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1-Chloro-10-[3-(dimethylamino)propyl]phenothiazine Hydrobromide (1-Chloropromazine Hydrobromide), $C_{17}H_{19}ClN_2S.HBr$

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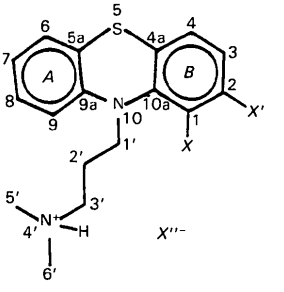
Abstract. $M_r = 399{\cdot}8$, orthorhombic, *Pbca*, $a = 10{\cdot}166\ (5)$, $b = 11{\cdot}190\ (2)$, $c = 32{\cdot}93\ (1)$ Å, $U = 3746$ Å^3, $Z = 8$, $D_x = 1{\cdot}418$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71073$ Å, $\mu = 24$ cm^{-1}, $F(000) = 1632$, $T = 293$ K, final $R = 0{\cdot}042$ for 1227 observed reflections. This apparent antidepressant non-neuroleptic promazine analogue has a decidedly synclinal conformation, unlike the antipsychotics promazine and 2-chloropromazine. This result supports the view that a synclinal noncoplanar side-chain conformation is associated with the antidepressant activity of compounds of the tricyclic class and is also consistent with current conformational theories of antipsychotic action, which, in contrast, require an approximately coplanar (synperiplanar) side-chain conformation.

Introduction. As part of our investigation of conformational requirements for antipsychotic (neuroleptic) and antidepressant activities in the *N*-aminopropyl substituted phenothiazine and dihydrodibenzazepine series (Martin, Kim, Yamamura & Horn, 1980; Grol, Dykstra, Schunselaar, Westerink & Martin, 1982; Martin, Paradkar, Peng, Speth, Yamamura & Horn, 1980) we report the crystal structure of the title compound, 1-chloropromazine hydrobromide (1). The salt was chosen since the protonated form of the base is generally considered to be the physiologically relevant species. In contrast to the behavior of promazine (2), chlorpromazine (3) and other 2-substituted promazines, 1-chloropromazine (1) lacks potency in animal tests correlated with clinical antipsychotic activity (Green, 1967; Kaiser & Setler, 1981, p. 885). On the other hand, it exhibits in animals behavioral properties commonly associated with the tricyclic antidepressant drugs such as imipramine (Kaiser & Setler, 1981, pp. 885, 1034). We have found, in addition, that (1) (like the tricyclic antidepressants) is a moderately potent inhibitor of the monoamines 5-hydroxytryptamine (serotonin) and norepinephrine in synaptosomal preparations obtained from rat brain (Kramer, Dort, Hallberg, Hintermeister, Svensson & Nelson, 1984). A variety of studies indicate that the observed differences in pharmacological properties between 1- and 2-chloro substituted promazines [(1) and (3)] cannot be due to differences in their physical and chemical properties such as pK_a, surface tension and oil/water partition coefficients (Green, 1967; Zographi & Munshi, 1970; Murthy & Zographi, 1970). It has been speculated that the introduction of a chlorine atom at the 1-position creates a *peri* steric interaction with the dimethylaminopropyl side chain to force it out of the plane of the tricyclic system (Kaiser & Setler, 1981, p. 1034). Thus, a noncoplanar side-chain conformation is believed to be important for antidepressant activity, while a more nearly planar conformation is apparently associated with antipsychotic potency. The present study was undertaken in an attempt to investigate this question and to determine if three-dimensional similarities exist between (1) and the monoamines.



	X	X'	X''
(1)	Cl	H	Br
(2)	H	H	Cl
(3)	H	Cl	Cl

Experimental. 1-Chloropromazine free base was prepared by alkylation of 1-chlorophenothiazine (Hallberg & Martin, 1983) with *N,N*-dimethyl-3-bromopropylamine according to the procedure of Craig, Lester, Saggiomo, Kaiser & Zirkle (1961), except that sodium hydride was used as the base instead of sodium amide. The crude free base was chromatographed on neutral alumina (1:1 toluene/hexane, 1% triethylamine), dissolved in ether, and converted to the

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hydrobromide by adding anhydrous hydrogen bromide in ether. Three recrystallizations of the salt from butanol gave colorless needles, m.p. 442–444 K. Crystal dimensions 0·5 × 0·5 × 0·2 mm. Syntex $P2_1$ four-circle diffractometer. Cell constants from 20 reflections with $14 < 2\theta < 24°$. Numerical absorption correction with transmission factors from 0·335 to 0·560. $2\theta_{max} = 45°$. Range of *hkl*: 0–10, 0–12, 0–34. Three check reflections every 97 data points showed 0·3% change during data collection. Space group identified as *Pbca* (No. 61) with systematic absences: $0kl$, $k = 2n + 1$; $h0l$, $l = 2n + 1$ and $hk0$, $h = 2n + 1$. 1227 of 2450 reflections with $I > 3\sigma(I)$ used in F^2 refinement. $R_{int} = 0·042$. Structure solved by *MULTAN*80 (Main *et al.*, 1980) using 262 highest E values; all non-H atoms found in first E map. Refinement of non-H atoms with isotropic temperature factors gave $R = 0·150$, final refinement (199 parameters) was of non-H atoms with anisotropic temperature factors and H atoms, found in difference maps, with isotropic temperature factors; $wR = 0·042$, $S = 1·7$, weighting scheme of Corfield, Doedens & Ibers (1967) with $p = 0·03$. $(\Delta/\sigma)_{max} = 0·1$. $\Delta\rho = -0·4$–$0·5$ e Å^{-3} near Br. Atomic scattering factors from Cromer & Waber (1974) and anomalous-dispersion factors from Cromer (1974). Programs *SDP* (Frenz, 1978), including plotter program *ORTEP* (Johnson, 1976), run on PDP 11/34.

Discussion. Table 1 lists the final positional and equivalent isotropic thermal parameters, and Table 2 and Fig. 1 compare the conformational parameters of the apparent antidepressant 1-chloropromazine hydrobromide (1) with those of the known antipsychotic 2-chloropromazine hydrochloride (3) (Dorignac-Calas & Marsau, 1972).*† In the molecules in Fig. 1, the horizontal axis is defined by C(8) and C(2), and the vertical axis by N(10) and S. Arbitrary spheres of identical size are used for all atoms.

Table 1. *Positional parameters and their e.s.d.'s*

	x	y	z	B_{eq}(Å^2)*
Br	0·47682 (7)	0·76937 (6)	0·46666 (3)	4·99 (2)
Cl	0·7469 (2)	0·6766 (2)	0·39536 (7)	5·77 (5)
C(10a)	0·9844 (6)	0·6818 (6)	0·3561 (2)	3·2 (2)
C(1)	0·8859 (6)	0·6123 (6)	0·3736 (2)	4·0 (2)
C(2)	0·8941 (7)	0·4886 (6)	0·3751 (2)	4·6 (2)
C(3)	0·9988 (7)	0·4332 (6)	0·3571 (3)	5·7 (2)
C(4)	1·0918 (8)	0·4989 (7)	0·3362 (2)	5·6 (2)
C(4a)	1·0863 (7)	0·6238 (7)	0·3358 (2)	4·1 (2)
S	1·2088 (2)	0·7045 (2)	0·31117 (7)	6·29 (6)
C(5a)	1·1150 (7)	0·8318 (7)	0·2964 (2)	5·2 (2)
C(6)	1·1521 (8)	0·8907 (8)	0·2613 (3)	7·6 (3)
C(7)	1·088 (1)	0·9958 (8)	0·2528 (3)	9·0 (3)
C(8)	0·9860 (9)	1·0362 (8)	0·2774 (3)	8·8 (3)
C(9)	0·9424 (9)	0·9797 (7)	0·3119 (2)	7·0 (2)
C(9a)	1·0139 (7)	0·8713 (6)	0·3217 (2)	4·5 (2)
N(10)	0·9752 (5)	0·8076 (5)	0·3564 (2)	3·9 (1)
C(1′)	0·9869 (7)	0·8663 (6)	0·3957 (2)	4·1 (2)
C(2′)	1·1279 (7)	0·8988 (6)	0·4084 (2)	3·9 (2)
C(3′)	1·1273 (6)	0·9456 (6)	0·4515 (2)	3·4 (2)
N(4′)	1·2591 (5)	0·9758 (4)	0·4681 (2)	3·0 (1)
C(5′)	1·3246 (7)	1·0734 (6)	0·4461 (2)	4·0 (2)
C(6′)	1·2480 (8)	1·0039 (8)	0·5122 (2)	5·1 (2)

* $B_{eq} = \frac{4}{3}[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$.

Table 2. *Conformational parameters for* (1) *and* (3)

	(1)	(3)
Torsion angles in central ring (°)		
C(10a)–C(4a)–S–C(5a)	−31·5 (5)	−37·1
C(4a)–S–C(5a)–C(9a)	33·5 (6)	36·5
S–C(5a)–C(9a)–N(10)	−6·2 (8)	−2·2
C(5a)–C(9a)–N(10)–C(10a)	−32·4 (8)	−43·4
C(9a)–N(10)–C(10a)–C(4a)	35·2 (7)	43·8
N(10)–C(10a)–C(4a)–S	1·7 (5)	1·9
Angle between aromatic rings (°)	145·6 (8)	137·8
Twist [av. of C(5a)–C(9a)–C(10a)–C(4a) and C(9a)–C(5a)–C(4a)–C(10a)] (°)	2·0 (1)	−0·2
Skew [C(5a)–C(4a) – C(9a)–C(10a)] (Å)	0·26 (1)	0·28
Distance of C(1′) below C(9a)–N(10)–C(10a) plane (Å)	−0·614 (7)	0·43
Angle of C(1′)–N(10) to C(9a)–N(10)–C(10a) plane (°)	−24·9 (8)	16·7
Sum of angles around N(10) (°)	353·7 (9)	357·1
Angle between C(1′)–N(10)–C(9a) and C(1)–C(10a)–C(4a) planes (°)	54·4 (8)	38·9
Angle between C(1′)–N(10)–C(10a) and C(9)–C(9a)–C(5a) planes (°)	51·6 (8)	37·2
Torsion angles involving side chains (°)		
C(9)–C(9a)–N(10)–C(1′)	−62·7 (7)	−24·0
C(1)–C(10a)–N(10)–C(1′)	68·2 (7)	25·4
C(9a)–N(10)–C(1′)–C(2′)	−63·2 (6)	−70·8
C(10a)–N(10)–C(1′)–C(2′)	88·9 (6)	128·7
N(10)–C(1′)–C(2′)–C(3′)	−173·5 (6)	−124·2*
C(1′)–C(2′)–C(3′)–N(4′)	177·7 (7)	174·5*
C(2′)–C(3′)–N(4′)–C(5′)	63·4 (6)	97·7*
C(2′)–C(3′)–N(4′)–C(6′)	−171·9 (6)	−140·7*
Distance of N(4′) from A ring plane (Å)	4·850 (5)	4·12
Distance of N(4′) from B ring plane (Å)	4·758 (5)	3·71
Distance of N(4′) from center of A ring (Å)	6·35 (2)	6·18
Distance of N(4′) from center of B ring (Å)	6·57 (2)	6·70

* These values are in doubt owing to incorrect coordinate for C(3′) in (3).

* The crystal and molecular structure of 2-chloropromazine base has also been determined (McDowell, 1969).

† Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and bond distances and angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39690 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

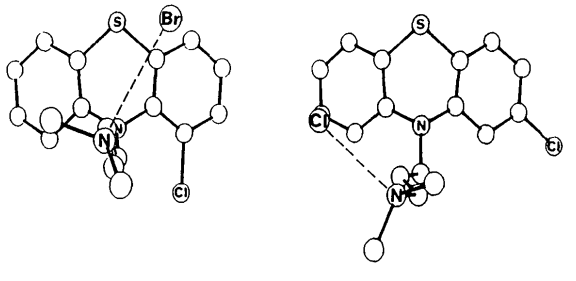

Fig. 1. *ORTEP* drawings of (1) (left) and (3). Dashed lines indicate hydrogen bonds.

The central ring in (1) is much flatter than that in (3), as indicated by the torsion angles around this ring and the 7·8° larger angle between the aromatic rings in (1) [Table 2; promazine (2), whose coordinates were unavailable, has a 140° angle between aromatic rings (Rodgers, Horn & Kennard, 1976)]. There is a significant bend of the chlorine away from the center of the molecule as shown by the Cl–C(1)–C(2) and Cl–C(1)–C(10a) angles.

The most striking conformational difference between (1) and (3) is the position of C(1′) relative to the ring system: In (3) it is *intra** [or synperiplanar, *i.e.* toward C(9) and C(1)], lying 0·43 Å below the C(9a)–N(10)–C(10a) plane and making a 16·7° angle with it, whereas in (1) it is *extra** (or synclinal), 0·61 Å *above* the plane at 24·9°. This is no doubt to minimize the *peri* steric interaction with the chlorine. The observed existence of the side chain of (1) in the synclinal conformation supports the view of Kaiser & Setler (1981, p. 1034) that antidepressant activity in the tricyclic class requires a side-chain conformation that is non-coplanar with both of the benzo rings. It is noteworthy that compounds of the imipramine type can easily achieve this type of conformation (Hallberg, Hintermeister, Martin, Bates & Ortega, 1984).

The apparent lack of neuroleptic activity of (1) (Kaiser & Setler, 1981, pp. 885, 1034) can similarly be explained by its preference for the synclinal conformation. Two different conformational theories have been proposed to explain neuroleptic potency of (3) and related drugs, which are believed to bind to dopamine receptors in the central nervous system to act as antagonists for dopamine and thus exert their antipsychotic actions. The dopamine overlapping hypothesis (Horn & Snyder, 1971; Feinberg & Snyder, 1975) proposes that the side chain of (3) is folded over in the direction of the aromatic ring bearing the chlorine atom, placing the dimethylamino group and the substituted ring in a spatial arrangement that corresponds to the amino group and the catechol system of dopamine in its antiperiplanar (*trans*) conformation. This hypothesis is supported, in part, by the solid-state structure of the rigid neuroleptic drug butaclamol, which contains an antiperiplanar β-phenylethylamine moiety in its structure (Humber, Bruderlein & Voith, 1975). A second theory, suggested by Janssen (1970), proposes an *S* conformation of the side chain with respect to one of the aromatic rings as being required for antipsychotic activity. Support for this idea comes from the observed neuroleptic potencies of the piperidylidenedibenzocycloheptanes (Kaiser, Warren & Zirkle, 1974), the 5-aryltetrahydro-β-carbolines (Harbet, Plattner, Welch, Weissman & Koe, 1980) and the pyrroloisoquinolines (Olson *et al.*, 1981). In both the dopamine overlapping and *S* conformations, the side chain is synperiplanar and approximately coplanar.

The torsion angles involving the side chain are rather different in (1) and (3). After the first two (Table 2), which further describe the *synclinal* arrangement in (1) and synperiplanar arrangement in (3), they are probably governed largely by the position of the halide ion, and are not significant with regard to activity in view of the flexibility of the chain. The side chain in (1), except for being synclinal rather than in the C(9a)–N(10)–C(10a) plane, quite closely resembles that in 4-chloroimipramine hydrochloride (Hallberg *et al.*, 1984). Fig. 2 shows intra- and intermolecular side-chain–halide-ion orientation.

* In a theoretical study of phenothiazine, Malreau & Pullman (1964) described the behavior of the central ring in terms of a folded conformation wherein the nitrogen substituent can assume two possible conformations (interconvertible by ring and nitrogen inversion processes): a synperiplanar conformer (designated *intra*) in which the substituent lies virtually in the planes of the two benzo rings and a synclinal conformer (designated *extra*) in which the substituent is essentially orthogonal to the benzo ring planes.

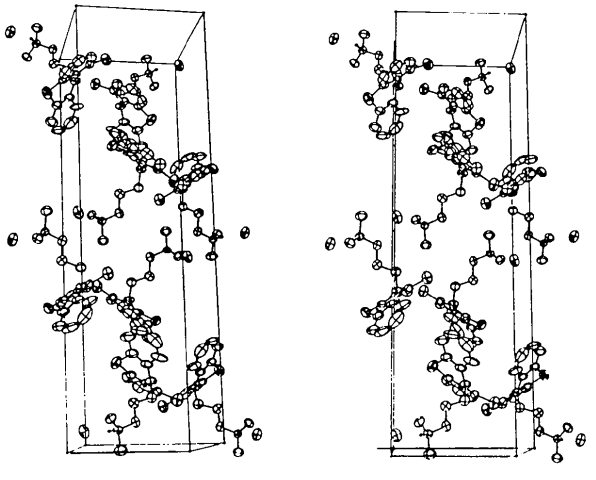

Fig. 2. *ORTEP* drawing of a unit cell, *c* axis vertical, *b* axis horizontal. Hydrogen atoms attached to carbon have been omitted for clarity.

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Structure of (25*R*)-3β-Hydroxy-5α-spirostan-12-one Monohydrate (Hecogenin), $C_{27}H_{42}O_4.H_2O$*

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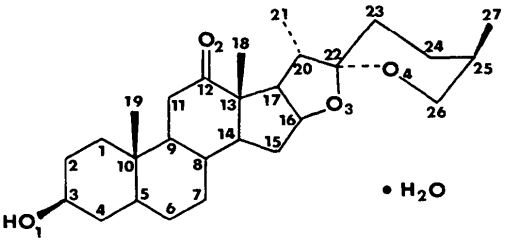
Abstract. $M_r = 448{\cdot}6$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}815$ (2), $b = 9{\cdot}582$ (1), $c = 32{\cdot}839$ (4) Å, $V = 2459{\cdot}1$ (5) Å^3, $Z = 4$, $D_x = 1{\cdot}21$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 0{\cdot}656$ mm^{-1}, $F(000) = 984$, $T = 293$ K, $R = 0{\cdot}044$ for 1807 observed reflections. The six-membered rings have chair conformations. The substituents at C(3) and C(25) are equatorial. The five-membered rings adopt a conformation intermediate between half-chair and β-envelope. The structure consists of sheets of molecules parallel to the *ac* plane, linked by hydrogen bonds *via* a molecule of water.

Introduction. The naturally occurring sapogenin, 3β-hydroxy-5α-spirostan-12-one monohydrate (hecogenin) (1) was isolated from tubers of the plant *Polianthes tuberosa* by chromatography. Hecogenin has been suggested as a promising raw material for the partial synthesis of cortisone (Djerassi, Ringold & Rosenkranz, 1951). As yet, no structural study of hecogenin has been reported. It was of interest to determine the crystal structure of (1) in order to ascertain its conformation and molecular geometry.



(1)

Experimental. Colourless crystal 0·13 × 0·34 × 0·30 mm. Nicolet *R*3 four-circle diffractometer. Lattice parameters from 25 machine-centred reflections with $14{\cdot}9 < 2\theta < 28{\cdot}5°$. 1999 reflections with $3 < 2\theta < 115°$, 1807 independent with $I > 2{\cdot}5\sigma(I)$, index range *h*

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