Pharmacological implications of the X-ray structure of a rigid analogue of the tricyclic antidepressants

Although the tricyclic antidepressants as a class are potent competitive inhibitors of the uptake of noradrenaline into nerve endings (Horn, Coyle & Snyder, 1971; Maxwell, Ferris & others, 1974), they are structurally unlike this neurotransmitter. It is of interest, therefore, to attempt to decide the preferred conformations these drugs might possess at the noradrenaline uptake site and to compare these with the preferred conformation of noradrenaline at the same site (Horn, 1973). In general, the tricyclic antidepressants have an unsubstituted 3-carbon side chain which terminates in a substituted amino group and, quite obviously, this side chain could adopt any of a number of low energy conformations at the uptake site. Recently we have reported the X-ray structures of two such drugs, iprindole HCl (Rodgers, Kennard & others, 1974) and imipramine HCl (Post, Kennard & Horn, 1974), the former drug being a weak inhibitor of biogenic amine uptake (Horn & Trace, 1974).

To gain a better understanding of the actual overall conformational requirements of potent inhibitors of noradrenaline uptake we have determined the crystal and molecular structure of the recently reported rigid tricyclic analogue, *N,N*-dimethylspiro [5H- dibenzo [a,d] cycloheptene-5,1′-cyclohexan]-4′-amine (Carnmalm, Jacupovic & others 1974) Fig. 1A. Prismatic crystals of the free base (grown in diethylether) were supplied by Dr. N. Stjernstrom of Astra Lakemedel Pharmaceuticals, Sweden. The molecule crystallizes in the monoclinic system with cell dimensions $a = 6{\cdot}649$ Å, $b = 30{\cdot}90$ Å, $c = 8{\cdot}477$ Å, $\beta = 102{\cdot}41°$ and space group Cc. There are four molecules in the unit cell. Intensities were measured with an automatic diffractometer and used to derive the normalized structure factors (Es). The structure was solved using reflexions with $E \geqslant 1{\cdot}2$, by a non-centrosymmetric direct method program involving the use of magic integers (White & Woolfson, 1975; G. M. Sheldrick, private communication), and refined to an R factor of 0·082. The analysis indicates that the dihedral angle between the planes of the benzene ring is 120·24°. The distance between the nitrogen atom and the centre of ring A is 5·53 Å and that between the nitrogen atom and the centre of ring B is 7·23 Å (Fig. 1B). Full structural details will be published elsewhere.

This drug is known to be a potent competitive inhibitor of noradrenaline uptake into synaptosomes (Carnmalm & others, 1974) and therefore probably binds to the same transport site as noradrenaline (Maxwell & others, 1974). As it is a more or less rigid molecule the values for the various distances found in the crystal structure will be very closely similar to these occurring at the uptake site. There is increasing evidence that the preferred conformation of noradrenaline at its uptake site is the

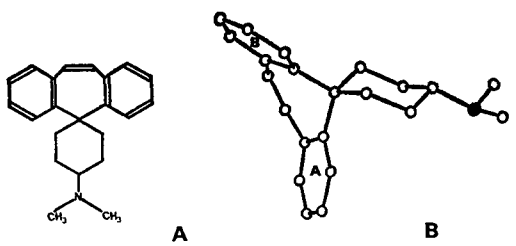

FIG. 1. A. Chemical formula. B. Conformation found in the crystal structure. A and B indicate the benzene rings used in the distance and dihedral angle calculations, ●—N.

fully staggered *trans* form (Horn & Snyder, 1972; Miller, Fowble & Patil, 1973). This is the preferred conformation found in the crystal structure (Carlstrom & Bergin, 1967) in solution by nmr analysis (Ison, Partington & Roberts, 1973) and by theoretical calculation (Kier, 1969). Based on the crystallographic data (Carlstrom & Bergin, 1967) the distance of the terminal nitrogen atom of noradrenaline from the centre of the aromatic ring is calculated as 5·09 Å. It has been suggested (Horn, 1973) that one aromatic ring of the tricyclic nucleus and the terminal amino group could occupy the binding areas that the equivalent functions in noradrenaline normally interact with at the noradrenaline uptake site. The results of a comparison of the above distance of 5·09 Å in noradrenaline with the distances of the two equivalent moieties found in this rigid analogue show that one of them is very similar i.e. 5·53 Å, whilst the other is much larger i.e. 7·23 Å; these data therefore support the above hypothesis.

We thank the Medical Research Council for financial support and the Science Research Council for the diffractometer.

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April 21, 1975

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