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The Crystal and Molecular Structure of the Tricyclic Antidepressant Chlorimipramine Hydrochloride: 3-Chloro-5-(3-dimethylaminopropyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine Hydrochloride*

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The structure of chlorimipramine hydrochloride, $C_{19}H_{23}N_2Cl.HCl$, monoclinic, space group $P2_1/c$, with a = 15·506 (3), b = 8·605 (1), c = 14·031 (4) Å, β = 96·69 (2)°, Z = 4, was determined by the symbolic addition procedure and refined by block-diagonal least squares to an R of 0·048 for 2569 diffractometer-measured reflexions. The dihedral angle between the aromatic-ring mean planes is 123° and the tricyclic moiety has twist and skew values of 17·6° and 0·66 Å respectively. The dimethylaminopropyl side chain exhibits a *gauche–trans* rotamer which is unusual, in the solid state, for compounds of this type. Conformational parameters for the seven-membered hetero-ring in the title compound, and related tricycles, are discussed.

Introduction

Chlorimipramine (clomipramine or Anafranil[R]†) is a clinically effective tricyclic antidepressant which is also used in the treatment of obsessional and phobic states (Beaumont, 1975). One of the most striking pharmacological aspects of the molecule is the ability to potently inhibit re-uptake of 5-hydroxytryptamine (5-HT) into nerve endings; in this respect it is more potent than imipramine (Horn & Trace, 1974), another widely used tricyclic antidepressant, the structure of which has recently been reported (Post, Kennard & Horn, 1975). It is possible that the inhibitory effect of chlorimipramine upon 5-HT re-uptake may be related to its antidepressant action (Horn, 1976). In a continuation of attempts to gain a better understanding of which structural and conformational requirements are important for drugs of this class to exhibit such activity, the crystal structure of chlorimipramine hydrochloride has been determined.

Experimental

A sample of chlorimipramine hydrochloride was obtained through the courtesy of Geigy Pharmaceuticals. Single crystals were grown from chloroform/xylene mixtures and precession and Weissenberg photographic studies showed the crystal system to be monoclinic, with systematic absences $0k0$: k odd; $h0l$: l odd, uniquely determining the space group $P2_1/c$. Cell parameters were obtained by least-squares treatment of the 2θ values of 21 reflexions measured on a diffractometer.

Crystal data

$C_{19}H_{24}N_2Cl_2$	M_r = 351·32
Monoclinic	D_c = 1·26 g cm^{-3}
Space group $P2_1/c$	D_m = 1·25 (1) (by flotation)
a 15·506 (3) Å	Z = 4
b = 8·605 (1)	$F(000)$ = 744
c = 14·031 (4)	λ(Cu $K\alpha$) = 1·54178 Å, Ni filtered
β = 96·69 (2)°	μ(Cu $K\alpha$) = 31·4 cm^{-1}
U = 1859·4 Å^3	Data collection temperature 20 (1)°C

For data collection, a crystal fragment of trapezoidal shape, with average dimensions 0·47 × 0·39 × 0·14 mm, was mounted with **c*** parallel to the φ axis of a Picker card-automated diffractometer, equipped with a scintillation detector having a helium-filled collimation tube (crystal–detector distance 55 cm) and a pulse-height analyser. Data were collected throughout the range $2\theta \leq 130°$ with the θ–2θ scan mode operating at 2° min^{-1} in 2θ; a 20 s background count was recorded at the higher 2θ limit. Scan ranges were 1·8° for $2\theta <$ 90° and 2·4° for $90 \leq 2\theta \leq 130°$. Three reflexions were monitored periodically for scaling purposes, to allow for crystal deterioration and instrument fluctuation; the largest of these scaling factors was 1·03. 3164 independent reflexions were recorded, of which 595 had $I \leq I$(thresh.) [where I(thresh.) is a predetermined threshold count value of 0·1 × total background or 80, whichever is greater]; these were treated

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as unobserveds and excluded during refinement. Lorentz and polarization corrections were applied to the raw data and, because of the irregular crystal shape and a high absorption coefficient, an absorption correction calculated with the Gaussian integration formula (Busing & Levy, 1957) was also applied (maximum and minimum transmission factors 0·66/0·34). A correction for secondary extinction with the equations of Pinnock, Taylor & Lipson (1956) was made at a later stage.

Structure solution and refinement

Overall scale and temperature factors for the data were derived by means of a Wilson plot (Wilson, 1942), and normalized structure factors (E's) were calculated. The structure was solved in a straightforward manner by use of the symbolic addition procedure (Karle & Karle, 1966); all 23 non-hydrogen atoms appeared in the top 27 peaks of an E map calculated with 241 phased E's $\geq 1{\cdot}74$. The structure was refined by block-diagonal least squares to an R of 0·083 after allowance for anisotropic thermal motion. A difference Fourier then showed sites for all H atoms and these were included in subsequent stages to be refined isotropically. Convergence was attained at an R of 0·048 for the observed reflexions ($R = 0{\cdot}074$ with unobserveds included); for the observed data R_w* was 0·058. In the final stages the weighting scheme took the form: $\sqrt{w} = |F_o|/M$ for $|F_o| \leq M$; $\sqrt{w} = M/|F_o|$ for $|F_o| > M$, with $M = 23{\cdot}0$, and the function minimized was $\Sigma w(|F_o| - |F_c|)^2$. Final atomic coordinates and H thermal parameters are presented in Tables 1 and 2.* Scattering factors for elements other than H were taken from *International Tables for X-ray Crystallography* (1974); that for H was from Stewart, Davidson & Simpson (1965). Programs used were from the NRC crystallographic system (Ahmed, Hall, Pippy & Huber, 1973) and the figures are based upon *ORTEP* II plots (Johnson, 1970).

* $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]^{1/2}$.

Table 1. *Final atomic positional parameters* ($\times 10^4$) *with estimated standard deviations in parentheses*

	x	y	z
Cl(1)	4531 (1)	2801 (1)	1471 (1)
Cl(2)	−219 (1)	3880 (1)	3067 (1)
N(1)	2120 (1)	−131 (2)	4187 (1)
N(2)	4455 (1)	2678 (3)	3615 (2)
C(1)	937 (2)	1757 (3)	3747 (1)
C(2)	318 (2)	2726 (3)	3968 (2)
C(3)	90 (2)	2812 (4)	4885 (2)
C(4)	558 (2)	1917 (4)	5571 (2)
C(5)	1709 (2)	144 (4)	6271 (2)
C(6)	2540 (2)	−741 (4)	6144 (2)
C(7)	2385 (2)	−3611 (4)	5728 (2)
C(8)	2177 (2)	−4795 (4)	5075 (3)
C(9)	1935 (2)	−4436 (3)	4133 (3)
C(10)	1906 (2)	−2914 (3)	3837 (2)
C(11)	2117 (2)	−1717 (3)	4492 (2)
C(12)	2359 (2)	−2049 (3)	5458 (2)
C(13)	1244 (2)	959 (3)	5404 (2)
C(14)	1449 (2)	859 (3)	4448 (2)
C(15)	2441 (2)	116 (3)	3254 (2)
C(16)	2972 (2)	1571 (3)	3211 (2)
C(17)	3851 (2)	1410 (3)	3811 (2)
C(18)	5348 (2)	2357 (5)	4070 (3)
C(19)	4163 (2)	4230 (4)	3899 (3)

Table 2. *Final hydrogen-atom positional* ($\times 10^3$) *and isotropic thermal parameters* ($Å^2 \times 10^3$) *with estimated standard deviations in parentheses*

	x	y	z	U_{iso}
H(1)	105 (2)	170 (3)	312 (2)	37 (7)
H(3)	−37 (2)	351 (4)	499 (2)	58 (9)
H(4)	42 (2)	199 (3)	617 (2)	46 (8)
H(51)	181 (2)	89 (4)	672 (2)	61 (9)
H(52)	129 (2)	−53 (3)	657 (2)	47 (8)
H(61)	294 (2)	3 (3)	588 (2)	47 (8)
H(62)	279 (2)	−109 (3)	678 (2)	52 (8)
H(7)	254 (2)	−372 (4)	630 (2)	57 (8)
H(8)	223 (2)	−577 (4)	532 (2)	82 (11)
H(9)	180 (2)	−529 (4)	366 (2)	62 (9)
H(10)	173 (2)	−265 (4)	321 (2)	62 (10)
H(151)	281 (2)	−75 (3)	313 (2)	42 (7)
H(152)	195 (1)	11 (3)	272 (2)	30 (6)
H(161)	305 (2)	173 (4)	252 (2)	62 (9)
H(162)	265 (2)	246 (4)	343 (2)	49 (8)
H(171)	416 (2)	48 (3)	367 (2)	37 (7)
H(172)	379 (2)	143 (3)	450 (2)	55 (8)
H(181)	551 (2)	139 (4)	383 (2)	70 (9)
H(182)	536 (2)	232 (4)	482 (3)	80 (11)
H(183)	564 (2)	322 (4)	394 (2)	75 (10)
H(191)	361 (2)	450 (4)	353 (3)	87 (12)
H(192)	407 (3)	415 (5)	456 (3)	98 (13)
H(193)	458 (2)	499 (4)	378 (2)	75 (10)
H(99)	442 (2)	273 (3)	297 (2)	39 (7)

Discussion

A view of the molecule is given in Fig. 1 and bond lengths and angles for non-hydrogen atoms are presented in Table 3. The structure exhibits a fold between the aromatic rings, and the dihedral angle between the relevant mean planes (Table 4) is 123°. The dimethylaminopropyl side chain extends away from the central hetero-ring of the tricycle in a manner best described by the torsion angles listed in Table 5.

* Lists of structure factors, anisotropic thermal parameters and bond lengths and angles involving H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32528 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

The configuration at the C(15)–C(16):C(16)–C(17) bonds is close to *gauche–trans* and is the first occurrence of such a rotamer at that position in these types of molecule in the solid state, and one which is predominant for imipramine hydrochloride in $CDCl_3$ solution (Abraham, Kricka & Ledwith, 1974). For free imipramine in solution, the same study finds no evidence for attainment of a preferred conformer. The positively charged amino group in the side chain, therefore, appears important in this respect; as must its interaction with the chloride ion and, to a certain extent, the solvent. Under physiological conditions amino protonation is most likely achieved, though possibly in the presence of counter ions other than Cl^-. The results for NMR solution studies of imipramine, or related compounds, with other anions would be of interest. Since some of the reported X-ray work has been performed with similar compounds in their protonated form, it is possibly surprising that *gauche–trans* conformers have not previously been observed in the solid state. This, however, is an indication of the small energy differences between rotamers and the effect which crystal-packing forces can have upon such an energy-sensitive system.

The bonding parameters of chlorimipramine hydrochloride, with few exceptions, closely parallel those of imipramine hydrochloride (Post, Kennard & Horn, 1975). Overall conformational characteristics for the tricyclic moiety of the present compound are similar to those of imipramine I; there are two molecules [(I) and (II) corresponding to (*A*) and (*B*) in the original paper] in the asymmetric unit for the latter structure. Some conformational parameters for these molecules, and others containing analogous tricyclic systems, are presented in Table 6, from which general features are apparent for this structural type. There is an asymmetry to the fold of the tricycle. The atom labelling (Fig. 2) for all molecules listed in Table 6 is set such that the line of fold lies approximately along $b\cdots X$, with atom *b* closer to plane *A*, than *a* is to plane *B*. In

Table 3. *Bond lengths* (Å) *and angles* (°) *involving the non-hydrogen atoms, with estimated standard deviations in parentheses*

C(1)–C(2)	1·377 (4)	C(8)–C(9)	1·367 (5)
C(1)–C(14)	1·393 (3)	C(9)–C(10)	1·373 (4)
C(2)–C(3)	1·373 (4)	C(10)–C(11)	1·394 (4)
C(2)–Cl(2)	1·742 (3)	C(11)–C(12)	1·393 (4)
C(3)–C(4)	1·373 (4)	N(1)–C(11)	1·431 (3)
C(4)–C(13)	1·387 (4)	N(1)–C(14)	1·426 (3)
C(13)–C(14)	1·415 (3)	N(1)–C(15)	1·469 (3)
C(5)–C(13)	1·513 (4)	C(15)–C(16)	1·503 (4)
C(5)–C(6)	1·525 (4)	C(16)–C(17)	1·522 (4)
C(6)–C(12)	1·486 (4)	C(17)–N(2)	1·484 (4)
C(7)–C(12)	1·395 (4)	N(2)–C(18)	1·481 (4)
C(7)–C(8)	1·383 (5)	N(2)–C(19)	1·480 (4)
C(2)–C(1)–C(14)	121·3 (2)	C(7)–C(12)–C(11)	117·3 (3)
C(1)–C(2)–C(3)	121·4 (3)	C(4)–C(13)–C(5)	116·2 (2)
C(1)–C(2)–Cl(2)	118·9 (2)	C(4)–C(13)–C(14)	117·2 (2)
C(3)–C(2)–Cl(2)	119·7 (2)	C(5)–C(13)–C(14)	126·5 (2)
C(2)–C(3)–C(4)	117·0 (3)	C(1)–C(14)–C(13)	118·5 (2)
C(3)–C(4)–C(13)	124·6 (3)	C(13)–C(14)–N(1)	122·1 (2)
C(13)–C(5)–C(6)	117·9 (2)	C(1)–C(14)–N(1)	119·4 (2)
C(5)–C(6)–C(12)	110·8 (2)	C(11)–N(1)–C(14)	117·7 (2)
C(12)–C(7)–C(8)	122·2 (3)	C(11)–N(1)–C(15)	114·7 (2)
C(7)–C(8)–C(9)	119·4 (3)	C(14)–N(1)–C(15)	118·5 (2)
C(8)–C(9)–C(10)	120·2 (3)	N(1)–C(15)–C(16)	113·6 (2)
C(9)–C(10)–C(11)	120·6 (3)	C(15)–C(16)–C(17)	111·2 (2)
C(10)–C(11)–C(12)	120·4 (2)	C(16)–C(17)–N(2)	112·0 (2)
C(10)–C(11)–N(1)	121·0 (2)	C(17)–N(2)–C(18)	111·2 (2)
C(12)–C(11)–N(1)	118·6 (2)	C(17)–N(2)–C(19)	113·2 (2)
C(6)–C(12)–C(7)	123·8 (3)	C(18)–N(2)–C(19)	110·7 (2)
C(6)–C(12)–C(11)	118·9 (2)		

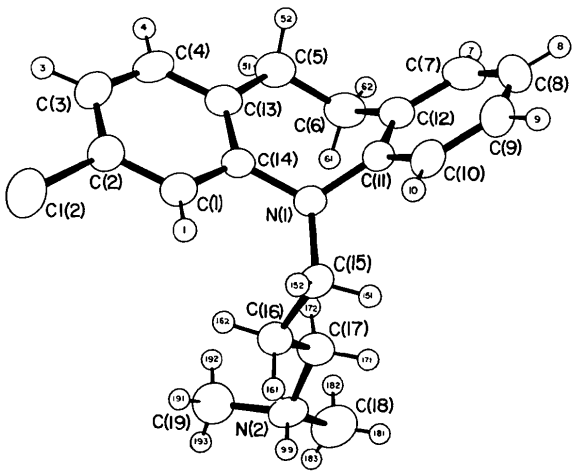

Fig. 1. Perspective view of the cation in chlorimipramine hydrochloride. Non-hydrogen atoms are represented by 50% probability thermal ellipsoids, and hydrogen atoms by spheres of arbitrary radius.

Table 4. *Equations of some least-squares mean planes [and displacements* (Å) *of atoms from these planes] for chlorimipramine hydrochloride*

Orthogonal axes *X*, *Y* and *Z* are based upon *a*, *b* and *c**.

Plane 1: $-0{\cdot}632X - 0{\cdot}751Y - 0{\cdot}192Z + 2{\cdot}714 = 0$
Plane 2: $0{\cdot}983X - 0{\cdot}054Y - 0{\cdot}174Z - 1{\cdot}492 = 0$
Plane 3: $-0{\cdot}856X - 0{\cdot}503Y - 0{\cdot}123Z + 2{\cdot}314 = 0$

Plane 1		Plane 2		Plane 3	
C(1)	0·007 Å	C(7)	0·001 Å	C(11)	0·115 Å
C(2)	−0·013	C(8)	0·002	C(12)	−0·091
C(3)	0·003	C(9)	−0·003	C(13)	0·087
C(4)	0·010	C(10)	0·001	C(14)	−0·112
C(13)	−0·015	C(11)	0·002	N(1)†	−0·565
C(14)	0·006	C(12)	−0·003	N(2)†	−4·862
C(5)†	−0·087	C(5)†	−1·424		
C(6)†	−0·308	C(6)†	−0·065		
N(1)†	0·031	N(1)†	0·056		
Cl(2)†	−0·082				

† These atoms were not included in the mean-plane calculations.

Table 5. *Some torsion angles* (°)

C(11)–N(1)–C(15)–C(16)	−142·4°	C(11)–C(12)–C(6)–C(5)	68·8°
N(1)–C(15)–C(16)–C(17)	71·2	C(12)–C(6)–C(5)–C(13)	−63·2
C(15)–C(16)–C(17)–N(2)	167·6	C(6)–C(5)–C(13)–C(14)	7·0
C(16)–C(17)–N(2)–C(18)	−170·0	C(5)–C(13)–C(14)–N(1)	3·4
C(16)–C(17)–N(2)–C(19)	64·8	C(13)–C(14)–N(1)–C(11)	50·1
N(1)–C(11)–C(12)–C(6)	4·9	C(14)–N(1)–C(11)–C(12)	−72·9

general *b* does lie slightly off plane *A*, but to an extent which is significantly and distinctly less than *a* from plane *B*. Because of the basic sp^2 character of atoms *c* and *f*, *a* and *A* are coplanar, as are *b* and *B* (see also Table 4). An effect, as a result of strain in the hetero-ring, producing asymmetric distortion in bond parameters is then apparent, since $\theta_a < \theta_b$ and the bridge angle $\varphi_a > \varphi_b$. This is the case for a variety of hetero atoms (and C) at *X*, with a bridge substituent at *Z*, and also appears independent of torsion angle in the *a*–*b* bond which has values from ~50–90°. {Three other structures containing a tricyclic nucleus, 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-ethyl-2-methylpyrrolidine.HBr (Tokuma, Nojima &

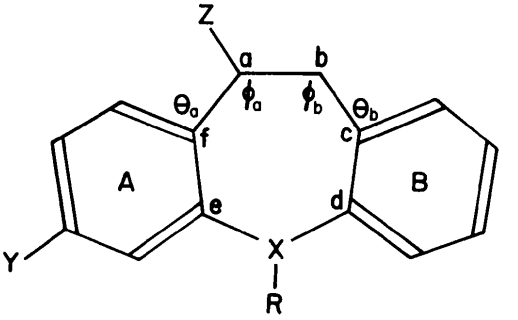

Fig. 2. The azepine nucleus including the labelling referred to in Table 6. For chlorimipramine: *X* = N, *Y* = Cl, *Z* = H and *R* = $-(CH_2)_3.N(CH_3)_2$.

Table 6. *Conformational parameters for some dibenz[b,f]azepines and related molecules*

	*X**	$\widehat{AB}$† (°)	Twist‡ (°)	Skew§ (Å)	*b* from *A*(Å)	*a* from *B*(Å)	θ_a (°)	θ_b (°)	φ_a (°)	φ_b (°)	$\tau_{a\cdot b}$¶ (°)	Reference
(1) Chlorimipramine.HCl	N	123	17·6	0·66	0·308	1·424	116·2	123·8	117·9	110·8	63·2	(i)
(2) Imipramine.HCl I	N	130	17·3	0·67	0·446	1·408	115·8	122·6	117·1	110·2	70·2	(ii)
(3) ‖ Imipramine.HCl II	N	123	8·4	0·61	0·04#	1·04#	116#	123#	122#	115#	49#	(ii)
(4) Silipramine.HCl	Si	142	21·4	0·31	0·72	1·40	115·9	120·3	117·7	113·2	92·4	(iii)
(5) 5-Methoxy-5-phenyl-10,11-dihydro-5*H*-dibenzo-[*b*,*f*]silepin	Si	138	16·9	0·29	0·46	1·23	115·6	119·9	118·4	112·0	88·3	(iv)
(6) 5-*p*-*N*,*N*-Dimethylamino-phenyl-10,11-dihydro-5*H*-dibenzo[*b*,*f*]silepin	Si	137	20·8	0·33	0·66	1·48	116·1	120·3	117·9	113·2	90·7	(v)
(7) Oxyprothepine	S	104	11·9	0·35	0·147	1·302	114·1	121·2	117·2	112·7	49·2	(vi)
(8) Dexclamol.HBr	C	120	14·8	0·54	0·220	1·368	112·3	121·2	120·0	107·4	62·3	(vii)
(9) ‖ 5,5-Diphenyl-10,11-dihydro-5*H*-dibenzo-[*b*,*f*]germepin	Ge	156	1·0	0·19	0·05#	0·70#	120#	119#	120#	114#	101#	(viii)

Substituent *R* (see Fig. 2) is as follows: (1), (2) and (3) $-(CH_2)_3.\underset{H}{N^+}(CH_3)_2$; (4) $\langle^{(CH_2)_3.\underset{H}{N^+}(CH_3)_2}_{(CH_3)}$; (5) $\langle^{(C_6H_5)}_{(OCH_3)}$;

(6) $\langle^{(C_6H_4).N(CH_3)_2}_{H}$; (7) not substituted; (8) rings fused to *A*; (9) $\langle^{(C_6H_5)}_{(C_6H_5)}$. *Y* = *Z* = H (see Fig. 2), except for (1) *Y* = Cl, *Z* = H; and (7) *Y* = H, *Z* = $[N_2(CH_2)_4].(CH_2)_3.OH$.

References: (i) Present work. (ii) Post, Kennard & Horn (1975). (iii) Corey, Corey & Glick (1976). (iv) Paton, Cody, Corey, Corey & Glick (1976). (v) Corey, Corey & Glick (1975). (vi) Koch & Evrard (1974). (vii) Bird, Bruderlein & Humber (1976). (viii) Corey, Corey, Glick & Dueber (1972).

* See Fig. 2 for ring substituent positions.
† Angle between planes *A* and *B*.
‡ The average of torsion angle *cdef* and *efcd* (see also Corey, Corey & Glick, 1975).
§ Distance $(c\cdots f)$–$(d\cdots e)$ (see also Corey, Corey, Glick & Dueber, 1972).
¶ Torsion angle *fabc*.
‖ Molecule exhibits disorder in the ethano-bridge region.
Values with high associated e.s.d.'s because of ethano-bridge disorder.

Morimoto, 1968), 5-(bromomethylene)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (Larsson, 1970), and butaclamol.HBr (Bird, Bruderlein & Humber, 1976), have been omitted from Table 6 because angular differences, of the magnitude found relevant above, would be insignificant with respect to the published estimated standard deviations. Data derived for the ethano-bridge regions of (3) and (9) in Table 6 are also subject to large e.s.d.'s but are included for the disorder aspect discussed below.} It is of interest that the values of θ_a and φ_a, *i.e.* those angles in the maximum planar part of the tricycle, are similar to those (115 and 127° respectively) found in the related 5*H*-10,11-dioxodihydrodibenz[*b*,*f*]azepine (Denne & Mackay, 1970) for which *A*, *B*, *a* and *b* are nearly coplanar. Some other conformational trends for the heterocycle have been discussed previously (Corey, Corey & Glick, 1975, 1976).

In solution, the tricyclic moiety of a number of 5*H*-dibenz[*b*,*f*]azepines (and imipramine itself) is known to exist as an equilibrium state of conformational isomers, with hetero-ring inversion and ethano-bridge flip (caused by torsion about the *a*–*b* bond) being the important isomerization modes (Abraham, Kricka & Ledwith, 1974; Ellefson, Swenton, Bible & Green, 1976). The latter effect would result in a reversal of the roles of *a* and *b*; *i.e.* after a bridge flip, *a* would be closer to plane *B* than *b* is to *A* (Table 6). In passing from one bridge-flip position to another, the twist angle would decrease, pass through zero and then increase with opposite sign. It is noteworthy that the two molecules in Table 6 which exhibit ethano-bridge disorder (the remainder of the molecule is well defined by the X-ray analyses) each have a low twist angle, as can be anticipated for a ring system in which the bridge is at an intermediate flip position. The torsion angle at *a*–*b* would be, formally, close to zero for such a ring conformation, even though the analyses yield apparently high values, and result in an eclipsed configuration for the ethano-bridge H atoms. The observed disorder is, therefore, most probably the result of a random relaxation of bond parameters in an attempt to minimize the unfavourable steric and energetic condition of the system. It is of interest that in the case of the germepin (Corey, Corey, Glick & Dueber, 1972) the twist angle is very close to zero and the bridge atoms appear disordered to a larger extent, judging from bond values in the region, than in imipramine II, for which the twist angle has a slightly higher value.

A packing diagram for chlorimipramine hydrochloride is given in Fig. 3. The chloride ion is hydrogen bonded to the amino nitrogen atom [N(2)···Cl(1) = 3·026 (2) Å] with geometry compatible with tetrahedral bonding about N(2) (Table 7), as would be expected for the positively charged N atom. The lattice consists of layers of ionic interaction parallel to *bc*, centred at $x = \frac{1}{2}$. The propyl side chain and tricyclic moieties lie away from this region and are not involved in any unusually short intermolecular contacts.

The coarse parameters which have been previously employed with the neuroleptics (Horn, Post & Kennard, 1975) to measure molecular compatibility with the possible spatial requirements for dopamine receptor blockade are, in this case: a distance of 4·87 Å between aromatic-ring centres (*A*···*B*), and ring centres to amine distances [*A*···N(2), *B*···N(2)] of 6·55 and 6·11 Å. Another parameter of possible significance is an estimate of the height of the amine group from the ring system, which could be taken as the perpendicular distance of N(2) from the extended mean plane of atoms C(11)→C(14); this value is 4·86 Å to the same

Table 7. *Geometry around the amine nitrogen atom* N(2)

N(2)···Cl(1)	3·026 (2) Å		
H(99)–N(2)–C(17)	105 (2)°	Cl(1)–N(2)–C(17)	108 (1)°
H(99)–N(2)–C(18)	113 (2)	Cl(1)–N(2)–C(18)	107 (1)
H(99)–N(2)–C(19)	104 (2)	Cl(1)–N(2)–C(19)	107 (1)
Cl(1)–H(99)–N(2)	171 (1)		

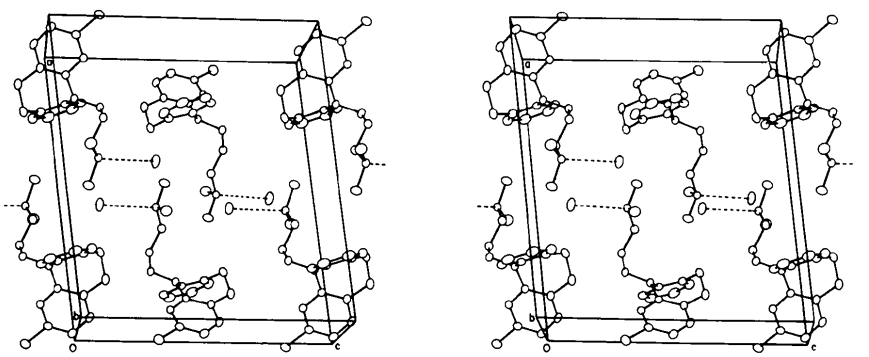

Fig. 3. Packing diagram for chlorimipramine hydrochloride with hydrogen atoms omitted for clarity. Broken lines connect the chloride ion, Cl(1), to the amine nitrogen atom, N(2).

side as N(1) (Table 4). The small energy differences between side-chain rotamers (Horn, Kennard, Motherwell, Post & Rodgers, 1974) and the conformational lability of the tricyclic moiety in solution, restrict confident application of data derived from the solid state to the relationship of structure to activity under physiological conditions. However, for tricyclic neuroleptic compounds, the use of values of the type defined above does allow qualitative conclusions to be drawn with regard to drug activity (Horn, Post & Kennard, 1975), and it is hoped to extend and improve this approach with the antidepressants. Recent studies with related, and conformationally rigid, spiro tricyclic compounds [*i.e.* there is a spiro C atom at *X* (Fig. 2)] (Rodgers, Kennard, Sheldrick & Horn, 1976; Carnmalm, Johansson, Rämsby, Stjernström, Ross & Ogren, 1976) may well provide more definitive stereochemical information concerning the molecular requirements for effective uptake site blockade.

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