. In that circumstance, the same acceptor nucleus could form virtually collinear H bonds of optimal 3-Å length, both with bromocriptine and with the 3*H*-benz[*e*]indole. Studies with other dopaminergic agents containing H-bonding pyrrolo groups would be needed to establish rigorously the location of the acceptor nucleus tentatively identified above.

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The DA receptor model shown in Figure 2 (thin lines) was derived from an analysis of the DA antagonists of the butaclamol/isobutaclamol series,[24,25] and it represents discrete binding sites on the receptor macromolecule. It was concluded from that study[25] that the site that binds the phenyl ring of dopamine was at least as large as two adjacent and coplanar benzene rings. Inspection of the fit of compound 4 to the receptor model reveals that its benzene ring binds to the α region of the aromatic binding site[25] and its pyrrole ring is located over the β region of the same site. It was the binding of a phenyl ring of isobutaclamol to the β region of the aromatic binding site via a $\pi-\pi$ interaction that was deemed responsible for its high affinity for the DA receptor.[25] In the interaction of the 3*H*-benz[*e*]indole 4 with the DA receptor, the pyrrole ring functions as an exceptionally good surrogate for the hydroxyl group because it not only retains hydrogen-bond donor capacity but can also participate in a $\pi-\pi$ interaction with the β region of the aromatic binding site.

The mode of interaction of bromocriptine and of the benz[*e*]indole 4 with the DA receptor is in general agreement with the models proposed by McDermed et al.,[27] Seiler and Markstein,[13] and Neumeyer et al.[28] with the difference, however, that while these authors stress the importance of a binding site for a phenolic hydroxyl group, the present work places more weight on the location and directional vector of H-bond donor groups that can interact with a common acceptor nucleus. In contrast, the model recently described by Grol et al.,[29] which has a binding site to accommodate the hydroxyl groups of (-)-**5**- and (+)-7-hydroxy(dipropylamino)tetralin and two binding sites for their nitrogen atoms, is not in concurrence. These two agonists can be readily fitted to the model described herein, as indicated in Figure 2. By using the low-energy conformation identified by Loughney and Treasurywala[26] and superimposing the nitrogens and the aromatic rings, the hydroxyl groups of the (-)-**5**- and (+)-7-hydroxy(dipropylamino)tetralins are situated at points A and B, respectively, and can thus particate in H-bond formation with the same acceptor nucleus with which the benz[*e*]indole 4 and bromocriptine are proposed to interact.

In conclusion, the present study has provided strong support for the concept that a phenolic hydroxyl group and a pyrrolo ring can exert similar functions at the DA receptor site, and it has allowed an analysis of a possible mode of H-bond formation between DA agonists and the DA receptor macromolecule.

Experimental Section

Chemistry. Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 225 spectrophotometer. ^{1}H NMR spectra were determined in the indicated solvent on a Varian CFT-20 instrument with tetramethylsilane as internal standard. Chemical shifts are given in δ units, and coupling constants are in Hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained on an LKB-9000S spectrometer and ultraviolet spectra on a Zeiss DMR-21 spectrophotometer. C, H, N analyses were measured on a Perkin-Elmer 240 analyzer. Silica gel 60 F-254 (Merck) was used for thin-layer chromatography (TLC). Partition coefficients were determined by the method of Leo et al.[30] Concentrations of compounds in the aqeuous and octanol phases were determined by HPLC.

***N*,*N*-Dipropyl-7-methoxy-1,2,3,4-tetrahydro-2-naphthylamine (10) Hydrochloride.** A solution of 7-methoxy-1,2,3,4-tetrahydro-2(1*H*)-naphthalenone[16] (35.1 g, 0.20 mol), di-*n*-propylamine (109 mL, 0.80 mol), and *p*-toluenesulfonic acid monohydrate (34 g, 0.2 mol) in dry benzene (1 L) was refluxed under nitrogen with continuous water removal for 48 h until an aliquot showed little or no carbonyl in the infrared spectrum. At this point, the benzene was replaced by ethanol (600 mL, anhydrous) and the solution was transferred to a 2-L Parr bottle to be hydrogenated over PtO_2 (1.0 g) under 2 atm at room temperature for 2.5 h. The solution was filtered through α-floc and concentrated, and benzene was added. The organic solution was made basic with 10% sodium hydroxide and washed with water. The product was extracted with 5% hydrochloric acid, and the solution was made basic with 10% sodium hydroxide to yield the title product that is extracted in ether. After drying and evaporation to dryness, a brown liquid (36.5 g) was obtained. A sample was purified by chromatography through a column of silica gel using 2% methanol–chloroform mixture as eluant. The hydrochloride salt was prepared and crystallized from methanol and ether as a white solid in a hemihydrate form: mp 155–157 °C; IR ($CHCl_3$) 3650 and 3380 (OH), 2400 (NH), 1260 and 1160 cm^{-1} (OCH_3); ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 6 H, J = 6.8), 1.9 (m, 6 H), 2.9 (m, 9 H), 3.75 (s, 3 H), 6.8 (m, 3 H), 10.9 (br s, 1 H). Anal. ($C_{17}H_{29}ClNO_{1.5}$) C, H, N.

***N*,*N*-Dimethyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (11) Hydrochloride.** A mixture of 7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine[16] (35.9 g, 0.203 mol), 98% formic acid (49 mL, 1.30 mol), and 37% formaldehyde (36.9 mL, 0.451 mol) was placed in a 500-mL flask and heated on a steam bath for 1.5 h. The reaction mixture was then concentrated under reduced pressure, neutralized with 10% sodium hydroxide (150 mL), and extracted with ether (3×). The ether extracts were dried and evaporated to give a red oil (41.5 g). To ethereal HCl (110 mL) in a 3-L flask, under nitrogen at 0 °C, was added dropwise a solution of this compound in ether (300 mL). After the mixture was stirred mechanically for 4 h, the pink solid was filtered, washed with ether, and converted back to the pure free base (38.6 g) with 10% sodium hydroxide. A sample of the hydrochloride salt was crystallized from methanol and ether to afford a white solid: mp 222–225°C; IR (Nujol) 2550 (NH), 1260 and 1165 cm^{-1} (OCH_3); ^{1}H NMR ($CDCl_3$, free base) δ 2.35 (s, 6 H), 1.65 (m, 2 H), 2.7 (m, 5 H), 3.7 (s, 3 H), 6.75 (m, 3 H). Anal. ($C_{13}H_{20}NOCl$) H, N; C: calcd, 64.58; found, 63.95.

1,2,3,4,5,8-Hexahydro-7-methoxy-*N*,*N*-dipropyl-2-naphthalenamine (12). A solution of *N*,*N*-dipropyl-7-methoxy-1,2,3,4-tetrahydro-2-naphthylamine (**10**; 17.3 g, 0.066 mol) in tetrahydrofuran (200 mL) and 2-propanol (200 mL) was added with stirring to liquid ammonia (500 mL) supported in a dry ice-2-propanol bath. Sodium (30 g, 1.3 mol) was added in small pieces over 0.5 h. After the blue color disappeared (~2 h), methanol (130 mL) was added and the ammonia was allowed to evaporate overnight after removal of the cooling bath. The residue was diluted with water (1 L) and extracted three times with ether. The ether extracts were dried ($MgSO_4$) and concentrated, giving a yellow solid (13.6 g). It was recrystallized from a mixture of acetone and water to give a white solid: 12.7 g; mp 47–51 °C; IR ($CHCl_3$) 1692, 1664 and 1600 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 6H, J = 7), 1.4 (m, 4 H), 3.50 (s, 3 H), 4.55 (s, 1 H). Anal. ($C_{17}H_{29}NO$) C, H, N.

1,2,3,4,5,8-Hexahydro-7-methoxy-*N*,*N*-dimethyl-2-naphthalenamine (13). A procedure identical with that for making **12** was used for converting **11** (19.3 g, 0.094 mol) into **13** as a brown oil (17.5 g) used as such for the next step: ^{1}H NMR ($CDCl_3$) δ 1.5 (m, 2 H), 2.0 (m, 4 H), 2.3 (s, 6 H), 2.6 (s, 4 H), 2.9 (m, 1 H), 3.55 (s, 3 H), 4.6 (s, 1 H).

***N*-[7-(Dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide (18) Hydrobromide.** A solution of 1,2,3,4,5,8-hexahydro-7-methoxy-*N*,*N*-dipropyl-2-naphthalenamine (**12**; 24.8

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g, 0.094 mol) in a mixture of acetone (415 mL), water (55 mL), and ethereal HCl (207 mL) was stirrd at room temperature for 1.5 h. Then, the solution was basified with sodium carbonate and extracted with ether. The ether extracts were dried ($MgSO_4$) and concentrated, giving crude **14** as a brown oil (20.5 g): IR ($CHCl_3$) 1710 (weak) and 1660 (strong carbonyl), 1620 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) 0.80 (t, J = 7, 6 H), 5.8 (s, 1 H). A solution of **14** (18.4 g, 0.074 mol) and hydroxylamine hydrochloride (22 g, 0.32 mol) in ethanol (211 mL) and pyridine (197 mL) was stirred at room temperature overnight. The mixture was concentrated, dissolved in water, and basified with excess sodium bicarbonate. The organic material was extracted into chloroform, dried ($MgSO_4$), and concentrated to give **16** as a red oil (18.9 g): ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7, 6 H), 5.9 and 6.6 (s, 1 H), 8.5 (br s, 1 H). Acetic anhydride (15.2 mL, 0.15 mol) was added to a stirred solution of **16** (21 g, 0.080 mol) in acetic acid (170 mL). The mixture was stirred for 20 min, and anhydrous gaseous HBr was slowly passed through the solution until a temperature of 75 °C was attained. The flow of HBr was stopped and the dark solution stirred at 85 °C for 2 h. The solution was concentrated under reduced pressure and poured into a sodium carbonate solution (400 mL). The acetamide **18** hydrobromide (9.6 g) precipitated out and was collected by filtration. The basic filtrate was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated to afford a brown oil (9.3 g) that was chromatographed through silica gel with 5% methanol in chloroform as eluant. Evaporation of the eluates afforded 3.5 g of the title product as free base. A sample of **18**·HBr salt was recrystallized from methanol to give an analytical sample: mp 282–285 °C; IR (Nujol) 3230, 3170 and 3110 (NH), 2650 cm^{-1} (NH), 1680 cm^{-1} (carbonyl); ^1H NMR (free base, $CDCl_3$) δ 0.85 (t, J = 7, 6 H), 1.5 (m, 6 H), 2.1 (s, 3 H), 2.45 (m, 4 H), 2.75 (m, 5 H). Anal. ($C_{18}H_{29}BrN_2O$) C, H, N.

***N*-[7-(Dimethylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide (19).** A solution of *N*,*N*-dimethyl-1,2,3,4,5,8-hexahydro-7-methoxy-2-naphthalenamine (**13**; 17.3 g, 0.0835 mol) in acetone (373 mL), water (48 mL), and ethereal hydrochloric acid (183 mL) was stirred at room temperature for 1.25 h. The solution was concentrated and basified with solid sodium carbonate and a saturated sodium carbonate solution (20 mL). The product was extracted three times with dichloromethane. The aqueous phase was saturated with sodium chloride and extracted again four times with dichloromethane. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to give **15** as a brown oil (15.37 g): IR ($CHCl_3$) 1665 cm^{-1} (conjugated ketone); ^1H NMR ($CDCl_3$) δ 2.25 (s, 6 H), 5.65–6.10 (m, 1 H). A solution of **15** (15.37 g, 0.0795 mol) and hydroxylamine hydrochloride (19.5 g, 0.280 mol) in ethanol (181 mL) and pyridine (171 mL) was stirred at room temperature overnight. Ether (370 mL) was added at 0 °C and **17**·HCl (9.17 g) was collected by filtration as a white precipitate: mp 211–213 °C; IR (Nujol) 3280 (OH), 2550 cm^{-1} (NH); ^1H NMR (free base, $CDCl_3$) δ 2.25 (s, 6 H), 5.85 (s, 1 H). Anal ($C_{12}H_{21}ClN_2O$) C, H, N. Acetyl chloride (2 mL, 28 mmol) was added to **17**·HCl (489 mg, 2 mmol), and the reaction mixture was stirred at room temperature for 1 h. The acetyl chloride was decanted, and the residue was evaporated with ether twice. After treatment with 10% sodium hydroxide, the product was extracted three times with chloroform. The organic layers were dried ($MgSO_4$) and evaporated to give a brown oil that was put on a column of silica gel (2.5 g) and eluted with mixtures of methanol (0, 2, 4, 6, 8, and 10%) in triethylamine–ethyl acetate–benzene (1:3:6). Compound **19** (308 mg) was obtained as an oil. Upon trituration in hexane, a beige powder (176 mg) was obtained: mp 89–91 °C; IR ($CHCl_3$) 3420 and 3300 (NH), 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.1 (s, 3 H), 2.35 (s, 6 H), 7.1 (m, 3 H). Anal. ($C_{14}H_{20}N_2O$) C, H, N.

1,2,3,4-Tetrahydro-N^2,N^2-dipropyl-2,7-naphthalenediamine (20) Di-2(*Z*)-butenedioate. A suspension of **18** hydrobromide (3.0 g, 8.1 mmol) in water was treated with 1 N sodium hydroxide (100 mL), and the resulting free base was extracted in benzene. The solvent was removed and the residue heated at reflux in 2 N HCl (37 mL) for 2 h. After cooling, the solution was basified with 1 N sodium hydroxide and extracted three times with benzene. The organic extracts were dried ($MgSO_4$) and concentrated to afford a red oil (1.76 g). The dimaleate salt was prepared in acetone and ether and crystallized from methanol and ether: mp 124–126 °C; IR (Nujol) 2650 (NH), 1590 and 1355 cm^{-1} (COO^-); ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7, 6 H), 1.66 (m, 6 H), 2.90 (m, 8 H), 6.05 (s, 4 H), 6.40 (m, 2 H), 6.75 (d, J = 8, 1 H). Anal. ($C_{24}H_{34}N_2O_8$) C, H, N.

1,2,3,4-Tetrahydro-N^2,N^2-dimethyl-2,7-naphthalenediamine (21) Dihydrochloride. Acetyl chloride (28 mL) was added to the 7-(*N*,*N*-dimethylamino)-2,3,4,4a,5,6,7,8-octahydronaphthalenone 2-oxime hydrochloride (**17**·HCl; 7.5 g, 0.030 mol), and the reaction mixture was stirred at room temperature for 1 h. The acetyl chloride was decanted and the residue rinsed with ether (2×) and put under high vacuum for a few minutes. The resulting foam was then treated with 2 N hydrochloric acid (80 mL) at reflux temperature (oil bath at 145 °C) for 40 min. The reaction mixture was then cooled down and poured into ice-cooled 10% sodium hydroxide (80 mL). The basic solution was extracted with benzene (3×) and saturated with sodium chloride and extracted again (2×). The combined extracts were dried over $MgSO_4$, filtered, and evaporated to afford a dark red oil (5.32 g). The oil was dissolved in chloroform (20 mL) and cooled in an ice bath, and ethereal HCl (30 mL) was added portionwise to form the dihydrochloride salt which was precipitated with ether. After the mixture was stirred for $^1/_2$ h, the precipitate (6.1 g) was collected by filtration and dried under vacuum. It was used as such for the next step. A sample was recrystallized from methanol and ether to give gold crystals: mp 278 °C dec; IR (Nujol) 2700 cm^{-1} (NH); ^1H NMR ($CDCl_3$, free base) δ 2.3 (s, 6 H), 6.6 (m, 3 H). Anal. ($C_{12}H_{20}Cl_2N_2$) C, H, N.

***N*-[7-(Dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-(hydroxyimino)acetamide (22).** The 1,2,3,4-tetrahydro-N^2,N^2-dipropyl-2,7-naphthalenediamine (**20**; 3.1 g, 12.4 mmol) in water (37 mL) was carefully treated with 5% HCl (30 mL), hydroxylamine HCl (2.88 g, 41 mmol), and anhydrous sodium sulfate (11.9 g, 82 mmol). The mixture was brought to a boil, and immediately a boiling solution of chloral hydrate (2.56 g) in water (38 mL) was added and the combined mixture kept boiling for 1 h. It was cooled, and diluted ammonium hydroxide (8 mL of concentrated NH_4OH in 80 mL of H_2O) was added. The product precipitated out and was filtered and redissolved in ethyl acetate. The filtrate was extracted with ethyl acetate (3×), and the ethyl acetate solutions were combined, dried, and evaporated to dryness to afford a brown solid (4.78 g). A sample was crystallized from dichloromethane: mp 82–85 °C; IR ($CHCl_3$) 3550 and 3200 (OH), 3380 (NH), 2600 and 1900 (zwitterions), 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.9 (t, J = 7, 6 H), 1.55 (m, 6 H), 2.7 (m, 11 H), 7.2 (m, 4 H), 8.05 (s, 1 H), 11.0 (br s, 1 H). Anal. ($C_{18}H_{27}N_3O_2$) C, H, N.

***N*-[7-(Dimethylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-(hydroxyimino)acetamide (23).** A procedure identical with that for making **22** was used for converting **21** (6.1 g, 0.023 mol) into **23** (5.24 g, 0.020 mol) as a yellow solid (mp 169–170 °C) used as such for the next step: ^1H NMR (Me_2SO) δ 1.70 (m, 2 H), 2.25 (s, 6 H), 2.65 (m, 5 H), 6.95 (d, J = 7, 1 H), 7.30 (d, J = 7, 1 H), 7.35 (s, 1 H), 7.60 (s, 1 H), 9.90 (br s, 2 H).

6,7,8,9-Tetrahydro-8-(dipropylamino)-3*H*-benz[*e*]indole-1,2-dione (24). *N*-[7-(Dipropylamino)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-(hydroxyimino)acetamide (**22**; 3.66 g, 11.54 mmol) was added at 0 °C to a rapidly stirred solution of concentrated H_2SO_4 (61 mL) and water (6.1 mL). After stirring for 1 h at 0 °C, the reaction mixture was warmed up to 75 °C for 0.5 h. Then, the solution was cooled to room temperature, poured onto cracked ice (600 mL), and basified with concentrated ammonium hydroxide (150 mL). The product was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and evaporated to dryness to afford a red foam (2.78 g). A sample was crystallized from ether–hexane to afford an analytical sample: mp 124–126 °C; IR ($CHCl_3$) 3420 and 3260 (NH), 1725 and 1740 cm^{-1} (carbonyls); ^1H NMR ($CDCl_3$) δ 6.6 (d, J = 8, 1 H), 7.15 (d, J = 8, 1 H), 8.6 (br s, 1 H). Anal. ($C_{18}H_{24}N_2O_2$) C, H, N.

6,7,8,9-Tetrahydro-8-(dimethylamino)-3*H*-benz[*e*]indole-1,2-dione (25). A procedure identical with that for making **24** was used for converting **23** (4.98 g, 0.019 mol) into **25**. Upon extraction with chloroform, part of the product (1.95 g) was insoluble and collected by filtration. More product (0.574 g) was obtained from the chloroform layer after evaporation to dryness and trituration with a small amount of chloroform: mp 181–184 °C; IR (Nujol) 2900 (NH), 1715 and 1743 cm^{-1} (carbonyls); ^1H

NMR (Me_2SO) δ 2.2 (s, 6 H), 6.55 (d, J = 8, 1 H), 7.2 (d, J = 8, 1 H).

6,7,8,9-Tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (4) 2(*Z*)-Butenedioate. To a cooled suspension of lithium aluminium hydride (1.5 g, 38.9 mmol) in tetrahydrofuran (100 mL) under nitrogen was added dropwise a solution of 2,3-dioxo-*N*,*N*-dipropyl-4,5,6,7-tetrahydro-1*H*-benz[*e*]indol-5-amine (**24**; 1.17 g, 3.89 mmol) in tetrahydrofuran (25 mL), and the mixture was stirred at room temperature for 2 h. The excess of lithium aluminium hydride was destroyed by careful addition of a 10% mixture of water in tetrahydrofuran (50 mL). The inorganic salts were fitered off through Celite and washed with tetrahydrofuran. The filtrate was concentrated, and water was added. The product was extracted in ether. The organic extracts were dried ($MgSO_4$) and concentrated to dryness to afford a green oil (1.17 g) that was chromatographed through a column of silica gel using chloroform and 1%, 3%, and 5% methanol–chloroform mixture as eluant. Evaporation of the eluates afforded the title compound (595 mg) as a free base. The free base (440 mg, 1.62 mmol) in ether was treated with maleic acid (188 mg, 1.62 mmol) in acetone to afford the maleate salt. Crystallization from methanol and ether gave green crystals: 325 mg; mp 164–165 °C; IR (Nujol) 3180 (NH), 2600 (NH^+), cm^{-1} 1580 (COO^-); ^1H NMR ($CDCl_3$) δ 1.0 (t, J = 7, 6 H), 1.9 (m, 6 H), 3.1 (m, 9 H), 6.25 (s, 2 H), 6.4 (m, 1 H), 6.82 (d, J = 8.8, 1 H), 7.2 (m, 2 H), 8.8 (s, 1 H), 11.5 (br s, 2 H). Anal. ($C_{22}H_{30}N_2O_4$) C, H, N.

6,7,8,9-Tetrahydro-*N*,*N*-dimethyl-3*H*-benz[*e*]indol-8-amine (6). A procedure identical with that for making 4 was used for converting **25** (0.898 g, 3.5 mmol) into **6** as a dark green oil that crystallized spontaneously. A green powder (460 mg) was obtained upon trituration with ether. A sample was chromatographed on silica gel to afford the pure product: mp 191–197 °C; IR (Nujol) 2900 cm^{-1} (NH); ^1H NMR (Me_2SO) δ 2.3 (s, 6 H), 2.5 (m, 7 H), 6.35 (m, 1 H), 6.60 (d, J = 8, 1 H), 7.10 (d, J = 8, 1 H), 7.20 (d, J = 2, 1 H), 11.3 (s, 1 H). Anal. ($C_{14}H_{18}N_2$) C, H, N.

6,7,8,9-Tetrahydro-3-methyl-*N*,*N*-dipropyl-3*H*-benz[*e*]-indol-8-amine (5) Hydrochloride. The 6,7,8,9-tetrahyro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine obtained from the maleate salt ($4{\cdot}C_4H_4O_4$; 500 mg, 1.3 mmol) by treatment with 10% sodium hydroxide was dissolved in ether (5 mL) and added slowly with stirring to a suspension of sodium amide, prepared from clean sodium (50 mg, 2.17 mmol) in liquid ammonia (5 mL) containing ferric nitrate (10 mg). After the mixture was stirred for 15 min, methyl iodide (0.2 mL, 3.2 mmol) was added dropwise, and the mixture was stirred 50 min longer before the ammonia was allowed to evaporate. The residue was treated with water and ether, and the ether layer was separated, washed with water, dried, and evaporated to give a brown oil (325 mg) that was passed through a column of silica gel (10 g) using 10% benzene in ether as eluant. Evaporation of the eluates afforded an oil (300 mg) that was taken back in ether and treated with ethereal hydrochloric acid. The resulting suspension was stirred for a few hours, and the pure title product was collected by filtration as a white solid: 270 mg; mp 131–134 °C; IR ($CHCl_3$) 2450 cm^{-1} (NH^+); ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7, 6 H), 2.0 (m, 6 H), 3.1 (m, 9 H), 3.75 (s, 3 H), 7.0 (m, 4 H), 11.0 (br s, 1 H). Anal. ($C_{19}H_{29}ClN_2$) C, H, N.

6,7,8,9-Tetrahydro-*N*,*N*,3-trimethyl-3*H*-benz[*e*]indol-8-amine (7) 2(*Z*)-Butenedioate. A procedure identical with that for making **5** was used for converting **6** (400 mg, 1.9 mmol) into **7**. The crude product from the reaction was chromatographed on silica gel with a mixture of triethylamine–ethyl acetate–benzene (1:3:6) and increasing amount of methanol (0,2,4%) to afford the pure product (205 mg). This was taken back in ether and treated with maleic acid (104 mg) dissolved in acetone (2 mL). Filtration of the precipitate afforded the title product as a white solid: 273 mg; mp 174–175 °C; IR (Nujol) 2500–2700 cm^{-1} (NH^+); NMR (free base, $CDCl_3$) δ 2.45 (s, 6 H), 2.2 (m, 2 H), 3.05 (m, 5 H), 3.82 (s, 3 H), 6.52 (d, J = 4, 1 H), 7.15 (m, 3 H). Anal. ($C_{19}H_{24}N_2O_4$) C, H, N.

Pharmacology. Animals. Experiments were performed on male Swiss albino mice (21–25 g) or male Sprague–Dawley rats (weights indicated in each method). The animals were housed in air-conditioned quarters lit between 0700 and 1900 h daily maintained at a temperature of 24 ± 2 °C.

Materials. In addition to the test compounds the following drugs were used: bromocriptine methanesulfonate (CB-154) (generous gift of Sandoz Pharmaceuticals); reserpine injection USP (Serpasil, Ciba); 6-hydroxydopamine (6-OHDA) hyrobromide (Aldrich Chemical Co.). The 6-OHDA was prepared for use as previously described,[19] and the other compounds were dissolved in distilled water or suspended in distilled water with a few drops of Tween 80. Solutions were prepared fresh on the day of the experiment. All doses refer to the base.

Rotational Behavior in Unilaterally 6-OHDA-Lesioned Rats. The method, based on that originally reported by Ungerstedt,[18] has recently been described in detail.[19] Groups of 4–5 rats were used repeatedly at intervals of not less than 1 week. Animals were dosed with compound and immediately placed in a rotometer. Rotational behavior was recorded continuously until it ceased. Results were expressed as the total number (mean ± SEM) of contralateral turns produced as a result of drug administration.

Reversal of Akinesia in Bilaterally 6-OHDA-Lesioned Rats. The method based on that originally reported by Smith and Young[20] has recently been described in detail[31]. Briefly, 4 days after bilateral lesioning of the anterolateral hypothalamus using 6-OHDA, rats were placed in an open field. Ambulation was measured during 2-min test periods over a 2-h time interval. The placement of all four limbs in one square was taken as one ambulation score. The results were expressed as cumulative ambulation scores obtained over 2 h.

Antagonism of Reserpine-Induced Catalepsy in Mice. The method of Johnson et al.[21] was followed. Groups of 10–12 mice were injected ip with reserpine, 5 mg/kg, 17 h before the sc administration of test compounds. Catalepsy was assessed prior to and 0.5, 1, 2, 3.5, and 5 h after drug administration. Catalepsy was tested in a quantal manner as follows: the mice were individually placed on a rubber stopper, 5 cm in diameter and 2.5 cm in height, and observed for 3 min. Mice that remained on the corks during this period were considered to be cataleptic. The results are expressed as ED_{50} values, the dose that antagonized reserpine-induced catalepsy in 50% of mice.

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