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On the Stereochemistry of Dopaminergic Ergoline Derivatives

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SUMMARY

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Three-dimensional structures of bromocriptine hydrochloride, bromocriptine free base, and apomorphine hydrochloride are compared in order to delineate those portions of the molecules responsible for dopaminergic activity. It is shown that the orientation of the nitrogen atom lone pair electrons in the ergoline derivatives is not necessarily fixed by the configuration at the asymmetrical carbon atom, and it is suggested that stereochemical comparisons should be based primarily on superpositions of electronegative moieties, rather than aromatic nuclei.

Since the discovery of therapeutically useful dopamine agonist activity in a number of ergoline derivatives such as bromocriptine, considerable interest has developed in delineating the portions of the ergoline molecular structure responsible for dopaminergic properties. Such information could serve as a basis for the synthesis of new dopamine agonists; it is best obtained from consideration of similarities in 3-dimensional stereochemistries of several dopaminergics, preferably those having limited conformational freedom. Thus we recently elucidated the structure of a bromocriptine salt (1) and compared it stereochemically with apomorphine hydrochloride (2) (Structure 1b) by maximally fitting their common dopamine-like elements, as shown by boldface lines in Structures 1a and 1b. The 3-dimensional fit is shown stereoscopically in Fig. 1. This method of comparison has been criticized (3, 4) on the basis of differing absolute configurations at the asymmetrical carbon atoms in the two compounds (C-5 and C-6a in Structures 1a and 1b, respectively); however, it is not the chirality at the asymmetrical center that is important per se, it is the effect on the over-all stereochemistries caused by the differing chiralities. Inspection of Fig. 1 shows that the gross conformational shape of the two molecules is similar, and that the *positions* of the corresponding electronegative atoms (the methylated nitrogen atoms in each and the pyrrole nitrogen atom in bromocriptine and the 11-hydroxyl oxygen atom in apomorphine) are closely similar ($N \ldots N$ = 0.22 A, $N \ldots O$ = 0.39 A).[3] The protons on the charged nitrogens in these two salts point in opposite *directions*, however, and if receptor binding involves a protonated nitrogen as hydrogen bond donor, that could argue against this mode of comparison. This argument is considerably weakened, though, by (a) lack of information about the state of protonation of the nitrogen atom at the receptor site and (b) a crystal structure determination of unprotonated bromocriptine[4] in which the nitrogen atom lone-pair of electrons is oriented in the direction opposite to the proton in the bromocriptine salt structure. Figure 2 shows stereoscopically the ergoline portions of the protonated and unprotonated bromocriptine structures maximally superposed; the opposite nitrogen atom lone-pair orientations in the two structures is effected by a twist of the nitrogen atom-containing ring, while the other parts of the molecules, including the tricyclic ring systems not shown, remain conformationally similar ($N \ldots N$ = 0.10 A, pyrrole $N \ldots N$ = 0.03 A). Figure 3 illustrates stereoscopically the ergoline portion of unprotonated bromocriptine molecule superposed with the active enantiomer of apomorphine hydrochloride in the manner shown in Structures 1a and 1b; the over-all fit ($N \ldots N$ = 0.15 A, $N \ldots O$ = 0.38 A) closely resembles that of protonated bromocriptine and apomorphine (Fig. 1) and, despite the differing chiralities at the asymmetrical carbon atoms in the two, the nitrogen atom lone-pair direction is the same for both. It thus appears that the direction of the nitrogen atom lone-pair electrons is dependent on environment, and the absolute configuration at the asymmetrical carbon atom does not definitively fix the nitrogen atom lone-pair orientation.

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[3] Distances between atoms in superposed molecules depend upon the parts of the molecules chosen to be maximally fitted; individual values quoted are meant only as a guide for comparing "goodness-of-fit" of functional groups when different models of comparison are used.

[4] H. P. Weber, personal communication.

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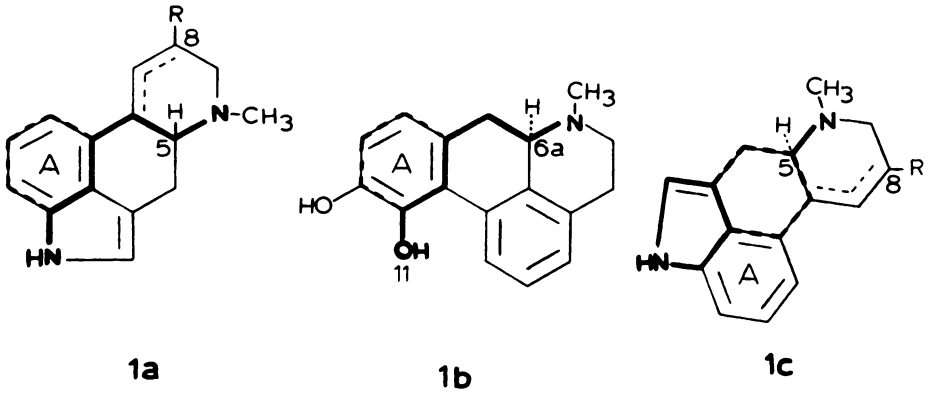


STRUCTURE 1.

Nichols (3) and Bach *et al.* (4) have proposed an alternative mode of comparison of the structures of apomorphine and ergoline derivatives. On the basis of retention of similar chirality at the asymmetrical carbon atoms in the two molecules, they have suggested that the pyrrolethylamine of ergolines corresponds to the phenylethylamine of apomorphine (Structures 2a and 2b). It seems to us that this proposal, as it stands, is not suitable, as it places emphasis on the correspondence of the aromatic pyrrole ring with the phenyl (*A*) ring of apomorphine and ignores the more important (in our opinion) correspondence of the electronegative pyrrole nitrogen with the 11-hydroxyl oxygen atom.[5] Figure 4 is a stereoscopic diagram of the ergoline portion of bromocriptine (protonated) fit in the above manner to apomorphine hydrochloride; the over-all conformations are similar, but the positions of the aromatic ring electronegative atoms do not coincide (pyrrole *N* . . . *O*-10 = 1.89 A, pyrrole *N* . . . *O*-11 = 2.76 A).

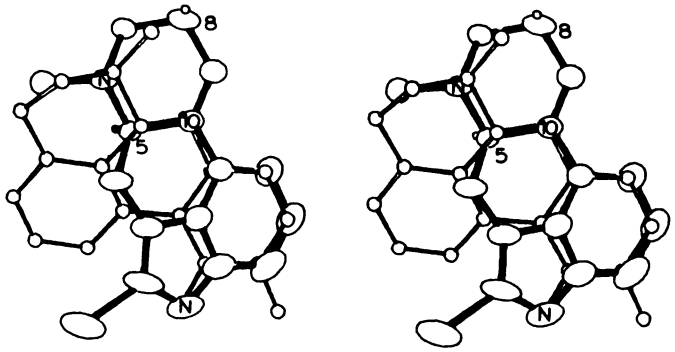


FIG. 1. *Stereoscopic view of the ergoline system of bromocriptine methanesulfonate (large ellipsoids, dark bonds) superposed on R(−) apomorphine hydrochloride (small circles) so that dopamine-like parts of the molecules are maximally fitted*

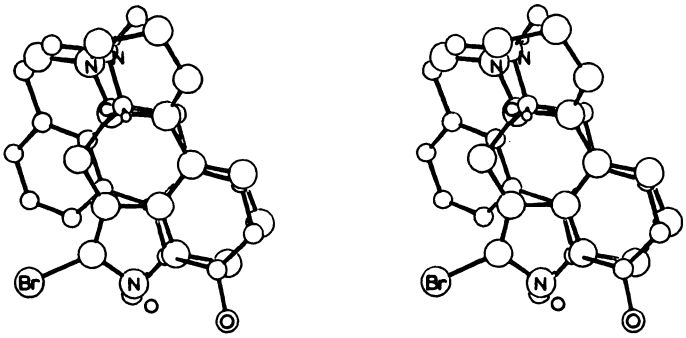


FIG. 3. *Stereoscopic diagram of bromocriptine free base (large circles) superposed on apomorphine (small circles) as in Fig. 1*

[5] A similar correspondence, between the ergoline pyrrole nitrogen and the *m*-hydroxyl of octahydrobenzo[f]guinolines, has been proposed by Cannon (5).

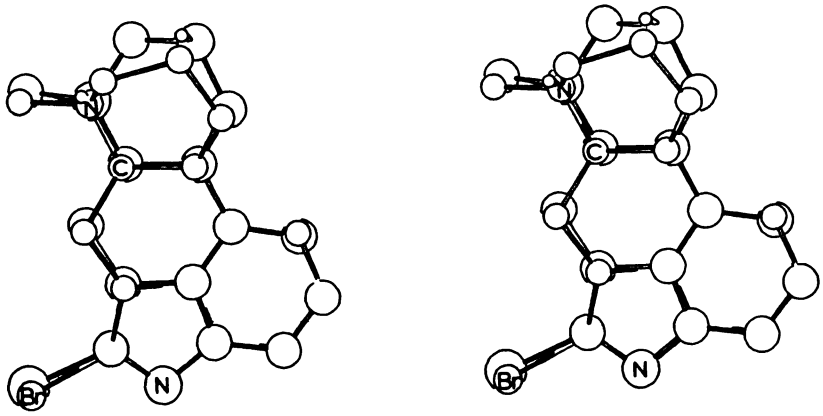
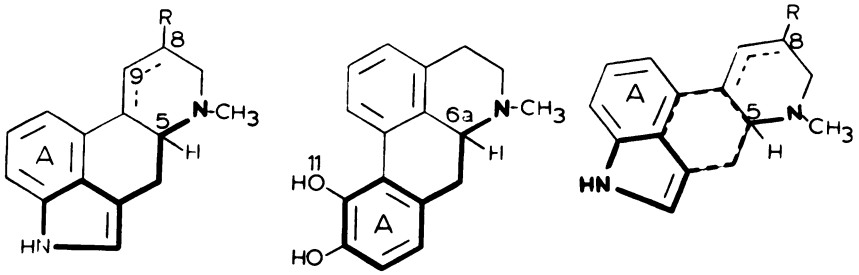


FIG. 2. *Stereoscopic view of the superposition of the ABCD ring systems of protonated (large circles) and unprotonated (small circles) bromocriptine*



2a 2b 2c

STRUCTURE 2.

Although one could rationalize the above discrepancy by invoking receptor flexibility, it seems to us that, if retention of similar chirality at C-6a/C-5 is desired, a better alternative would be to fit the two molecules *not* so that the aromatic rings correspond, but so that the pyrrole nitrogen atom and the 11-hydroxyl oxygen atom coincide, while keeping the over-all planes of the molecules as parallel as possible. This scheme of fitting is shown (for ease of comparison) schematically in both Structures 1c and 2c, and in 3-dimensional form in Fig. 5 for the protonated forms of bromocriptine and apomorphine. The conformations of the two molecules are reasonably similar and the positions of the electronegative moieties agree well ($N \ldots N$ is 0.2–0.3 A and $N \ldots O$ is 0.3–0.8 A depending on molecular portions chosen for fitting).

From the above considerations one must conclude that there is at present insufficient structural evidence to establish definitively the exact dopaminergic moiety in the ergoline derivatives. Opposite chirality at a particular carbon atom in the active enantiomers of apomorphine and bromocriptine when dopamine-like portions are compared does not necessarily affect the stereochemistry at the aliphatic amine groups. Molecular superpositions restricted to holding similar chirality at the carbon atom in question seem more reasonable, in our view, if the corresponding electronegative atoms are fitted than if aromatic nuclei are fitted. To arrive at more explicit answers will require careful synthetic and structural experimentation, and detailed 3-dimensional comparisons of active and inactive analogues. The recently described (4) synthetic attempts to isolate and identify the dopaminergic portion of ergolines do not, if dopamine agonist activity requires the electronegative atom on the A-ring rather than the ring itself, distinguish between the models described above.

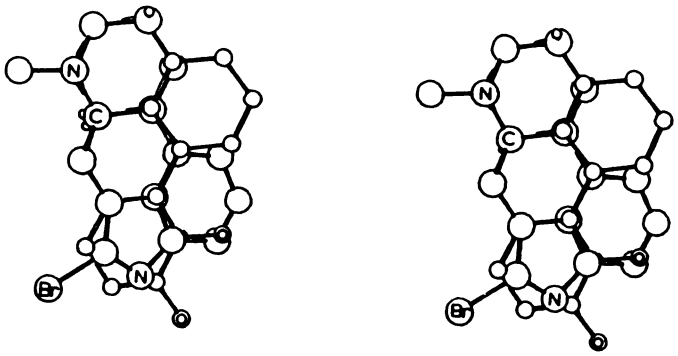


FIG. 4. *Stereoscopic drawing of ergoline portion of protonated bromocriptine (large circles) superposed on R(−) apomorphine so that the pyrrolethylamine of the former is fitted to the phenylethylamine of the latter*

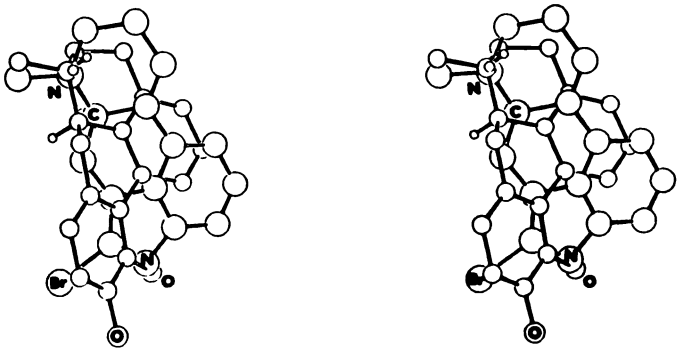


FIG. 5. *Stereoscopic view as in Fig. 4 but superposed so that corresponding electronegative atoms (see text) are fitted*

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