Antipsychotic phenothiazine drugs and the significance of the X-ray structure of promazine HCl

JOHN R. RODGERS, ALAN S. HORN*, OLGA KENNARD†, *University Chemical Laboratory, Lensfield Road, Cambridge and *M.R.C. Neurochemical Pharmacology Unit, Department of Pharmacology Medical School, Hills Road, Cambridge, U.K.*

The antipsychotic actions of the phenothiazine neuroleptics are thought to be predominantly mediated through a blockade of dopamine receptors in the brain (Carlsson & Lindqvist, 1963; Horn & Snyder, 1971; Bunney, Walters & others, 1973; Horn, Cuello & Miller, 1974). It has also been suggested (Horn & Snyder, 1971) that chlorpromazine is able to block dopamine receptors due to a possible complementarity between certain portions of the X-ray structures of chlorpromazine and dopamine. Support for this idea was obtained from a detailed conformational analysis of 15 drugs of the tricyclic class (Horn, Post & Kennard, 1975). Results from a variety of animal tests (Zirkle & Kaiser, 1970) and clinical data (Klein & Davis, 1969) have shown that potent neuroleptics of this group usually have a chain of three carbon atoms separating the terminal amino function from the nucleus, together with a substituent at the 2-position of the phenothiazine ring system. Although the need for a 2-substituent is common to at least 4 classes of neuroleptics (the phenothiazines, thioxanthenes, dibenzo-diazepines and dibenzo-oxazepines (Zirkle & Kaiser, 1970) its function is unclear. The strict positional specificity of this phenomenon (Horn & others, 1975; Zirkle & Kaiser, 1970) is unlikely to be explicable solely in terms of a lipid solubility effect (Green, 1967). In order to obtain information about any possible conformational or structural effects these substituents might have on drugs of this class we have determined the crystal and molecular structure of the unsubstituted drug promazine HCl and have compared certain of its molecular parameters with those of related drugs containing a –Cl [chlorpromazine, base (McDowell, 1969) and HCl (Dorignac-Calas & Marsau, 1972)]-CF_3, [triflupromazine HCl, (Phelps & Cordes, 1974)] or –OCH_3, [methoxypromazine maleate, (Marsau & Gauthier, 1973)] group at the 2-position.

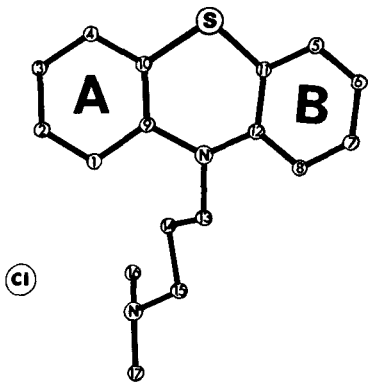

FIG. 1. The conformation of promazine HCl in the solid state as determined by X-ray crystallographic analysis.

Crystals of promazine HCl were grown as colourless plates from a xylene–chloroform solvent mixture. X-ray crystallographic studies showed that the molecule crystallizes in the monoclinic system—$a = 11{\cdot}802$ Å, $b = 11{\cdot}499$ Å, $c = 13\,408$ Å, $\beta = 111{\cdot}63°$—with a space group of $P\,2_1/c$. There are four molecules in the unit cell. The intensities were recorded with an automatic computer controlled diffractometer and were used to derive normalized structure factors (Es). The structure was solved by direct methods using reflections with $E \geqslant 1{\cdot}2$ by a centrosymmetric direct method program (G. M. Sheldrick, in preparation) and refined to a present R factor of 0·11. Full crystallographic details will be published elsewhere.

From Table 1, I it can be seen that the introduction of a –Cl or –CF_3 substituent at the 2-position in promazine leads to only very slight changes in the values of the two dihedral angles (C_6–C_6 and C_6SN–C_6SN) and of the CSC and CNC bond angles. There is a larger difference, however, in the dihedral angles as a result of introducing a 2-methoxy group, although again the values of the CSC and CNC bond angles are hardly affected. It must be borne in mind, however, that the structure of the latter drug was determined as the maleate salt and this might affect the packing of the molecules and hence the dihedral angles. It is of interest that the introduction of a methyl substituent onto the N atom of the reference ring system, phenothiazine, does change the value of the dihedral angle (Table 1, I) whilst once again it has little or no effect on the CSC or CNC bond angles. The values in Table 1, II clearly show that the 2-substituents do not appear to have any appreciable effects on any of the bond lengths tabulated. None of the groups –Cl, –CF_3 or –OCH_3 appear to have any direct effect on the conformation of the side chain as can be seen by a comparison of the distances of the terminal N atom from the centres of the two benzene rings (Table 1, III).

Promazine is known to be a much weaker antipsychotic agent than chlorpromazine or trifluprazine (Klein & Davis, 1969) and it is probably best classified as a sedative tranquillizer. It is also known to be weaker

† M.R.C. External Staff.

Table 1. *I. Dihedral angles between the best planes for the benzene rings, (C_6–C_6), and for the benzene ring including the sulphur and nitrogen atoms, C_6–SN–C_6–SN, (values in degrees). II. Comparison of distances in Å in the phenothiazine nucleus, estimated standard deviations in parentheses. III. Distances of the terminal nitrogen from the ring centres in Å* Fig. 1.

	I (Degrees)				II (Å)						III (Å)	
	C_6–C_6	C_6SN–C_6SN	S C_{11} C_{10}	C_{12} C_9 N	S–C_{10}	S–C_{11}	N–C_9	N–C_{12}	C_1–C_2	C_2–C_3	A–N§	B–N
Phenothiazine base*	153		99	121	1·770 (3)‡		1·406 (2)‡		1·387 (5)‡			
N-Methylphenothiazine base†	143		97	118	1·764 (2)	1·764 (2)	1·402 (2)	1·402 (2)	1·387 (2)	1·377 (4)		
Promazine HCl	140	138	99	117	1·77 (1)	1·76 (1)	1·41 (2)	1·46 (2)	1·39 (2)	1·36 (2)	6·09	7·39
Chlorpromazine HCl††	137	137	99	118	1·78	1·74	1·40	1·40	1·40	1·37	6·70	6·18
Chlorpromazine base	139	137	97	118	1·75 (1)	1·75 (1)	1·40	1·41	1·40	1·39	5·12	6·81
Triflupromazine HCl Conformation A	136	134	97	115	1·75 (1)	1·77 (1)	1·47 (2)	1·42	1·40	1·38	6·38	6·42
Conformation B	145	141	96	117	1·73 (1)	1·74 (1)	1·40 (2)	1·41	1·40	1·40	6·28	7·28
Methoxypromazine mal.	157	154	99	122	1·766	1·750 (7)	1·409 (7)	1·416 (8)	1·410 (9)	1·377 (9)	6·35	6·64

* Bell, Blount & others (1968).
† Chu & Van der Helm (1974).
†† These values have been calculated from the atomic co-ordinates.
‡ Published average values.
§ The A ring is the one containing the 2-substituent.
In the case of triflupromazine 2 conformations (A and B) were found in the solid state (Phelps & Cordes, 1974).

than chlorpromazine both in animal tests of neuroleptic activity (Zirkle & Kaiser, 1970) and in inhibiting *in vitro* the dopamine sensitive adenylate-cylase system of the rat corpus-striatum (Miller, Horn & Iversen, 1974). That the nature of the 2-substituent is important is shown by the fact that 2-methoxypromazine is known to be less active clinically than chlorpromazine (Gosline, Walters & Saunders, 1959). From the limited X-ray data available on these compounds it would appear that the 2-substituent is not producing a large effect on any of the molecular parameters that can be obtained from the crystal structures. It is possible, however, that it may affect the presumed mobility of the phenothiazine ring system (Aroney, Hoskins & LeFevre, 1968; Aizenshtat, Klein & others, 1972) which probably does not have a 'fixed' dihedral angle in solution. An investigation of this possibility will require the use of other physical methods. In conclusion it would appear that the most likely effect of the 2-substituent is that of a direct interaction at the receptor site.

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