COMMUNICATIONS

Conformation of parent tricyclic nucleus in depressant compounds: the X-ray structure of dibenz [b, f] oxepine

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Dibenzo derivatives of the seven-membered rings cycloheptatriene, azepine and oxepine form the parent trinuclear systems of several tranquillizer or energizer psychotropic drugs (Bergmann & Aizenshtat, 1970). In particular, certain enamine and piperazine derivatives of 2-substituted dibenzoxepine possess notable psychopharmacological central-nervous-system depressant activity analogous to that of chlorpromazine (Seidlova, Pelz & others, 1969; Coscia, Causa & Giuliani, 1975). For such (tricyclic neuroleptic) drugs with a six- or seven-membered central ring, there is evidence that ability to block dopamine receptors in the brain, and thus to induce antipsychotic or other pharmacological action, is closely associated with molecular conformation (Horn, Post & Kennard, 1975; Rodgers, Horn & Kennard, 1976a). Since non-planarity and low aromaticity for the central ring appear to be probable requirements for high activity in tricyclic antidepressants, knowledge of the geometry assumed by the parent nuclei should be helpful in assessing the extent to which conformational complementarity aids drug action.

From crystals grown by Dr P. M. G. Bavin of SKF Laboratories Ltd., we have carried out an X-ray single-crystal analysis of the structure of dibenz [b, f]oxepine; this crystallizes in the orthorhombic system with four molecules in a unit cell of space group *Pnam* and dimensions a = 8.24 Å, b = 6.12 Å, c = 19.67 Å. After collection of intensities on an automatic computercontrolled four-circle X-ray diffractometer, the structure was solved by direct methods and refined to an R factor of 0.061. Full crystallographic details will be published elsewhere.

As Fig. 1 shows, the overall butterfly shape of the dibenz [b, f] oxepine molecule in the crystal involves a heterocyclic ring in a boat conformation; the C(10)-C(11) ethylenic bond (1.33 Å) and the oxygen atom both lie above the quaternary-carbon C(12)-C(13)-C(14)-C(15) plane and the benzene rings are bent below it. Since the molecule is symmetrical about the perpendicular mirror plane bisecting angle C(10)-O-C(11), Fig. 1 gives bond angles in one half of the molecule and lengths in the other. In more detail, with respect to the quaternary-carbon plane, the plane

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FIG. 1. Conformation of the dibenz [b,f] oxepine molecule determined in the crystal structure. In the left half, bond lengths (in Å) are shown between oxygen and carbon atoms; the corresponding bond angles (in degrees) are shown in the right half (hydrogen atoms are not shown). \bigcirc —C, \bigcirc —O.

C(15)-C(10)-C(11)-C(12) is inclined at 24° along C(12)-C(15) and the C(13)-O-C(14) plane at 57° along C(13)-C(14) (so that 'bow' and 'stern' planes of the boat are at 99° to one another). The dihedral angle of 134° between the almost completely planar benzene rings is rather smaller (i.e. the nucleus is less nearly planar) than in the corresponding tricyclic systems in which -O- is replaced by >NH or >C = O; preliminary structural reports give the dihedral angle as 145° in dibenz [b, f] azepine (Wimmer, 1963) and 141° in dibenz [b, f] tropone (Shimanouchi, Hata & Sasada, 1968). In NN-dimethyspiro[5H-dibenzo[a,d]cycloheptene-5,1'-cyclohexan]-4'-amine (Rodgers, Horn & Kennard, 1975; Rodgers, Kennard & others, 1976b), with a tetrahedral carbon at the 5-position, the dihedral angle in the crystal structure is 121°. For the phenothiazine system in promazine HCl (Rodgers & others, 1976a), it is also about 140°, but is 153° in the parent (Bell, Blount & others, 1968). As Rodgers & others (1976b) point out, substitution at the 2-position, particularly by -Cl or -CF₃, is unlikely to alter the conformation much. Further, the apparently rigid conformation found here is not necessarily that assumed in solution.

The expectation, inferred from chemical reactions and nmr measurements in solution (Bavin, Bartle & Jones, 1968), that any aromatic character of the sevenmembered ring is weak, is borne out in the crystal by pronounced non-planarity and marked alternation between single- and double-bond lengths along C(12)-C(11)-C(10)-C(15); also, the carbon-oxygen bond lengths correspond to single bonds.

To summarize, in the crystalline state, unsubstituted

dibenz [b, f] oxepine has an appreciably non-planar middle ring. Its overall molecular shape closely resembles that of tricyclic analogues containing 6- and 7-membered rings, viz: phenothiazine, and dibenz [b, f] azepine.

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REFERENCES

BAVIN, P. M. G., BARTLE, K. D. & JONES, D. W. (1968). J. heterocyclic Chem., 5, 327-330.

BELL, J. D., BLOUNT, J. F., BRISCOE, O. V. & FREEMAN, H. C. (1968). Chem. Commun., 1656-1657.

BERGMANN, E. D. & AIZENSHTAT, Z. (1970). In: Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry (Jerusalem Symposia, Vol. 2), pp. 349–356. Jerusalem: the Israel Academy of Sciences and Humanities.

COSCIA, L., CAUSA, P. & GIULIANI, E. (1975). Arzneimittel-Forsch., 25, 1261-1265.

HORN, A. S., POST, M. L. & KENNARD, O. (1975). J. Pharm. Pharmac., 27, 553-563.

RODGERS, J. R., HORN, A. S. & KENNARD, O. (1975). Ibid., 27, 859-860.

RODGERS, J. R., HORN, A. S. & KENNARD, O. (1976a). Ibid., 28, 246-247.

- RODGERS, J. R., KENNARD, O., SHELDRICK, G. M. & HORN, A. S. (1976b). Acta cryst., B32, 1293-1295.
- SEIDLOVA, V., PELZ, K., ADLEROVÁ, E., JIRKOVSKÝ, I., METYŠOVÁ, J. & PROTIVA, M. (1969). Colln Czech. chem. Commun. Engl. Edn, 34, 2258.
- SHIMANOUCHI, H., HATA, T., SASADA, Y. (1968). Tetrahedron Letters, No. 32, 3573-3574.

WIMMER, O. (1963). Quoted in HOPPE, W. (1969). Pure appl. Chem., 18, 465-488.

The effects of paracetamol on temperature and cardiovascular changes caused by pyrogenic contamination of chronically implanted arterial cannulae in the conscious, renal hypertensive cat

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The use of chronically implanted arterial cannulae to facilitate the recording of arterial pressure in conscious animals is a well established technique. The cannulae are commonly used with an arterial valve (Day & Whiting, 1972) to allow convenient connection to a pressure transducer.

We have used this technique in cats with mild, perinephritic, experimental hypertension (Page, 1939; Poyser, Shorter & Whiting, 1974). Aseptic surgical techniques were employed. PVC cannulae, sterilized overnight in 0.5% alcoholic Hibitane (ICI Ltd.), were inserted in the right carotid artery to the level of the thoracic aorta and were kept patent by injecting 2 ml of sterile heparinized (150 I.U. ml⁻¹, Pularin, Evans Medical), saline (Steriflex No. 1, Allen and Hanburys Ltd.) every second day. Rectal temperature was recorded with an electronic thermometer. A Bell and Howell 4–422–0001 pressure transducer and a Devices M.19 polygraph were used to record arterial pressure.

* Correspondence.

Heart rate was calculated from the pressure trace. Measurements were made at 15 min intervals. During observations the animals were lying unrestrained in their home cages. Ambient temperature was from 21 to 24° .

Pyrogen-like reactions were often observed, beginning 0.75 to 1.0 h after an injection of 2 ml of sterile, heparinized saline, used to clear the arterial cannula at the start of each experiment. Dey, Feldberg & others (1974) have observed a rise in rectal temperature in the cat following intracerebroventricular injection of sterile saline. The effect was prevented by pretreatment with chloramphenicol, suggesting bacterial growth in the cannulae as the source of pyrogen.

In our animals the presence of pyrogens was confirmed by withdrawing 0.5 ml of saline from the arterial cannulae of 5 cats, 18 h after washing through with sterile heparinized saline. These samples were pooled and compared with equivalent volumes of fresh heparinized saline in a standard pyrogen test in groups of 3 rabbits. The sum of the maximum temperature