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Stereochemical Characteristics of Dopamine Agonists: Molecular Structure of Bromocriptine and Structural Comparisons with Apomorphine

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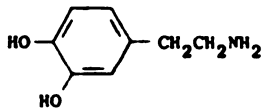
SUMMARY

CAMERMAN, NORMAN, LILLIAN Y. Y. CHAN, AND ARTHUR CAMERMAN. Stereochemical characteristics of dopamine agonists: Molecular structure of bromocriptine and structural comparisons with apomorphine. *Mol. Pharmacol.*, **16**, 729–736 (1979).

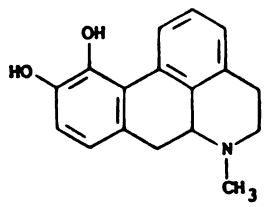
Crystals of bromocriptine methanesulfonate·0.5 isopropanol are monoclinic with cell dimensions $a = 13.991$, $b = 8.296$, $c = 17.596$ Å, $\beta = 97.09°$, space group $P2_1$ with two formula units per cell. The structure was determined by direct phasing and Fourier methods and refined to a residual of $R = 0.08$. The molecule of bromocriptine consists of two different similarly-oriented substituted-polycyclic systems connected by an amide linkage whose plane is roughly perpendicular to them. The absolute configuration has been verified crystallographically. The dopamine-like portion of the molecule has been compared conformationally with the active and inactive forms of apomorphine; conclusions regarding the stereochemistry of the agonist-receptor interaction have been drawn.

INTRODUCTION

Parkinson's disease is associated with a brain deficiency of the neurotransmitter dopamine. The efficacy of treatment with L-



dopa, the biosynthetic precursor of dopamine, is probably dependent on the extent of degeneration in the presynaptic nigrostriatal neurons, the site of conversion of L-dopa to dopamine and transport of the dopamine to the postsynaptic receptors. A therapeutic strategy that seeks to overcome this problem is to stimulate the postsynaptic dopaminergic receptors in the striatal neurons directly with dopamine agonists, such as apomorphine.



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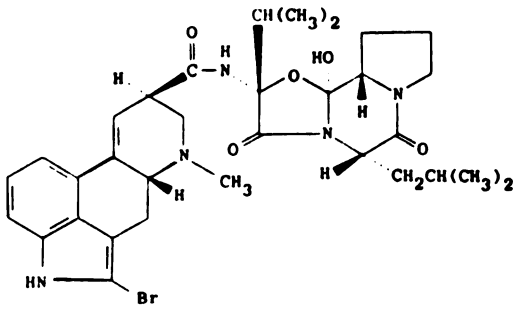

Bromocriptine (2-bromo-α-ergocryptine) was synthesized in a program of chemical modification of ergot alkaloids to achieve enhanced inhibition of prolactin secretion (1). Central nervous system activity of ergot alkaloids on autonomic functions have long been recognized, and dopaminergic effects of bromocriptine were soon described (2). Corrodi *et al.* corroborated the CNS dopaminergic action of bromocriptine and interpreted it as being due to postsynaptic stimulation of dopamine receptors (3). These findings led to the testing of bromocriptine as an antiparkinsonism agent in humans (4–8). In most of the clinical trials, treatment with bromocriptine, either alone or in combination with L-dopa, resulted in significant improvements in many patients, and bromocriptine is potentially a major new therapeutic agent in Parkinson's disease.

The dopaminergic properties of bromocriptine have also been demonstrated in recent binding studies with calf brain tissues. Bromocriptine has a strong affinity for postsynaptic dopaminergic receptors (9) (K_i = 2.5 nm); further, a linear relation has been shown to exist between *in vitro* postsynaptic receptor binding and therapeutic dose for antiparkinsonism effects (10). Thus there appears to be little doubt that bromocriptine can reach and stimulate postsynaptic CNS dopaminergic receptors, and that it is this property which is responsible for its antiparkinsonism activity.

We report here the results of a crystal and molecular structure determination of solvated bromocriptine methanesulfonate, and conformational comparisons of the molecule with apomorphine. The rationale for this endeavor was that comparisons of the three-dimensional structure of a complex molecule such as bromocriptine with other dopaminergics might reveal information about structural requirements for receptor binding, and about possible structural considerations for the design of new antiparkinsonism agents. Our findings have enabled us to form some conclusions regarding the stereochemistry of dopaminergic receptor binding with dopamine agonists.

METHODS

Colorless crystals of bromocriptine methanesulfonate (subsequently shown to contain approximately 0.5 moles isopropanol per mole of bromocriptine) were obtained by solvent evaporation in the cold from a solution containing a 1:1 mixture of methanol and isopropanol.

Crystal data (λCuKα = 1.54178 Å). Bromocriptine methanesulfonate·0.5 isopropanol: $C_{32}H_{40}BrN_5O_5 \cdot CH_3SO_3H \cdot 0.5\ (CH_3)_2CHOH$, formula weight 780.8; monoclinic, a = 13.991 (8), b = 8.296 (6), c = 17.596 (10) Å, β = 97.09 (8)°, U = 2026.7 Å^3, d_x = 1.28 g/cm^3, Z = 2; μ(CuKα) = 20.5 cm^{-1}; space group $P2_1$.

A well-formed prism, 0.2 × 0.15 × 0.7 mm in size, was chosen and the intensities of all independent reflections having 2θ (CuKα) ≤ 130° (corresponding to a minimum interplanar spacing of 0.85 Å) were measured on an automated four-circle diffractometer with Ni-filtered CuKα radiation using the $2\theta/\theta$ scan technique. The intensities were corrected for background, and structure amplitudes were derived in the usual way. No absorption corrections were applied. A total of 3714 unique reflections were measured, of which 3033 (82%) were considered to be observed ($I > 3\sigma(I)$) and were used in the refinement.

Structure determination and refinement. The structure was solved using the direct phasing program MULTAN: 292 reflections with $|E| > 1.65$ were input, and the best set of phases (R_{karle} = 0.22) were used to produce an E-map. The bromine atom was easily located due to its height on the electron density map and to the occurrence of a pseudo-mirror plane through its position, perpendicular to the crystal b-axis. The positions of 31 other atoms could also be

specified, 13 on the mirror plane and 18 (in the non-bromine containing poly-ring system) off it, thereby arbitrarily choosing one enantiomer. A Fourier electron density distribution phased on these atoms ($R = 0.35$) revealed the positions of 11 more atoms in the structure, and isotropic least-squares refinement and difference Fourier distributions then resulted in the location of all 48 non-hydrogen atoms of bromocriptine methanesulfonate ($R = 0.23$). Further refinement with anisotropic thermal parameters for Br and S and adjustment of the positions of three C atoms which had refined to the wrong side of the pseudo-mirror decreased R to 0.12. At this point a difference Fourier enabled the location of 43 hydrogen atoms (all except the H on the protonated nitrogen, N6, which was found on a subsequent difference map) and refinement (anisotropic thermal parameters for all nonhydrogen atoms, fixed isotropic $B = 7.5$ Å^2 for hydrogen atoms) converged at $R = 0.083$.

The absolute configuration of bromocriptine was verified by including the imaginary parts of the Br and S scattering factors and calculating structure factors for both possible enantiomorphic forms: the residuals were $R = 0.0815$ and 0.1086 for the correct and incorrect choices, respectively.

During the refinement procedure difference Fourier distributions indicated the presence of a partially-occupied disordered isopropanol site. Attempts were made to include the isopropanol molecule in the refinement, but because of the disorder the bond lengths and angles became erratic. We therefore omitted the molecule until after refinement of the bromocriptine methanesulfonate was complete, and then included a half-weighted isopropanol (hydrogens omitted) with reasonable bond parameters, positioned to best approximate the residual density, in a final structure factor calculation ($R = 0.080$ for the observed data). Throughout the calculations unit weights were used and the function minimized was $\Sigma\omega(|F_o|-|F_c|)^2$. Scattering factors were as cited for the real (11) and imaginary (12) components. The maximum shift/error in the final cycle of refinement was 0.85 (average shift/error = 0.25).

Table 1 lists the atomic fractional coordinates; the anisotropic thermal parameters, hydrogen positional parameters and a list of the observed and calculated structure factors are available from the authors on request.

RESULTS AND DISCUSSION

Description of the structure. Figure 1 is a stereoscopic view of the structure. Bromocriptine is comprised of two relatively flattish polycyclic systems oriented in somewhat similar manners (the angles between normals to "best" least-squares planes through each polycyclic skeleton is 18°), connected by an amide linkage whose plane is roughly perpendicular to the ring systems (angles between normals to the amide plane and rings C and E are 73° and 90°, respectively). The configurations at all of the asymmetric centers are confirmed as depicted by the structural formula given previously. Methanesulfonate ions are situated above and below the C ring of bromocriptine molecules, their charged SO_3^- ends interacting with N6. The disordered isopropanol site is at the top of Fig. 1.

Figure 2 shows the bond lengths and a few selected bond angles in the molecule, as well as the atomic numbering scheme and ring designations. The carbonyl carbon ... amide nitrogen (C18-N20) distance is 1.35Å, which along with the planarity of the group (maximum deviation of C8, C18, O19, N20, C2′ from the best plane through them is 0.03Å; torsion angle C8-C18-N20-C2′ = +177°), indicates a high degree of double bond character. The site of protonation in bromocriptine is N6, confirmed by near-tetrahedral values of the interatomic angles about the nitrogen. Because of limited precision the individual bond distances in the rings show some variation from expected values, but the average lengths of all similar bonds are consistent with normal values (e.g., average of the C = C distances is 1.38Å) and they require little comment. The bond angles are also near normal; a table of all interatomic angles may be obtained from the authors.

The conformations of the various rings in bromocriptine are as follows: rings A and D are planar (maximum atomic deviation

TABLE 1

Final positional parameters (fractional)

Atom	x	y	z
Br	0.0588(2)	0.6400	0.9365(1)
N1	0.2451(14)	0.5294(27)	0.9260(8)
C2	0.1669(17)	0.5919(28)	0.8854(10)
C3	0.1706(13)	0.6036(26)	0.8087(8)
C4	0.1101(13)	0.6644(24)	0.7404(8)
C5	0.1381(11)	0.5785(22)	0.6680(8)
N6	0.0853(10)	0.6547(21)	0.5969(6)
C7	0.1190(11)	0.5969(24)	0.5243(8)
C8	0.2241(12)	0.6519(24)	0.5244(8)
C9	0.2820(11)	0.6142(27)	0.5983(8)
C10	0.2476(11)	0.5787(21)	0.6629(8)
C11	0.3046(13)	0.5294(26)	0.7339(9)
C12	0.3990(14)	0.4622(32)	0.7416(11)
C13	0.4452(15)	0.4187(35)	0.8138(12)
C14	0.4042(18)	0.4379(36)	0.8781(13)
C15	0.3069(16)	0.5023(30)	0.8727(10)
C16	0.2643(12)	0.5443(25)	0.8021(9)
C17	−0.0231(12)	0.6269(39)	0.5901(9)
C18	0.2640(12)	0.5835(23)	0.4552(9)
O19	0.2750(9)	0.6675(17)	0.4015(6)
O1′	0.4094(8)	0.4005(15)	0.3773(6)
C2′	0.3214(13)	0.3322(23)	0.3986(9)
C3′	0.2510(14)	0.3450(24)	0.3230(9)
N4′	0.2980(9)	0.4306(19)	0.2721(7)
C5′	0.2589(12)	0.4782(29)	0.1945(9)
C6′	0.3353(13)	0.4765(31)	0.1408(10)
N7′	0.4262(10)	0.4389(23)	0.1715(7)
C8′	0.5095(14)	0.4485(32)	0.1248(10)
C9′	0.5957(14)	0.4237(34)	0.1805(10)
C10′	0.5653(12)	0.4546(31)	0.2600(10)
C11′	0.4622(13)	0.3945(23)	0.2509(8)
C12′	0.3944(12)	0.4721(22)	0.3029(8)
N20	0.2863(11)	0.4251(19)	0.4597(7)
C13′	0.3385(15)	0.1541(27)	0.4253(11)
C14′	0.3641(20)	0.0498(29)	0.3602(15)
C15′	0.4143(17)	0.1468(39)	0.4924(13)
O16′	0.1717(10)	0.2916(22)	0.3132(8)
C17′	0.2102(13)	0.6408(35)	0.1896(10)
C18′	0.1153(16)	0.6525(41)	0.2241(11)
C19′	0.0816(23)	0.8194(44)	0.2266(19)
C20′	0.0404(17)	0.5457(52)	0.1773(17)
O21′	0.3165(10)	0.5065(29)	0.0738(7)
O22′	0.4095(8)	0.6371(18)	0.3073(5)
S	0.1424(3)	0.1236(8)	0.6120(2)
OS1	0.2054(14)	0.2036(27)	0.5688(10)
OS2	0.1197(18)	−0.0275(22)	0.5891(11)
OS3	0.0569(12)	0.2199(23)	0.6113(10)
CS	0.1941(14)	0.1158(35)	0.7074(10)
Cip1	0.2640	−0.0100	0.0280
Cip2	0.3420	−0.1200	0.0200
Cip3	0.2860	0.0600	0.1080
Oip	0.2270	0.0680	−0.0400

from the planes is 0.01Å), B adopts a half-chair conformation with C5 0.59Å out of the plane of the other five atoms (max. dev. of other atoms is 0.03Å), and C is best described as a skewed chair, with C5 and C8 at the apices. In the other polycyclic system ring E approaches planarity (max. dev. 0.05Å), while F and G are half-chairs, with C12′ 0.65Å from the plane of the other five atoms (max. dev. 0.01Å) of ring F, and C10′ is 0.55Å from the plane of the other four (max. dev. of these four is 0.03Å) of ring G.

There is an intramolecular hydrogen bond in bromocriptine, from the hydroxyl group at C12′ to the amide carbonyl oxygen; the O22′ ... O19 separation is 2.67Å (H22′ ... O19 is 1.78Å) and the angle O22′-H22′ ... O19 is 149°. Along with the rigidity implied by the double bond character of the amide linkage, this serves to reduce conformational freedom in the molecule. The only degree of freedom remaining appears to be rotation of the ABCD ring system about the C8-C18 bond; however even this may be restricted somewhat by steric involvement of the isopropyl and isobutyl side chains on the EFG ring system, and by a possible weak interaction between H8 and the amide carbonyl oxygen (suggested by the observation that they adopt an eclipsed configuration, Fig. 1).[2] Although these interactions are individually weak, the total effect may be to enhance considerably the observed conformation, and they are at least suggestive that this may be the preferred conformation for bromocriptine.

There is only one intermolecular hydrogen bond between bromocriptine molecules

[2] The structure of the free base form of bromocriptine (unprotonated at N6) has recently been determined (Weber, H. P., personal communication). In that structure there is a hydrogen bond from N20-H to N6 (vs N20-H to a methanesulfonate in the protonated structure presented here); the rest of the molecule is conformationally similar to bromocriptine methanesulfonate. The N20 ... N6 hydrogen bond serves to further stabilize this observed conformation by restricting rotation of the ABCD ring system, and thereby adds further independent support to our stereochemical conclusions about the side of receptor approach.

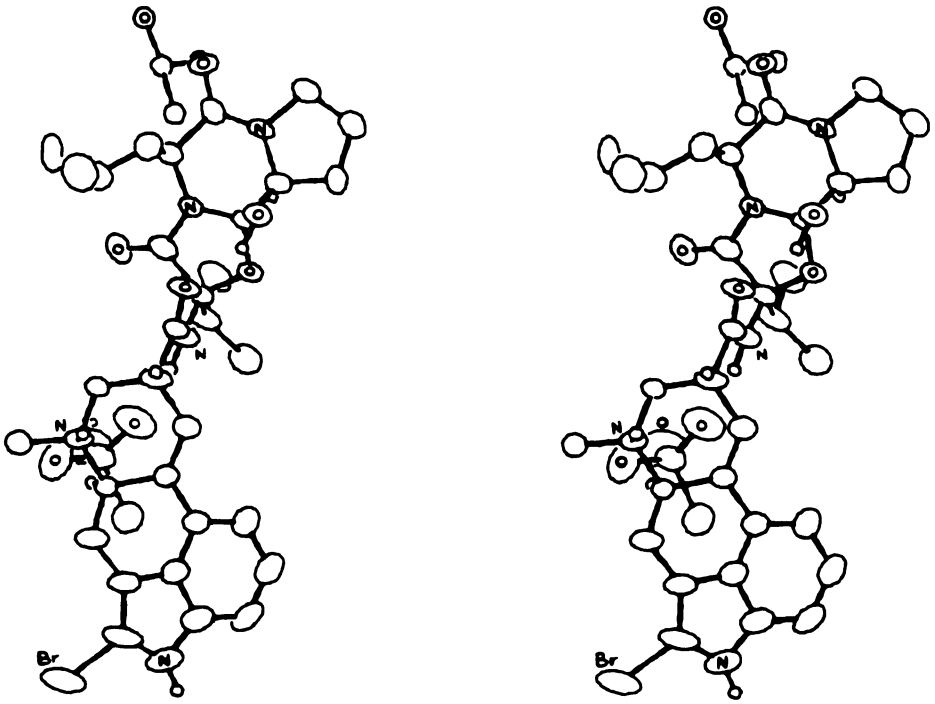

FIG. 1. *Stereoscopic view of bromocriptine methanesulfonate·0.5 isopropanol*
For clarity, only hydrogens at asymmetric centers or which take part in hydrogen bonding are shown (small circles). Unlabelled atoms are carbons.

in the crystal structure, from N1 to O21′ of another molecule (N . . . O distance is 2.68Å, H . . . O = 1.89Å, the angle N1-H1 . . . O21′ is 149°). The only other possible hydrogen bond donors in the molecule are the amide nitrogen (N20) and the protonated N6; these form contacts with different methanesulfonate ions: N20 . . . OS1 = 2.98Å (H20 . . . OS1 = 1.98Å), angle N20-H20 . . . OS1 is 167°; $^{+}$N6 . . . OS2 = 2.69Å (H6 . . . OS2 = 1.82Å), angle $^{+}$N6-H6 . . . OS2 = 171°. The carbonyl oxygen at C3′ (O16′) and the E-ring O1′ do not take part in intermolecular contacts; there are no H-bond donors available for them. The partially-occupied disordered isopropanol site, as expected, does not form any close intermolecular approaches.

Structural comparison of bromocriptine with apomorphine. It is of interest to compare stereochemically the dopamine-like portion of bromocriptine (N1-ring D-C10-C5-N6) with other dopaminergics; we have chosen apomorphine for such comparisons because it is one of the best characterized and most widely tested dopamine agonists, and because its rigid structure removes any problems of conformational variation under differing conditions.

Apomorphine has one asymmetric carbon atom and can therefore exist in two isomeric forms; the naturally-occurring isomer has the R(−) configuration. The S(+)-apomorphine stereoisomer has been synthesized (13) and shown to be inactive in producing rotational behavior in unilateral caudate-lesioned mice (13) and in eliciting stereotyped sniffing behavior in rats (14), both of which are tests for dopamine-receptor stimulation. In addition, although no postsynaptic dopamine receptor binding studies have been carried out with S(+)-apomorphine, the isomer has a low binding affinity (100-fold less than R(−)-apomorphine) for pre-synaptic dopamine receptors (15). Thus all of the available evidence in-

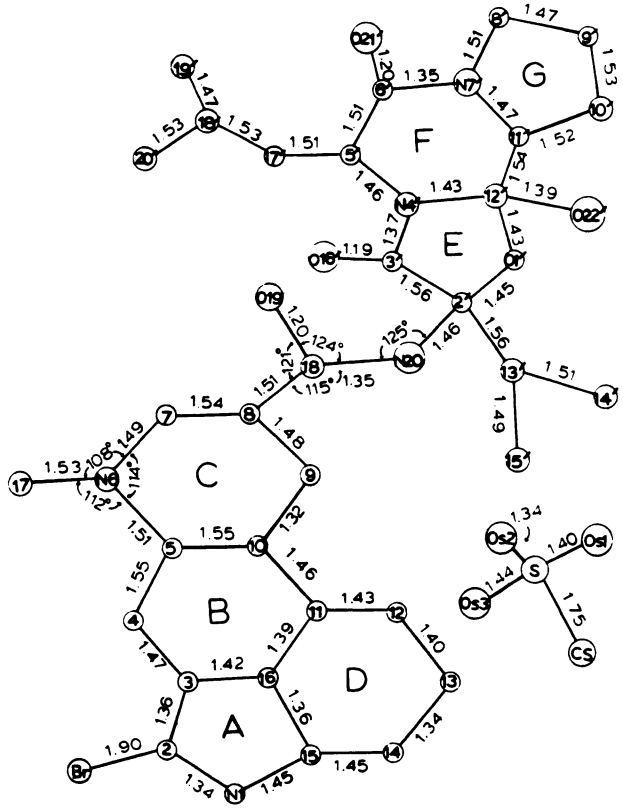

FIG. 2. *Bond distances and some valency angles in bromocriptine methanesulfonate; standard deviations are approximately 0.025Å and 1.5°*

dicates that dopaminergic activity resides almost entirely in the R(−) isomer of apomorphine. Since the structure of apomorphine hydrochloride is known (16, 17) this presents us with the opportunity to compare the dopaminelike portion of bromocriptine with both the active and inactive stereoisomers of apomorphine, and to see if stereochemical differences can explain activity differences.

Figure 3 is a stereoscopic view of the ABCD ring system of bromocriptine superimposed on (a) R(−)-apomorphine, and (b) S(+)-apomorphine, so that the dopaminelike features (N1-ring D-C10-C5-N6 in bromocriptine; corresponding entities in apomorphine) most closely overlap. Surprisingly, the degree of fit is *better* for bromocriptine with S(+)-apomorphine, the inactive isomer, than with the active R(−) form. This can be seen clearly in Fig. 3 and also from a comparison of torsion angles in the dopamine-like portions (Table 2). Obviously, dopamine agonist activity cannot be rationalized on the goodness-of-fit of these portions of the molecules alone. The main difference in the conformations of R(−) and S(+)-apomorphines involves the two rings *not* containing the dopamine moiety (left edge of molecules, Fig. 3); in R(−)-apomorphine the conformation is such that these rings bend *away from the viewer* as shown in Fig. 3, while in S(+)-apomorphine they are oriented sharply up *toward the viewer* (it is mandatory to view Fig. 3 stereoscopically to fully appreciate this difference.). It seems reasonable to conclude from these observations that *the approach of these agonists to the dopamine receptor must be from the side of the molecules closest to the viewer in Fig. 3*; the differing activities of the apomorphine isomers can then be rationalized by proposing that the upward extension of the two rings not con-

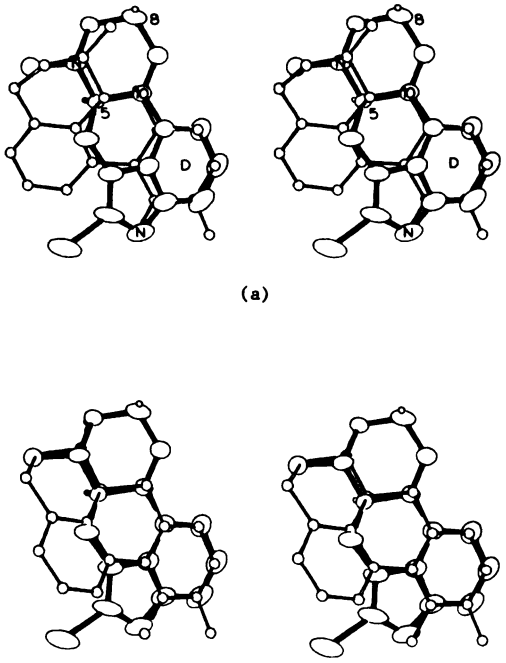

FIG. 3. *Stereoscopic view of the ABCD ring system of bromocriptine (dark bonds) superimposed on (a) R(−)-apomorphine, and (b) S(+)-apomorphine (light bonds) so that dopamine-like parts of the molecules are maximally fitted*

taining the dopamine moiety in S(+)-apomorphine blocks the approach of the dopaminergic portion to the receptor.[3]

Another piece of data which may be supportive of the above conclusion is the observation that C8-iso-bromocriptine is inactive as a dopamine receptor stimulator (18). Inspection of Fig. 1 indicates that if the positions of H8 and the amide-EFG ring system were interchanged at C8, the EFG system would sterically interfere with any approach (eg. by a receptor) to the side of the ABCD ring system toward the viewer.

Distances within the dopamine-like portion of bromocriptine are N6 ... center of D-ring = 5.18Å (5.13Å and 5.09Å in apomorphine and dopamine, respectively) and N6 ... N1 = 6.04Å (vs N ... OH distances of 6.48Å and 6.83Å in apomorphine and dopamine).

[3] These conclusions are valid, of course, only if the common structural elements in these compounds, the "dopamine-like" portions, are the bases of their dopaminergic properties.

TABLE 2

Torsion angles in the dopamine-like molecular portion

	Bromocriptine	S(+)-apomorphine	R(−)-apomorphine
C11-C10-C5-N6 (C6-C7-C8-N1)[a]	+171°	−178°	+178°
C12-C11-C10-C5 (C1-C6-C7-C8)[a]	+156°	+139°	−139°
C16-C11-C10-C5 (C5-C6-C7-C8)[a]	−23°	−39°	+39°
C11-C16-C15-N1 (C6-C5-C4-O2)[a]	−178°	−178°	+178°

[a] Atomic numbering for apomorphine is from (16).

In summary, we have determined and presented the three-dimensional structure of bromocriptine methanesulfonate. Stereochemical comparisons with the structures of the active and inactive isomers of apomorphine have led us to conclusions regarding the side of the molecule which interacts with dopamine receptors and the

conformational requirements for dopaminergic activity. We believe that the search for new and better dopamine agonists could profit by attention to these stereochemical conclusions.

ACKNOWLEDGMENT

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