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4-Chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H*-dibenz[*b,f*]azepine Hydrochloride (4-Chloroimipramine Hydrochloride), $C_{19}H_{23}ClN_2.HCl$

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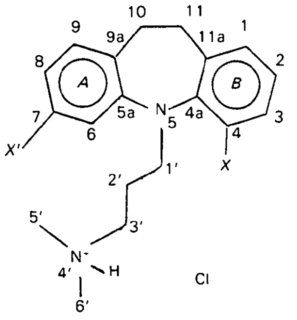
Abstract. $M_r = 351{\cdot}3$, monoclinic, $P2_1/c$, $a = 16{\cdot}972\,(1)$, $b = 10{\cdot}362\,(6)$, $c = 11{\cdot}018\,(3)$ Å, $\beta = 107{\cdot}40\,(4)°$, $U = 1849\,(2)$ Å^3, $Z = 4$, $D_x = 1{\cdot}262$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71073$ Å, $\mu = 3{\cdot}5$ cm^{-1}, $F(000) = 744$, $T = 293$ K, final $R = 0{\cdot}039$ for 2013 observed reflections. This antidepressant has a conformation with C(1′) not in the synperiplanar position but in the C(4a)—N(5)—C(5a) plane and synclinal to avoid steric interaction with the Cl on the *peri*-fused ring. The amino nitrogen is protonated and the crystal contains alternating ionic and aromatic layers.

Introduction. A solid-state study of the title compound, 4-chloroimipramine hydrochloride (1), is presented here in connection with our continuing investigation of conformational properties of tricyclic antidepressants of the imipramine type (Martin, Paradkar, Peng, Speth, Yamamura & Horn, 1980). We have recently discovered (Kramer, Dort, Hallberg, Hintermeister, Martin & Nelson, 1984) that 4-chloroimipramine is a potent selective inhibitor of neuronal uptake of 5-hydroxytryptamine (5-HT, serotonin). It is of interest, therefore, to compare the three-dimensional structure of this compound with solid-state structures of the tricyclic antidepressants imipramine (2) (Post, Kennard & Horn, 1975) and 3-chloroimipramine (3) (clomipramine; Post & Horn, 1977).



	X	X′
(1)	Cl	H
(2)	H	H
(3)	H	Cl

Experimental. 4-Chloroimipramine free base was prepared by alkylation of 4-chloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (Hintermeister, 1984) with *N,N*-dimethyl-3-bromopropylamine essentially according to the procedure of Craig, Lester, Saggiomo, Kaiser & Zirkle (1961), except that sodium hydride instead of sodium amide was used as the base. The crude reaction mixture was chromatographed on neutral alumina (1:1 toluene/hexane, 1% triethylamine). The purified free base was dissolved in anhydrous ether and converted to the hydrochloride by adding anhydrous hydrogen chloride in ether. Recrystallizations from methanol gave colorless needles, m.p. 485 K. Crystal dimensions $0{\cdot}38 \times 0{\cdot}28 \times 0{\cdot}13$ mm. Syntex four-circle diffractometer. Cell constants from 20 reflections with $14 < 2\theta < 25°$. No absorption corrections since both crystal and μ small. $2\theta_{\max} = 50°$. Range of *hkl*: 0–20, 0–12, −13–12. Three check reflections every 97 data points showed <1% change during data collection. Space group identified as $P2_1/a$ (No. 14, cell choice 3) with systematic absences: $h0l$, $h = 2n + 1$ and $0k0$, $k = 2n + 1$. Prior to initiating solution of structure space group was transformed to $P2_1/c$ (No. 14, cell choice 1). 2013 of 3262 reflections with $I > 3\sigma(I)$ used in F^2 refinement. $R_{\rm int} = 0{\cdot}039$. Structure solved by *MULTAN*80 (Main *et al.*, 1980) using 266 highest E values; all non-H atoms found in first E map. Refinement of non-H atoms with isotropic temperature factors gave $R = 0{\cdot}131$, final refinement (208 parameters) was of non-H atoms with anisotropic temperature factors, H atoms in calculated positions with isotropic temperature factors; $wR = 0{\cdot}037$, $S = 1{\cdot}6$, weighting scheme of Corfield, Doedens & Ibers (1967) with $p = 0{\cdot}03$. $(\Delta/\sigma)_{\max} = 0{\cdot}01$. $\Delta\rho = -0{\cdot}3$–$0{\cdot}2$ e Å^{-3}. 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

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

	x	y	z	B_{eq}(Å^2)*
Cl(−1)	0·44255 (6)	0·04547 (8)	0·74477 (7)	5·48 (2)
Cl	0·71845 (5)	0·26258 (7)	0·40576 (7)	3·84 (2)
N(5)	0·7789 (1)	0·5126 (2)	0·3233 (2)	2·72 (5)
N(4')	0·5488 (1)	0·7687 (2)	0·0387 (2)	2·96 (5)
C(1)	0·8214 (2)	0·5957 (3)	0·6629 (3)	3·43 (7)
C(2)	0·7886 (2)	0·4911 (3)	0·7073 (2)	3·80 (7)
C(3)	0·7559 (2)	0·3896 (3)	0·6276 (2)	3·44 (7)
C(4)	0·7564 (2)	0·3951 (3)	0·5030 (2)	2·78 (6)
C(6)	0·8450 (2)	0·4519 (3)	0·1668 (3)	3·61 (7)
C(7)	0·9095 (2)	0·4503 (3)	0·1156 (3)	4·33 (7)
C(8)	0·9804 (2)	0·5172 (3)	0·1750 (3)	4·64 (8)
C(9)	0·9847 (2)	0·5862 (3)	0·2830 (3)	4·21 (8)
C(10)	0·9322 (2)	0·6769 (3)	0·4513 (3)	3·90 (7)
C(11)	0·8553 (2)	0·7160 (3)	0·4873 (3)	3·54 (7)
C(11a)	0·8198 (2)	0·6033 (3)	0·5369 (2)	2·75 (6)
C(4a)	0·7863 (2)	0·5027 (3)	0·4540 (2)	2·49 (6)
C(5a)	0·8487 (2)	0·5197 (3)	0·2771 (2)	2·80 (6)
C(9a)	0·9197 (2)	0·5915 (3)	0·3360 (2)	3·07 (6)
C(1')	0·6953 (2)	0·5133 (3)	0·2343 (2)	2·84 (6)
C(2')	0·6714 (2)	0·6434 (3)	0·1716 (2)	2·86 (6)
C(3')	0·5828 (2)	0·6390 (3)	0·0871 (2)	2·93 (6)
C(5')	0·5969 (2)	0·8340 (3)	−0·0351 (3)	3·74 (7)
C(6')	0·4609 (2)	0·7566 (3)	−0·0370 (3)	4·67 (8)

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

and Fig. 1 conformationally compare 4-chloroimipramine (1) with the two independent molecules of imipramine [(2*a*) and (2*b*); Post *et al.*, 1975] and 3-chloroimipramine [(3); Post & Horn, 1977] previously observed in X-ray studies.[*][†] In Fig. 1, the molecules are oriented similarly with benzene rings folded back and similar twists in the seven-membered ring. The horizontal axis is defined by C(3) and C(7), and the vertical axis by N(5) and the C(10)–C(11) midpoint. Arbitrary spheres of identical size are used for all atoms.

The conformation of the seven-membered ring in (1) is very similar to those of the other imipramines (Table 2, top). The ring chlorine in (1) is presumably responsible for the slightly greater angle between the aromatic rings and slightly greater 'twist' (Table 1). The ring chlorine in (1) is displaced slightly away from the side chain since Cl–C(4)–C(4a) > Cl–C(4)–C(3) by 2·1 (2)°.

(1) shows a different side-chain conformation from the other imipramines. The sum of angles around N(5) is 360° instead of the usual 348–355°; (1) has C(1') essentially in the C(4a)–N(5)–C(5a) plane instead of 0·34–0·82 Å out of it in the synperiplanar direction, *i.e.* toward C(4) and C(6). The C(1')–N(5) bond in (1) is in this plane rather than making an angle of 13–35° with it. This effect also shows in the first two torsion angles involving the side chain. It is no doubt a result of a steric interaction with the Cl attached to the *peri* ring at C(4). N(5) in (1) is thus sp^2 hybridized, but to show that overlap between the p oribital on N(5) and the adjacent p orbitals on C(4a) and C(5a) is not too good, the angles between the C(1')–N(5)–C(5a) and C(11a)–C(4a)–C(4) planes and between the C(1')–N(5)–C(4a) and C(6)–C(5a)–C(9a) planes are included in Table 2: in (1) they are within the 36–71° range observed in the other compounds.

The remaining aspects of the conformations of the side chains as shown in Fig. 1 and Table 2 are not the same in any of the structures, thus showing the great flexibility of the side chain. The conformation assumed

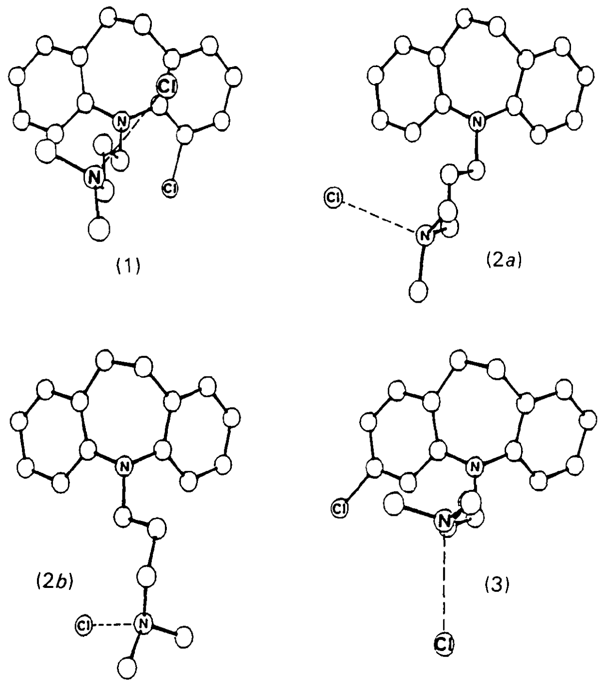

Fig. 1. *ORTEP* drawings of (1)–(3). Dashed lines indicate hydrogen bonds.

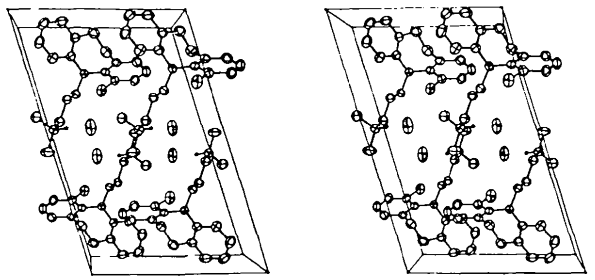

Fig. 2. *ORTEP* drawing of a unit cell; *b* towards reader, *c* horizontal. All hydrogen atoms attached to carbon have been omitted for clarity.

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[*] The *Chemical Abstracts* system used to number (1) differs from that used to number (2) and (3).

[†] 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 39689 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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

	(1)	(2*a*)	(2*b*)	(3)
Torsion angles in seven-membered ring (°)				
C(4a)–C(11a)–C(11)–C(10)	−66·5 (2)	−68·0	−69·2*	−68·8
C(11a)–C(11)–C(10)–C(9a)	69·9 (3)	70·2	49·1*	63·2
C(11)–C(10)–C(9a)–C(5a)	−16·4 (3)	−17·6	5·7*	−7·0
C(10)–C(9a)–C(5a)–N(5)	−3·4 (3)	0·1	−1·9	−3·4
C(9a)–C(5a)–N(5)–C(4a)	−40·3 (3)	−44·7	−57·8	−50·1
C(5a)–N(5)–C(4a)–C(11a)	65·6 (3)	67·7	68·0	72·9
N(5)–C(4a)–C(11a)–C(11)	−6·0 (2)	−5·6	3·8*	−4·9
Distance from C(10) to plane of *B* ring (Å)	1·35 (3)	1·41	1·04*	1·42
Distance from C(11) to plane of *A* ring (Å)	0·52 (3)	0·45	0·04*	0·31
Angle between aromatic rings (°)	132·5 (3)	130·0	123·0	123·4
Twist [av. of C(5a)–C(9a)–C(11a)–C(4a) and C(9a)–C(5a)–C(4a)–C(11a)] (°)	19·2 (4)	17·3	8·4	17·6
Skew [C(9a)–C(11a) – C(5a)–C(4a)] (Å)	0·681 (6)	0·67	0·61	0·66
Distance of C(1′) below C(4a)–N(5)–C(5a) plane (Å)	0·022 (3)	0·58	0·82	0·34
Angle of C(1′)–N(5) to C(4a)–N(5)–C(5a) plane (°)	0·9 (3)	23·5	33·6	13·3
Sum of angles around N(5) (°)	360·0 (5)	354·7	348·3	350·9
Angle between C(1′)–N(5)–C(5a) and C(11a)–C(4a)–C(4) planes (°)	63·4 (3)	54·6	55·4	70·8
Angle between C(1′)–N(5)–C(4a) and C(6)–C(5a)–C(9a) planes (°)	39·5 (3)	36·3	49·2	65·0
Torsion angles involving side chain (°)				
C(6)–C(5a)–N(5)–C(1′)	−38·8 (3)	−15·6	−19·3	−17·3
C(4)–C(4a)–N(5)–C(1′)	61·2 (2)	39·2	27·7	37·3
C(5a)–N(5)–C(1′)–C(2′)	−70·6 (2)	−68·4	−159·7	−71·3
C(4a)–N(5)–C(1′)–C(2′)	110·3 (2)	137·1	58·8	142·5
N(5)–C(1′)–C(2′)–C(3′)	−176·7 (2)	180·0	160·5	−71·2
C(1′)–C(2′)–C(3′)–N(4′)	170·0 (2)	173·5	60·9	−167·6
C(2′)–C(3′)–N(4′)–C(5′)	58·5 (2)	−66·7	64·2	−64·8
C(2′)–C(3′)–N(4′)–C(6′)	−177·0 (2)	164·4	−172·4	170·0
Distance of N(4′) from *A* ring plane (Å)	4·407 (2)	3·68	2·24	4·01
Distance of N(4′) from *B* ring plane (Å)	4·572 (2)	3·60	1·16	3·72
Distance of N(4′) from center of *A* ring (Å)	6·47 (1)	6·25	6·54	6·55
Distance of N(4′) from center of *B* ring (Å)	7·00 (1)	7·22	6·08	6·11

* These values are in doubt owing to slight disorder in C(10) and C(11) in (2*b*).

in each case points the N(4′)–H bond toward the Cl^-, which is found in a very different position in each case. Fig. 2 illustrates this point and shows the alternating ionic–aromatic regions in the crystal parallel to the *bc* plane.

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