A Molecular Mechanics Approach to the Understanding of Presynaptic Selectivity for Centrally Acting Dopamine Receptor Agonists of the Phenylpiperidine Series

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Molecular mechanics (MMP2) calculated geometries and conformational energies have been employed in an attempt to elucidate the molecular basis for presynaptic dopamine receptor selectivity of centrally acting agonists of the phenylpiperidine series. A receptor interaction model based on the McDermed receptor concept, on superimpositions of calculated structures, and on conformational analysis is presented. The model focuses on the interaction between *N*-alkyl substituents and the receptor. From comparisons with rigid structures having either agonistic or antagonistic properties it is concluded that the presynaptically selective compound (*S*)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine ((*S*)-3PPP) is acting as an agonist in one rotameric form and as an antagonist in another one. The selectivity of (*S*)-3PPP and the nonselectivity of its enantiomer are suggested to be due to differences in the interactions between *N*-alkyl substituents and the receptor. The receptor model presented led to the hypothesis that the piperidine ring in the compounds studied should be equivalent to a *N*-methyl group in its receptor interactions. Examples are given in support of this idea. Presynaptic selectivity was predicted for an aminotetralin derivative and was also observed in subsequent testing.

The potential clinical usefulness of a centrally acting and selective dopamine (DA) autoreceptor (presynaptic receptor[1]) agonist as hypothesized by Carlsson[2] has initiated many research projects in recent years. The basis of this concept is that DA agonists with autoreceptor selectivity will impair dopaminergic function via a feedback down-regulation of DA synthesis without having any activating effects on postsynaptic DA receptors.

Apomorphine (**1**), and 5- and 7-hydroxy-2-(di-*n*-propylamino)tetralin (**2** and **3**, respectively), as well as *trans*-7- and *trans*-9-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo(*f*)quinoline (**4** and **5**, respectively) are very potent centrally acting DA receptor agonists. However, these compounds are nonselective, showing high potencies at pre- as well as postsynaptic receptors[3,4] (Table I).

The first compound claimed to be selective at DA autoreceptors was 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3PPP, **6**).[5] This compound is chiral, and its resolution revealed an interesting interaction between the two enantiomers. The *R*-(+) enantiomer has the classical profile with pre- as well as postsynaptic agonist properties. Since the racemic mixture was devoid of postsynaptic stimulatory properties, the *S*-(−) enantiomer must have an antagonistic effect on the postsynaptic stimulation of the *R*-(+) enantiomer. This was shown to be the case, and the profile of the *S*-(−) enantiomer is that of a presynaptic agonist with additional postsynaptic antagonistic properties.[6]

Chirality is a very critical feature of DA agonists. The active enantiomers of **2** and **4** have the same absolute configuration (*S*) at the carbon atom carrying the nitrogen atom. However, the opposite enantiomers are the active ones for the isomeric compounds **3** and **5**.[3,4] McDermed et al. rationalized these findings in terms of a receptor model that explains the shift in chirality for the active tetralin enantiomers.[7,8] This receptor model was developed from the investigation of essentially two compounds, **2** and **3**. These compounds were shown to be stereospecifically active in their *S* and *R* forms, respectively. In order to satisfy the stereochemical demand as well as the demand for a superimposition of the hydroxyl groups and the nitrogen atoms in the two molecules, McDermed turned one of these molecules 180° about a fictive axis through the molecular ring system before the molecular superimposition was done. An analogous fit is shown in Figure 1 for the tricyclic compounds discussed later in the present work. We have also emphasized this way of comparing the different structures by drawing them according to this concept in Charts I and II.

The *N*-alkyl groups have been found to play an important role for the pharmacological properties of the compounds studied in this work. The secondary amine (4a*S*,10b*S*)-**7** has been shown to be a presynaptically selective DA receptor agonist[3,4] but with less antagonistic effects on postsynaptic receptors than (*S*)-**6**.[6] However, its *N*-*n*-propyl analogue (4a*S*,10b*S*)-**4** is a potent agonist on pre- as well as postsynaptic receptors. Compound (*S*)-**6** is, as mentioned above, a presynaptic agonist but a postsynaptic antagonist. The corresponding *N*-*n*-butyl derivative, however, is a nonselective agonist, as are (*R*)-**6** and its *N*-*n*-butyl analogue.[9] In contrast, the *n*-butyl analogue of (4a*R*,10b*R*)-**5** is inactive at both receptors.[3,4] This is also the case for the *N*-*n*-butyl analogue of apomorphine.[10]

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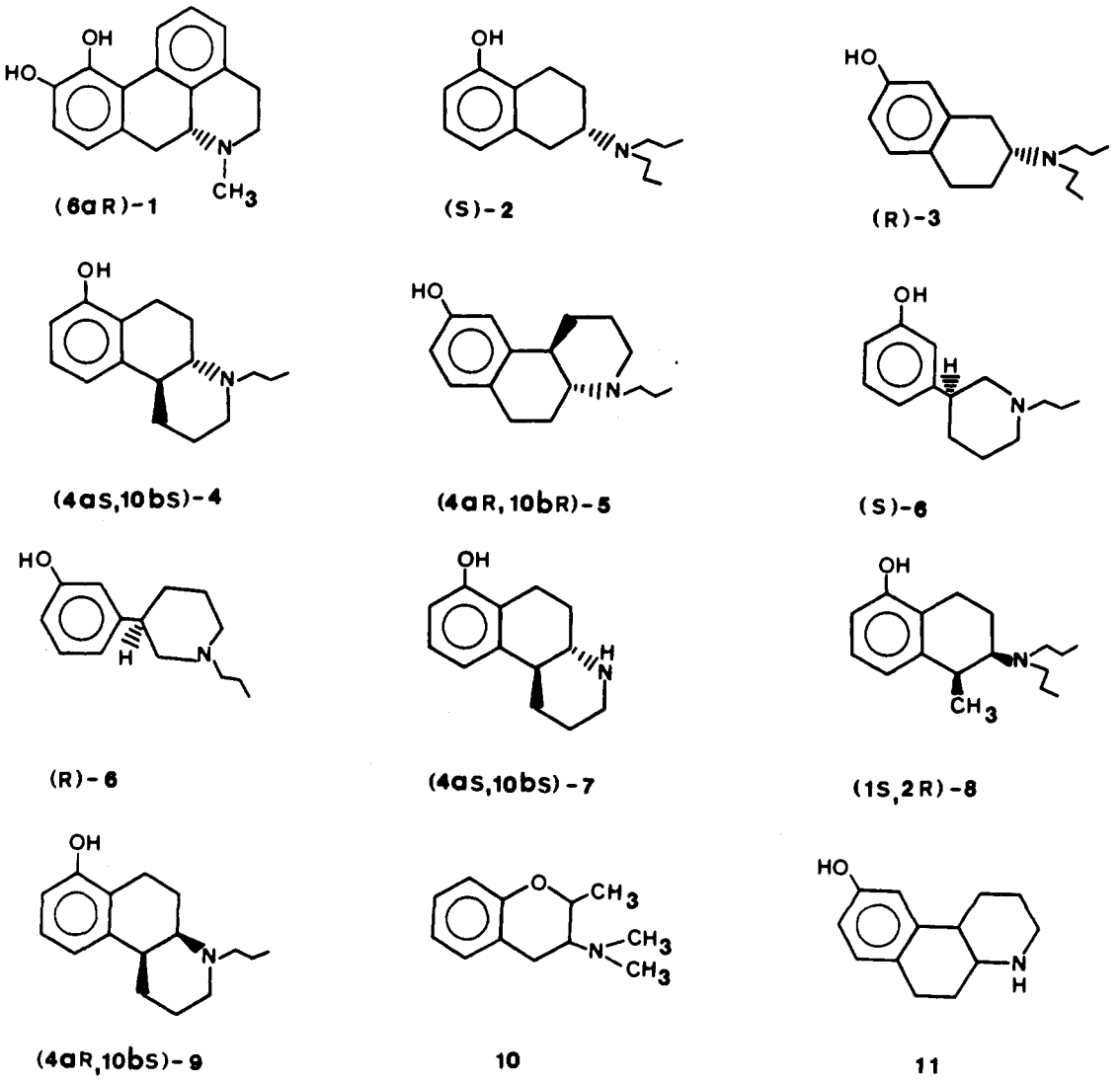
Table I. Pharmacological Data for Compounds Discussed

compd	presynaptic agonism ED_{50},[a] nmol/kg		postsynaptic agonism motor activity[b]	
	limbic	striatum	dose, μmol/kg	acc. counts/ 30 min
1[c]	190	220	2.3	361 ± 42
(*S*)-2[d]	3.7	3.7	0.31	155 ± 27
(*R*)-3[d]	9.5	11	0.31	46 ± 18
4a*S*,10b*S*)-4[d]	14	14	1.30	62 ± 11
(4a*R*,10b*R*)-5[e]	4	5	1.06	155 ± 32
(*R*)-6[f]	1 000	1 300	13	78 ± 14
(*S*)-6[f]	800	1 700	213	12 ± 2
(4a*S*,10b*S*)-7[e]	1 000	1 300	106	10 ± 5 (n.s.)[g]
11[e]	25 000	40 000	106	10 ± 4 (n.s.)
12[h]	I[i]	I	NT[j]	NT
13[h]	390	190	100	52 ± 11
14[e]	630	470	100	40 ± 16
15[e]	400	450	106	60 ± 9
16[h]	23	29	2	239 ± 25
17[h]	1 100	1 200	100	18 ± 9 (n.s.)
18[h]	I	I	I (at 2 μmol/kg)	I
19[h]	72	66	2	181 ± 9
(*S*)-20[k]	8 500	8 200	50	24 ± 8

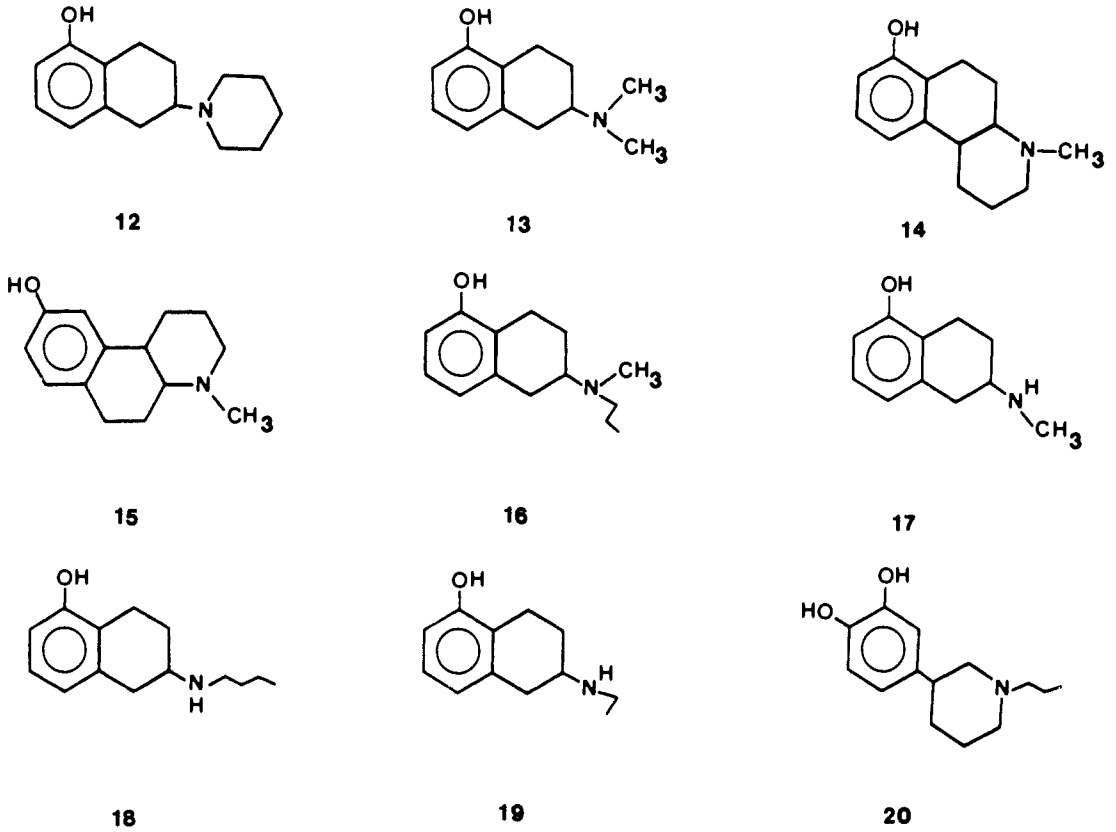
[a] Measured indirectly as inhibition of DA synthesis rate (see ref 4). [b] Motor activity measured in motility meters on reserpinized rats (see ref 4). [c] Data taken from ref 11. [d] Data taken from ref 4. [e] Data taken from ref 34. [f] Data taken from ref 9. [g] Not significant. [h] Data recalculated from 60 to 30 min from the data in ref 37. [i] Inactive. [j] Not tested. [k] Data taken from ref 27.

Chart I



Recently, Johansson et al.[11] and Svensson et al.[12] reported *cis*-(1*S*,2*R*)-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (8) to have antagonistic properties on both pre- (low doses) and postsynaptic (high doses) DA recep-

Chart II



tors in the CNS. This led us to test the possible antagonism of the more rigid analogue *cis*-(4a*R*,10b*S*)-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo(*f*)-quinoline (**9**), previously reported to be inactive as a DA receptor agonist.[3,4] Interestingly, this compound also shows antagonistic properties.[13] Such properties have also been demonstrated for the related aminotetralin analogue **10**.[14,15] These compounds, and especially the rigid compound (4a*R*,10b*S*)-**9**, are well-suited to be employed in attempts to deduce the geometrical requirements for antagonism of similar but more flexible molecules.

Previous studies indicate that there is an intimate relationship between central pre- and postsynaptic DA receptors, as pointed out by Carlsson.[16] He suggests that the difference between these receptors types is only a matter of receptor conformation, which shows up as differences in sensitivity to a given agonist. The autoreceptors are more sensitive to stimulation due to long-term low occupancy of endogenous DA than are the postsynaptic receptors, which have experienced long-term high receptor occupancy of endogenous DA. The autoreceptor selectivity exhibited by some compounds could thus stem from differences in receptor sensitivity and/or concomitant blockage of postsynaptic receptors.

In the present paper we use the McDermed receptor concept (see above) in conjunction with geometries and conformational energies calculated by molecular mechanics to discuss relationships between structure and pre- as well as postsynaptic receptor activation for the compounds shown in Charts I and II. Our main purpose is to elucidate the molecular basis of presynaptic selectivity. The recently reported antagonistic properties of some of these compounds (see above) are also included in the discussion. In particular, we wish to investigate if the conformational properties of the flexible compound 3PPP (**6**) may be correlated to the dual action of its *S* enantiomer. We will also attempt to rationalize the intriguing effects of the *N*-alkyl groups on central DA receptor activity and selectivity. A model for receptor interaction that includes the effects of *N*-alkyl groups is proposed. The pharmacological data used in the discussion are summarized in Table I.

Computational Methods

The conformational energies and energy-minimized molecular geometries of the compounds discussed in the present work were calculated by use of the MMP2 molecular mechanics program.[17] The force fields employed for the aliphatic amine and the enol parts of the the molecules have recently been published.[18,19]

It is not known whether the biologically relevant nitrogen type for the compounds studied is amine or ammonium. Since no complete force field including ammonium-type nitrogen has so far been developed, all calculations have been done on the unprotonated amines. In MM2/MMP2 the nitrogen lone pair is treated as a pseudo-atom, and this may serve to indicate the

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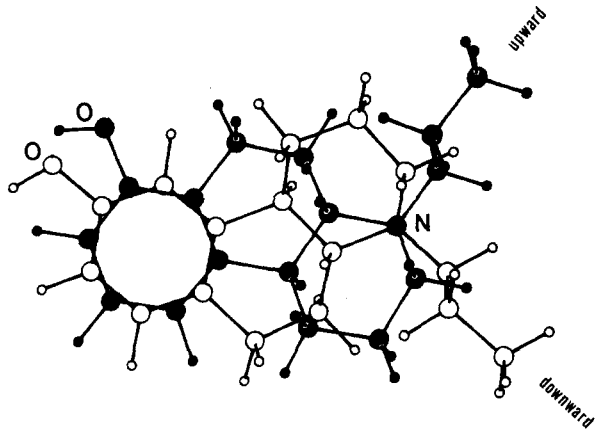

Figure 1. Superimposition of compounds (4a*S*,10b*S*)-**4** (black atoms) and (4a*R*,10b*R*)-**5** in their calculated lowest energy conformations. The superimposition defines two modes of receptor interaction and two N-alkyl directions.

direction of the NH bond in the protonated form. The uncertainty in the degree of charge on the nitrogen atom is of less importance in the present work, since the polar groups in the molecules studied are too distant to significantly affect the calculated geometries and conformational energies through electrostatic interactions.

Trial input structures to MMP2 were constructed by using the MOLBUILD module of the molecular modeling program MIMIC.[20,21] Least-squares fitting and molecular superimpositions were performed by using the MOLCOMP module of MIMIC.

Results and Discussion

Basic Model for Agonistic Pre- and Postsynaptic DA Receptor Interactions. The conformationally well defined ring structures of compounds (4a*S*,10b*S*)-**4** and (4a*R*,10b*R*)-**5** make them well-suited to define the geometrical requirements for interactions with central pre- and postsynaptic DA receptors. We then use the hypothesis discussed above that the two receptor types have identical, or at least very similar, geometrical requirements for receptor activation. Both compounds are very potent pre- and postsynaptic DA receptor agonists (Table I) and show high enantioselectivity.[3,4,22]

All data presented in Table I are in vivo data, and one has to bear in mind that transport and metabolism will affect the actual brain concentrations of the compounds tested. However, in most cases in this paper comparisons are made between compounds from the same structural class. This should ensure that they behave similar in terms of metabolism. The more lipophilic compounds should enter the brain more easily than the less lipophilic ones, but the data clearly show that lipophilicity per se does not determine the pre-/postsynaptic profile.

We assume that the nitrogen atom, the nitrogen lone pair (or in the case of a protonated nitrogen the hydrogen atom), the aromatic ring (represented by its center of gravity), and the hydroxyl group are involved in the activation of the receptors. Compounds **4** and **5** have of course very similar geometrical relationships between the aromatic ring and the nitrogen atom, but the calculated distances between the nitrogen atom and the hydroxyl oxygen are significantly different in the two molecules, 6.54 and 7.43 Å, respectively, indicating that this distance is not a particularly critical factor for DA agonists.[1]

Our basic model for agonistic DA receptor interaction is shown in Figure 1. It is constructed by superimposing

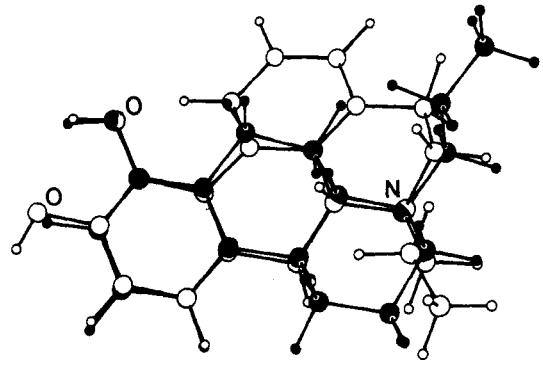

Figure 2. Least-squares superimposition of compounds (4a*S*,10b*S*)-**4** (black atoms) and (6a*R*)-**1** in their lowest energy conformations.

the nitrogen atoms and the midpoints of the aromatic rings in (4a*S*,10b*S*)-**4** and (4a*R*,10b*R*)-**5** in their calculated lowest energy conformers with the aromatic rings constrained to be coplanar. The *n*-propyl groups are shown in their lowest energy conformations. The "biologically active conformations" of the *N*-alkyl substituent will be discussed later. The calculated structure of (4a*S*,10b*S*)-**4** is in agreement with the conformer found by X-ray crystallography for the corresponding hydrochloride.[22] We assume that the hydroxyl groups in the two positions shown in Figure 1 may interact equally well with the receptor and that the two interaction modes represented by the two compounds activate the receptor equally well (see Table I). A similar but more qualitative superimposition has previously been presented by one of us.[3,4]

In Figure 1 the nitrogen atom–nitrogen lone pair vectors are almost orthogonal (±15°) to the plane containing the aromatic rings. The nitrogen atoms are located 0.19 Å above the aromatic plane, and the distance between the superimposed midpoints of the phenyl rings and the nitrogen atoms is 5.2 Å.

The active enantiomer of the potent dopamine agonists apomorphine (**1**) and *N*-*n*-propylnorapomorphine has been shown to have the *R* configuration.[23,24] The calculated lowest energy conformers of these molecules fit the model in Figure 1 exceedingly well. A least-squares superimposition of (*R*)-*N*-*n*-propylnorapomorphine and (4a*S*,10b*S*)-**4** is shown in Figure 2. The midpoints of the aromatic rings, the hydroxyl oxygens, the nitrogen atoms, and the nitrogen lone pair pseudo-atoms were included in the fitting, and the resulting mean distance between these atoms (points) after fitting is 0.06 Å.

The aminotetralins (*S*)-**2** and (*R*)-**3** are equipotent with (4a*S*,10b*S*)-**4** and (4a*R*,10b*R*)-**5** (Table I). Similar least-squares fittings as described above were done for the pairs (*S*)-**2**,(4a*S*,10b*S*)-**4** and (*R*)-**3**,(4a*R*,10b*R*)-**5**. The resulting mean distance in these cases are 0.03 and 0.02 Å, respectively. To obtain these close fits, the di-*n*-propylamino groups in (*S*)-**2** and (*R*)-**3** have to be rotated about the C(ring)–N bond into a conformation calculated to be 0.49 kcal/mol higher in conformational energy than the one with the lowest energy. This conformer corresponds to one of the two molecules in the unit cell of the hydrochloride of compound **2**, according to an X-ray diffraction study.[25] (The second molecule in the unit cell corresponds to the calculated lowest energy conformer.)

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(21) Von der Lieth, C. W.; Carter, R. E.; Dolata, D. P.; Liljefors, T. *J. Mol. Graphics* **1984**, *2*, 117.
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(25) Giesecke, J. *Acta Crystallogr. Sect. B: Struct. Crystallogr. Cryst. Chem.* **1980**, *36*, 110.

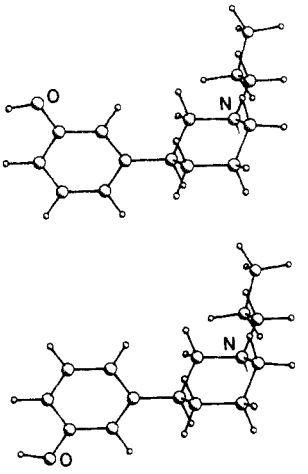

Figure 3. Calculated stable conformers of (*S*)-**6**.

All of these compounds, which are strong agonists on both pre- and postsynaptic DA receptors, thus fit almost perfectly one of the two interaction modes defined in Figure 1 with the molecules in or close to their lowest energy conformers. The inactive enantiomers, as expected, all show very bad fits to the model.

The superimposition shown in Figure 1 defines two different directions for the N-substituents, which will be refered to as "upward" and "downward". Previous studies indicate that the "downward" direction can at most accomodate an *n*-propyl group, while the "upward" direction does not show this restriction.[3,4] The effect of *N*-alkyl substituents will be discussed in detail below.

Conformational Analysis of 3PPP (6). Agonist Conformation. The calculated lowest energy conformers of (*S*)-**6** are shown in Figure 3. There is no significant energy difference between these two conformers. The aromatic ring closely bisects the piperidine ring, as also calculated for the analogous equatorial phenyl cyclohexane.[26] This type of conformation is also found in the crystal structures of the hydrobromide salts of (*S*)-**20**[27] and the methoxy analogue of (*R*)-**6**.[28] An X-ray study of the hydrochloride salt of (*S*)-**6** shows two conformations with respect to the torsion about the pivot bond.[29] However, in this case the molecular conformations are strongly influenced by crystal packing and extensive hydrogen bonding, and a direct comparison with the calculated conformers is precluded.

In the calculated conformation, the nitrogen lone pair of (*S*)-**6** or (*R*)-**6** is almost parallel to the plane of the phenolic ring. However, in our model for agonist interaction (Figure 1) the nitrogen lone pair direction is close to perpendicular to the aromatic plane. To fit the model, (*S*)-**6** and (*R*)-**6** must thus be rotated about the central single bond into a higher energy conformation.

The calculated potential energy curve for rotation about the central bond in (*S*)-**6** is shown in Figure 4. The energy barrier between the two stable rotamers is calculated to be 3.0 kcal/mol. The conformation denoted by an asterisk in Figure 4 is the one showing a maximum fit to the hydroxyl oxygen, the midpoint of the aromatic ring, the nitrogen atom, and the nitrogen lone pair of (4a*S*,10b*S*)-**4**

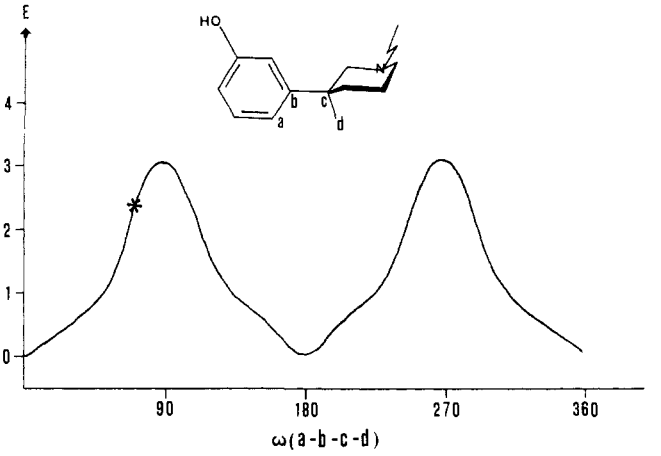

Figure 4. Calculated potential energy curve for rotation about the central bond in (*S*)-**6**. Energies (*E*) are in kcal/mol and dihedral angles (ω) are in degrees.

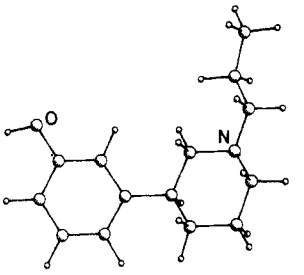

Figure 5. Calculated agonist conformation of (*S*)-**6** with respect to the ring system. The *N*-propyl group is shown in its preferred conformation.

and thus to the agonist model. The resulting mean distance between these atoms in the two molecules after fitting is 0.03 Å. The inferred agonist conformation of (*S*)-**6** with respect to the conformations of the two rings is shown in Figure 5. The corresponding results are of course valid for the pair (*R*)-**6** and (4a*R*,10b*R*)-**5**.

We conclude that (*S*)-**6** and (*R*)-**6** must rearrange conformationally to fulfill the geometric requirements for pre- and postsynaptic DA receptor agonism. The conformational energy required for this process is calculated to be 2.4 kcal/mol. The corresponding conformation is not an energy minimum for the isolated molecule (see Figure 4), so this conformation is presumably stabilized in the receptor cavity through lipophilic interactions involving the *N*-alkyl substituents. This will be discussed more fully below.

The conclusion that conformational energy is required for (*S*)-**6** and (*R*)-**6** to acquire their agonist state is well in line with the observed lower potencies of these compounds in presynaptic assays compared to those of the more rigid compounds **2**–**5**, which have the "correct" geometry in (or close to) their lowest energy conformations (see Table I).

Antagonism. As discussed in the introduction (*R*)-**6** is a classical dopaminergic agonist with both pre- and postsynaptic activity. Compound (*S*)-**6**, however, is a presynaptic agonist but a postsynaptic antagonist. Compounds (1*S*,2*R*)-**8**[11,12] and (4a*R*,10b*S*)-**9**[13] have both been shown to have antagonistic properties at central DA receptors. The preferred conformation of (1*S*,2*R*)-**8** is calculated to have an axial methyl group and thus an equatorial dipropylamino group, in agreement with the conformer found by X-ray crystallography.[30] This conformer

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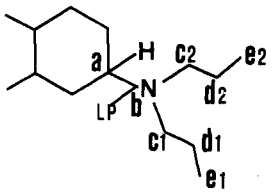
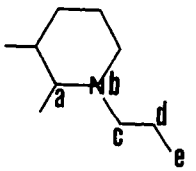
Table II. Calculated Propyl Group Conformers (Cutoff at 2 kcal/mol) for Compounds (*S*)-**2**, (*R*)-**6**, and (4a*R*,10b*R*)-**5**



(S)-2



(4aR,10bR)-5

(R)-6

ω1=a-b-c1-d1 ; ω4=b-c2-d2-e2 ω1=a-b-c-d

ω2=b-c1-d1-e1; ω5=H-a-b-LP ω2=b-c-d-e

ω3=a-b-c2-d2

compd	conf no.	dihedral angle, deg ω_1	ω_2	ω_3	ω_4	ω_5	conf energy, kcal/mol
(4a*R*,10b*R*)-**5**	1	-56.5	179.1				0.0
	2	-175.6	-169.5				0.30
	3	-179.9	-55.0				0.65
(*R*)-**6**	1	60.9	169.9				0.0
	2	174.6	-170.7				0.03
	3	62.4	54.0				0.22
	4	173.3	-54.3				0.28
	5	-63.2	179.7				0.79
(*S*)-**2**	1	172.9	-169.2	-53.0	-170.2	-56.3	0.0
	2	169.8	-53.8	-54.2	-169.9	-57.1	0.23
	3	171.0	-168.6	-56.2	-55.6	-58.1	0.39.
	4	167.4	-52.4	-58.1	-54.8	-59.7	0.41
	5	49.3	170.8	-177.1	169.7	57.2	0.42
	6	-178.8	-169.9	61.3	178.6	174.6	0.49
	7	-63.3	-177.2	176.8	170.2	-178.1	0.60
	8	50.6	170.1	172.1	54.9	58.8	0.72
	9	52.6	57.2	-176.0	168.9	58.7	0.87
	10	55.8	55.2	-169.6	52.9	62.3	0.91
	11	177.4	-56.1	60.5	179.2	175.0	0.95
	12	-63.0	-179.1	-179.1	56.9	-176.5	1.12

is strongly preferred, as the equatorial methyl group/axial amino group arrangement is calculated to have >2.5 kcal/mol higher energy.[30] A least-squares fit between the hydroxyl oxygens, the aromatic midpoints, and the nitrogen atoms in (1*S*,2*R*)-**8** and (4a*R*,10b*S*)-**9** in their lowest energy conformations gives a resulting mean distance between fitted atoms of 0.04 Å. These compounds are thus very similar in this respect. However, if the nitrogen lone pairs are to be included in the fit a high-energy conformer (ca. + 6 kcal/mol) of (1*S*,2*R*)-**8** must be employed. The reason for this high conformational energy is severe steric repulsions between one of the *N*-*n*-propyl groups and the 1-methyl group. This indicates that the lone pair direction is not of decisive importance for antagonistic interaction.

A comparison of compounds (1*S*,2*R*)-**8**, (4a*R*,10b*S*)-**9**, and (*S*)-**6** reveals that a very close fit for the hydroxyl oxygens, the aromatic ring midpoints, and the nitrogen atoms for all three compounds may be obtained if (*S*)-**6** is rotated about the central bond to a C(sp^2)–C(sp^2)–C(sp^3)–H dihedral angle (a–b–c–d according to Figure 4) of 44°. The corresponding conformational energy is only 0.7 kcal/mol. The mean distance in the least-squares superimposition between (*S*)-**6** in this conformation and (4a*R*,10b*S*)-**9** is 0.03 Å. We thus suggest that (*S*)-**6** exerts its antagonistic interaction in this conformation (Figure 6). As will be discussed below, the actual conformation, agonistic or antagonistic, of (*S*)-**6** and (*R*)-**6** in the receptor interaction is mainly determined by the properties of the *N*-alkyl substituents.

The geometrical relationships between the agonistic and antagonistic modes are schematically shown in Figure 7.

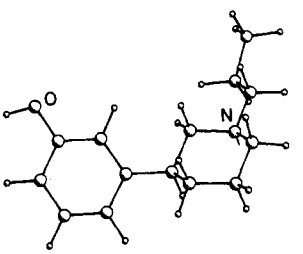


Figure 6. Calculated antagonist conformation for the ring system in (*S*)-**6**. The lowest energy *N*-propyl conformer is shown.

The nitrogens in the two modes are located on different sides of the aromatic plane. The lone pair directions are different, and the distance between the nitrogens is calculated to be 0.49 Å.

***N*-Alkyl Conformations.** The intriguing sensitivity of the pharmacological properties to the nature of the alkyl groups on the compounds studied in this work (see introduction) reflects the presence of two possible *N*-alkyl directions, as discussed above (Figure 1). As it has previously been suggested that an *n*-propyl group in the "downwards" direction "mimics" part of a piperidine ring in its interaction with presynaptic receptors,[3] we have undertaken an exhaustive conformational analysis of the *N*-*n*-propyl groups in compounds **2**–**6**. All staggered arrangements about the two torsional degrees of freedom for the propyl groups in compounds (*S*)-**2**, (4a*R*,10b*R*)-**5**, and (*R*)-**6** were used as trial input structures and energy-minimized by MMP2. The calculations for (*R*)-**6** were done with the phenol ring in the "agonist conformation". The

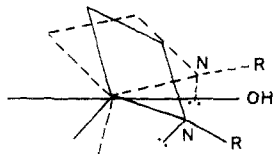


Figure 7. Geometrical relationships between calculated agonist (dashed line) and antagonist (solid line) conformations of (*S*)-**6** projected along the bond connecting the phenol and piperidine ring.

resulting low-energy conformers (cutoff at 2 kcal/mol above the lowest energy conformer in each case) are summarized in Table II.

Compound (4a*R*,10b*R*)-**5** (and accordingly (4a*S*,10b*S*)-**4** has three low-energy *n*-propyl conformers. Other stable conformers are calculated to be of at least 2.7 kcal/mol higher energy due to the presence of "forbidden" pentane interactions.[31] The lowest energy conformer has a lone pair (LP)–N–C–C and a N–C–C–C anti arrangement, as is also shown by the X-ray structure of the hydrochloride of (4a*S*,10b*S*)-**4**.[22] All conformations with LP–N–C–C in a *g*+ state in (4a*S*,10b*S*)-**4** or a *g*− state in (4a*R*,10b*R*)-**5** are of high conformational energy (≥2.7 kcal/mol).

Since there is no substituent other than hydrogen alpha to the nitrogen atom in (*S*)-**6** (and (*R*)-**6**), the *N*-propyl groups is more flexible in these molecules. Five low-energy conformers were found (Table II); the remaining four stable propyl group conformers have 2.5–3.8 kcal/mol higher energy than the most stable one. It is of interest to note that the *n*-propyl conformers in (4a*R*,10b*R*)-**5** corresponding to the low-energy conformers 1 and 3 in (*R*)-**6** are both of high conformational energy.

The presence of "forbidden" pentane interactions restricts the number of low-energy conformers in (*S*)-**2** and (*R*)-**3**. Although there are 5 degrees of torsional freedom for the *N*-*n*-propyl groups in each of these molecules (including rotations about C(ring)–N bonds), and thus 3^5 = 243 possible staggered arrangements, only 12 of these are without strong repulsive interactions of the "forbidden" pentane type. Conformational energies and dihedral angles for these conformers are given in Table II. Remaining conformers for (*S*)-**2** and (*R*)-**3** have conformational energies of at least 2.5 kcal/mol.

From these calculations it is clear that the propyl groups in compounds **2**–**6** are not likely to "mimic" part of a piperidine ring in their "active conformation". All conformations of this type involve "forbidden" pentane interactions and are therefore of high energy, which is not compatible with the high potency of compounds **2**–**5**.

The propyl groups in the two directions indicated in Figure 1 can not have the same "biologically active conformations" with respect to the dihedral angle LP–N–C–C. Such combinations involve strong repulsive interactions between the two propyl groups in (*S*)-**2** and (*R*)-**3**. Furthermore, the "active conformation" for the angle H–C(ring)–N–LP in these compounds is anti according to the model in Figure 1. Of the four conformers in Table II with this nitrogen lone pair direction (conformers 6, 7, 11, and 12) the two with lowest energies have a N–C–C–C anti conformation. The corresponding gauche conformers have conformational energies of ca. 1 kcal/mol higher than the anti. In addition, the requirement that the two propyl groups in **2** and **3** cannot both have the same conformation with respect to the LP–N–C–C angle implies that the

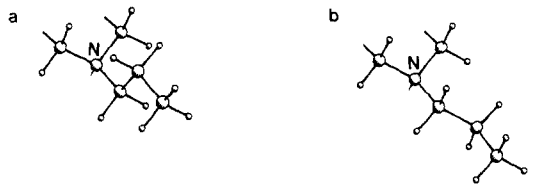


Figure 8. (a) Anti and (b) gauche conformers of the *N*-*n*-propyl group.

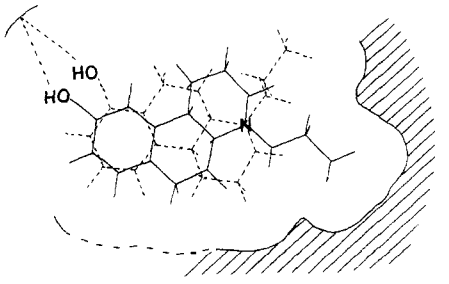


Figure 9. Schematic model for pre- and postsynaptic central DA receptor interaction.

propyl group in one of (4a*S*,10b*S*)-**4** and (4a*R*,10b*R*)-**5** must have a LP–N–C–C anti conformation. Since in such a conformation a N–C–C–C gauche arrangement leads to a high conformational energy (3.1 kcal/mol), this arrangement is excluded for an "active conformation" in these highly potent compounds. Combining the results in Table II, the most likely "active propyl conformation" is the one with a N–C–C–C anti conformation and a LP–N–C–C gauche or anti conformation, as shown in Figure 8.

Since there are no data from which it is possible to infer which of the two likely conformations is the "active" one in each of the two directions, "upward" and "downward" (Figure 1), and since the calculated conformational energies for conformers 6 and 7 of (*S*)-**2** (Table II) are very similar, we arbitrarily assume that an *N*-propyl group in the "upwards" direction has an anti conformation with respect to the dihedral angle LP–N–C–C and thus that the propyl group in the "downwards" direction has a gauche conformation. This choice will not affect the conclusions drawn in this work.

Model for DA Receptor Interaction. Based on the superimposition in Figure 1 and the results of the calculations in preceding sections, a schematic model for pre- and postsynaptic central DA receptor interaction has been constructed. A projection of this model is shown in Figure 9. The model is to be understood as a model for an "activated complex" related to the intrinsic activity (efficacy). By dissecting the biological response into affinity and intrinsic activity,[32,33] and considering that full agonists need to occupy only a fraction (1–5%) of the receptor population, it is feasible to assume that the agonistic effects measured for a homogenous series of compounds like the present one are more dependent on the intrinsic activity factor than on the affinity factor. This has been shown to be the case for N-alkyl derivatives of compounds **7** and **11**.[34]

The cavity that accomodates the molecules as shown in Figure 9 is defined by the complement to the combined van der Waals volumes of the molecules in the superimposition shown in Figure 1, with the *n*-propyl groups in the "active" conformations according to the discussion

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(32) Ariens, E. J. *Progr. Drug. Res.* **1966**, *10*, 429.
(33) Kenakin, T. P. *Pharmacol. Rev.* **1984**, *36*, 165.
(34) Wikström, H.; Andersson, B.; Svensson, K.; Hjorth, S.; Carlsson, A. Poster at the 14th Annual Meeting, Society for Neuroscience, Anaheim, CA, Oct 10–15, 1984.

above. Van der Waals radii according to MM2/MMP2 were employed.[17] The upper part of the cavity has intentionally been left open, since the steric restrictions in this direction seem to be small; N-substituents as large as phenethyl and the nonphenolic phenyl group in apomorphines can be accomodated[35] (see Figure 2). In the lower region, a section has been left undefined. This region has been proposed to accomodate the pyrrole part of the 13-hydroxy ergot metabolites not treated in this work.[3,4,36] The main features of the model are the narrow cleft complementary to an *n*-propyl group in the "downward" direction and the sterically "unrestricted upward" direction.

The model summarizes and rationalizes the experimental observations discussed above. It also explains the observed inactivity of compounds like **12**, which are too sterically demanding in the *N*-alkyl region. In addition it offers an explanation for the observation that an *N*-*n*-butyl group in the "downward" direction leads to an inactive compound for the *N*-*n*-butyl analogue of (4a*R*,10b*R*)-**5** but only to a moderate decrease in potency for the corresponding analogue of (*R*)-**6**.[3,4,9] In the latter case the *n*-butyl group may escape from the repulsive interactions in the "propyl cleft" through a LP–N–C–C/N–C–C–C *g*–/*g*– conformation with a conformational energy of ca. 4 kcal/mol. Such a "folded" conformation may be accomodated in the receptor cavity. More detailed studies on the precise type of folding must await further refinements of the lower part of the receptor model in Figure 9. A corresponding conformation in the *n*-butyl analogue of (4a*R*,10b*R*)-**5** has a very high conformational energy (>15 kcal/mol) due to strong repulsive interactions between the folded butyl group and the methylene group alpha to nitrogen. This makes the *n*-butyl analogue of compound (4a*R*,10b*R*)-**5** an inactive compound. The same argument may be used to rationalize the inactivity of the *n*-butyl analogue of (6a*R*)-**1**.[10] An "escape" from the propyl cleft through a LP–N–C–C anti arrangement does not explain the activity differences, as this is a low-energy conformer for both (4a*R*,10b*R*)-**5** and (*R*)-**6**.

Presynaptic Selectivity and Postsynaptic Antagonism. The model presented in Figure 9 suggests that the piperidine ring in the compounds studied in this work should approximately be equivalent to an *N*-methyl group in its interaction with the receptor. Only the ring methylene group alpha to the nitrogen atom may productively interact with the N-alkyl receptor sites. This suggestion is supported by the measured activities of compounds **13**–**15** (Table I), all three compounds having or mimicking a *N*,*N*-dimethyl substitution pattern. The three compounds have very similar pre- and postsynaptic activities. If it is assumed that the more lipophilic N-substituent (up to *n*-propyl) in the aminotetralins is interacting with the "propyl cleft",[37] a comparison of the experimental results for compounds **5** and **16**, both of which may have the *N*-propyl group in the "downward" direction and the *N*-methyl group in the "upward" direction, also supports this hypothesis (Table I). Furthermore, since compounds **7** and **17** both have or mimic a *N*-monomethyl substitution pattern, it leads to the prediction that these compounds should be pharmacologically equivalent at pre- and postsynaptic receptors. Previous studies[37] revealed that compound **17** is equivalent to **7** biochemically (presynaptic agonism) and shows no postsynaptic activation at 2 μmol/kg. In order to investigate the possible presynaptic selectivity of **17**, we administered 100 μmol/kg of this compound to reserpinized animals, and as can be seen in Table I no significant postsynaptic effect is elicited. Compound **17** is thus presynaptically selective, which was not recognized in the previous study.[37] The hypothesis in particular implies that the piperidine ring in (*S*)-**6** in its agonist conformation (Figure 5) acts as a methyl group with respect to the "propyl cleft", while the propyl group in the agonist conformation of (*R*)-**6** completely fills the cleft (Figure 10).

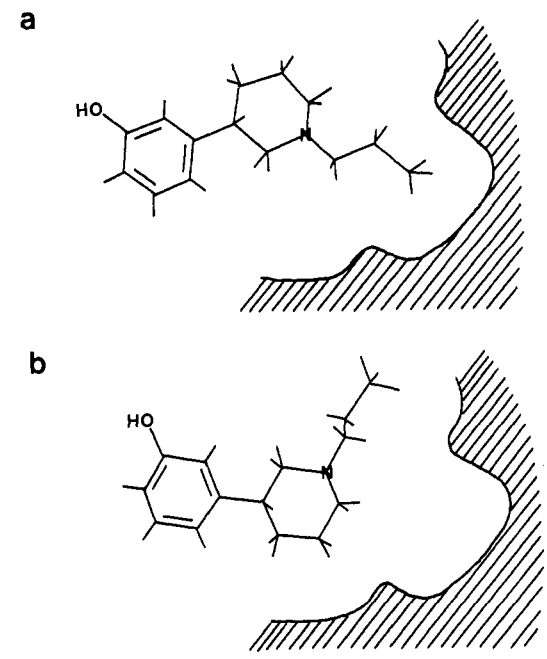

Figure 10. Suggested interactions between (a) (*R*)-**6** and (b) (*S*)-**6** and the DA receptor.

Even if the phenolic part and the nitrogen atom/nitrogen lone pair (or NH group) are correctly positioned, the activation of the receptors seems to be determined by a delicate balance of the lipophilicity and steric demands of the *N*-alkyl groups. A single *N*-methyl groups is sufficient for activating presynaptic receptors, as exemplified by compounds **17** and (4a*S*,10b*S*)-**7**, especially if it can be positioned in the "propyl cleft"; compound **11** has a very low presynaptic activity (Table I). The low activity of the mono(*n*-butylamino)tetralin **18** further supports this hypothesis.[37] This compound can not have its *n*-butyl group in the "downwards" direction. Thus, there will only be a hydrogen in the "propyl cleft" when this compound interacts with the receptor. The postsynaptic receptor seems to have a greater demand for lipophilicity around the nitrogen atom; compounds **17** and (4a*S*,10b*S*)-**7** are inactive at this receptor. An *N*-ethyl group or an *N*,*N*-dimethyl group, as in the postsynaptically active compounds **13**–**15** and **19**, seems to be the minimum requirement. For both types of receptors experimental data show that an elongation of an *N*-alkyl group (up to propyl) in the "downward" direction has a greater influence on the activity than a corresponding elongation in the "upward" direction.[34]

We thus suggest that the lack of postsynaptic agonism for (*S*)-**6** is due to the presence of only a "methyl group" (methylene group) in the "propyl cleft" in the agonist conformation. Although this substitution pattern gives high postsynaptic activity to the rigid compound (4a*S*,10b*S*)-**4**, the lipophilicity of the methylene group in

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(37) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Sanchez, D.; *J. Med. Chem.* **1979**, *22*, 1469.

the "downward" direction is not enough to stabilize the agonist conformation of (S)-6, considering that this compound requires 2.4 kcal/mol in conformational energy to acquire the active conformation (see above). Instead, the antagonist conformation, which requires less energy (0.7 kcal/mol), is employed. In contrast, the N-propyl group in the "downward" direction and the methylene group in the "upward" direction in (R)-6 suffice to stabilize its agonist conformation. If the lipophilicity of the N-alkyl groups in (S)-6 is increased by employing the n-butyl analogue (postsynaptically active),[9] the energy requirement for the conformational rearrangement of (S)-6 into its agonist conformation may be fulfilled. An additional factor explaining the postsynaptic agonism of the n-butyl analogue of (S)-6 may possibly be decreased postsynaptic antagonism due to N-alkyl sensitivity of postsynaptic blockage. This was shown to be the case for the N,N-di-n-butyl analogue of compound 8.[38] The impact of the N-alkyls on the agonist effects may be interpreted as an effect upon the intrinsic activity at the receptor level. Still another way to increase the intrinsic activity, at least postsynaptically, is represented by the catechol (S)-20 compared to (S)-6.[27] Since catechols are known to also stimulate D1 receptors,[1] this raises the possibility that the increased postsynaptic effects of these catechols may partly be due to D1 stimulation.[27]

Conclusions

The spatial relationships between the hydroxyl group, the aromatic ring, the nitrogen atom, and the nitrogen lone pair (or in the case of a protonated nitrogen atom, the NH bond) required for activation of central pre- and postsynaptic DA receptors seem to be identical or at least very similar. This implies that presynaptic selectivity can not be understood in terms of different geometric fits to the two receptor types. For the compounds studied in this work the determining factors for activity and selectivity are (i) the properties of the N-substituents, i.e., lipophilicity, steric requirements, conformational probabilities, and directionality ("upward"/"downward"); (ii) the conformational energy required for flexible molecules like 3PPP (6) to acquire a "correct" geometry; and (iii) the degree of aromatic hydroxylation.

The receptor interaction model presented here, which is based on the McDermed receptor concept, on superimpositions of structures calculated by molecular mechanics and on conformational analysis of N-alkyl substituents suggests that the piperidine ring is equivalent to a methyl group in its interaction with pre- and postsynaptic receptors. This hypothesis led to the prediction of presynaptic selectivity for compound 17, which was also observed in subsequent testing.

Compound 6 was first reported to be a DA autoreceptor selective agonist in its racemic form. Later resolution and testing of the pure enantiomers revealed that (S)-6 has a dual action. It stimulates the high-sensitive autoreceptors and blocks the low-sensitive postsynaptic receptors. Comparisons with rigid structures having either agonistic or antagonistic properties and conformational analysis of (S)-6 led to the conclusion that this compound is acting as an agonist in one rotameric form and as an antagonist in another rotameric form. Neither of these conformations is an energy minimum for the isolated molecule. The presynaptic selectivity for (S)-6 and the nonselectivity of (R)-6 are suggested to be due to the different N-alkyl properties in the "upward" and "downward" directions of these compounds in their "agonist conformations" and the conformational energy necessary to acquire these conformations. The proposed receptor interaction model may be further refined through similar analysis work for other classes of molecules active at central pre- and postsynaptic DA receptors.

Acknowledgment. We gratefully acknowledge Dr. Kjell Svensson and his staff for performing the additional behavioral studies needed to make Table I complete. We also thank Dr. Stephan Hjorth for recalculation of data from previous experiments, Miss Boel Göransson for help with the illustrations, and Dr. Robert E. Carter for linguistic criticism. H.W. acknowledges a Fogarty International Postdoctoral Fellowship with the aid of which part of this work was completed. This work was supported by grants from the Swedish Natural Science Research Council and the Swedish Medical Research Council.

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Synthesis and Dopaminergic Binding of 2-Aryldopamine Analogues: Phenethylamines, 3-Benzazepines, and 9-(Aminomethyl)fluorenes

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A series of 2-aryldopamine analogues were synthesized and evaluated for their effects on D_1 and D_2 dopamine receptors. The 2-phenyldopamine and 6-phenylbenzazepine analogues exhibited weak binding to both D_1 and D_2 receptors. The 9-(aminomethyl)fluorenes also exhibited weak D_2 binding; however, 2,5,6-trihydroxy-9*H*-fluorene-9-methanamine (**4b**) exhibited D_1 binding comparable to apomorphine. The binding activity has been correlated with the calculated torsion angle of the biphenyl portion of these molecules. Good D_1 dopamine binding occurs when the aromatic rings approach coplanarity; poor binding occurs when the aromatic rings are orthogonal.

The simplest example of a 2-aryldopamine is 6-(2-aminoethyl)[1,1'-biphenyl]-2,3-diol (**1a**, 2-phenyldopamine) in which the two aromatic rings of the biphenyl system are not part of a fixed ring system. This compound has been reported to be a very weak stimulator of dopamine-sensitive adenylate cyclase (D_1 dopamine receptor activity)[2] and a potent inhibitor of dopaminergic D_2 agonists in brain

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0022-2623/86/1829-1904$01.50/0