Table 5. *Hydrogen bond distances* (Å) *and angles* (°)

Key to symmetry operations

i	$1+x$	$\frac{1}{2}-y$	$z-\frac{1}{2}$		iii	x	$\frac{1}{2}-y$	$\frac{1}{2}+z$
ii	$x+\frac{1}{2}$	$\frac{1}{2}-y$	$\bar{z}$		iv	$\bar{x}$	$y+\frac{1}{2}$	$\frac{1}{2}-z$

X⋯H–Y		X⋯H		$\angle$X⋯H–Y
Cl(1)⋯N(1)	3·480 (3)	Cl(1)⋯H(5)	2·67 (3)	150
Cl(1)⋯N(1^i)	3·418 (3)	Cl(1)⋯H(4^i)	2·58 (3)	157
Cl(1)⋯N(2^{iv})	3·305 (3)	Cl(1)⋯H(10^{iv})	2·53 (3)	154
Cl(1)⋯N(3)	3·239 (2)	Cl(1)⋯H(13)	2·40 (2)	160
Cl(1)⋯N(4^i)	3·310 (3)	Cl(1)⋯H(19^i)	2·50 (3)	165
Cl(1)⋯N(4^{iv})	3·407 (2)	Cl(1)⋯H(18^{iv})	2·73 (3)	141
O(2)⋯O(6)	2·925 (4)	O(2)⋯H(2)	2·40 (4)	108
O(3)⋯O(6^i)	3·128 (4)	O(3)⋯H(3^i)	2·30 (6)	162
O(4)⋯N(3^{ii})	3·103 (4)	O(4)⋯H(12^{ii})	2·31 (2)	160
O(6)⋯O(1^{iii})	2·658 (3)	O(6)⋯H(1^{iii})	1·97 (2)	175

O(6)⋯O(2)=2·925 Å and O(6)⋯O(3^{iii})=3·128 Å. But, as can be seen from the temperature factors, they did not refine well.

Packing

The structure is built from two different kinds of layers oriented perpendicular to *a*. One consists of complex ions and Cl⁻ ions, the other of ClO₄⁻ ions and water molecules (Fig. 3). In the first layer each complex ion is surrounded by six Cl⁻ ions and each Cl⁻ ion by three complex ions. The closest approaches in this layer are six hydrogen bonds between a Cl⁻ ion and six amine groups (Table 5). The complex ions have two hydrogen bonds to the water–perchlorate layer,

one from the bridging hydroxy group to the water molecule, and one from an amine group to a ClO₄⁻ ion.

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Silipramine: a Group IV Analog of Imipramine Hydrochloride. The Crystal and Molecular Structure of 5-Methyl-5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[b,f]-silepin Hydrochloride Hydrate

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The structure of silipramine hydrochloride hydrate, C₂₀H₂₇NSi.HCl.H₂O, monoclinic, in space group P2₁/c with $a=15\cdot667$ (3), $b=9\cdot085$ (2), $c=14\cdot548$ (3) Å, $\beta=91\cdot16$ (2)°, $Z=4$, has been determined by iterative application of the Σ_2 relationship and refined by full-matrix least-squares techniques to a conventional R of 0·046 for 1896 counter reflections. The silipramine molecule adopts a folded boat conformation with a dihedral angle between benzo group planes of 141·8° and an extended dimethylaminopropyl side chain in the pseudo-axial position on the silicon heteroatom. Generalized parameters for the description of stereochemical features of dibenzoheteroepins are discussed.

Introduction

There is a general interest in the structural features of dibenzotricyclic derivatives because of their central nervous system activity (antidepressants and tranquilizers). As part of a synthetic and structural program of silicon analogs of tricyclic compounds, we wish to report the first solid state structural study of a

silicon analog of imipramine hydrochloride, a drug widely prescribed for treatment of depression. Silipramine hydrochloride (Fig. 1) 5-methyl-5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[b,f]silepin hydrochloride hydrate, differs from imipramine hydrochloride by replacement of Si–CH$_3$ for N in the central ring system. Biological activity of silicon-containing compounds has been documented (Voronkov, 1973, 1975). The activity of the title compound is presently under investigation. It has been demonstrated that the closely related system, (C$_6$H$_5$)$_2$Si(CH$_3$)CH$_2$CH$_2$CH$_2$N(CH$_3$)$_2$.HCl, shows tranquilizing activity (Barcza, 1974).

Experimental

The title compound, 5-methyl-5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[b,f]silepin hydrochloride hydrate was prepared by reaction of 5-methyl-10,11-dihydro-5H-dibenzo[b,f]silepin (Corey, 1972) with N,N-dimethylallylamine in the presence of chloroplatinic acid followed by reaction with gaseous HCl in (C$_2$H$_5$)$_2$O.CHCl$_3$. The salt was recrystallized from xylene–chloroform mixtures.*

A crystal (0·17 × 0·32 × 0·35 mm) with well developed (100), (011) and (01$\bar{1}$) faces was used for data collection. The crystal was attached to a glass fiber and mounted on a Syntex $P2_1$ diffractometer with the [01$\bar{1}$] direction approximately parallel to the instrument φ axis. The space group was assigned on the

* Details of the synthetic procedures will be published at a later date.

basis of rotation and axial photographs and counter data. Fifteen reflections with 2θ greater than 24° were centered with a programmed centering routine; cell parameters (Table 1) were obtained by least-squares refinement of these angles.

Table 1. Crystal data

C$_{20}$H$_{30}$ClNOSi	M.W. 364·00
Monoclinic	$D_c = 1·17$ g cm^{-3}
Space group $P2_1/c$	$D_m = 1·16$
$a = 15·667$ (3) Å	$Z = 4$
$b = 9·085$ (2)	$F(000) = 788$
$c = 14·548$ (3)	λ(Mo $K\alpha$) = 0·71069 Å
$\beta = 91·16$ (2)°	μ(Mo $K\alpha$) = 2·50 cm^{-1}
$U = 2070·3$ (7) Å^3	

All reflections with $2\theta \leq 50°$ were measured with a θ–2θ scan speed of 2·0 deg min^{-1}. Backgrounds were measured at each end of the scan (2θ scan range: 2θ Mo $K\alpha_1 - 1·0°$ to 2θ Mo $K\alpha_2 + 1·0°$) for a total time equal to one half the scan time. Intensity data were collected with Mo $K\alpha$ (graphite monochromator)
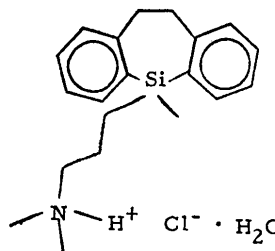

Fig. 1. Silipramine hydrochloride hydrate.

Table 2. *Final positional parameters* ($\times 10^4$) *and anisotropic thermal parameters* ($\times 10^4$) *with estimated standard deviations in parentheses*

Anisotropic thermal parameters are in the form exp $[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	4501 (3)	8803 (5)	4101 (3)	51 (3)	114 (7)	56 (3)	−20 (4)	−16 (2)	20 (4)
C(2)	5121 (3)	8397 (6)	3496 (4)	53 (3)	191 (10)	59 (3)	−38 (4)	−11 (2)	40 (5)
C(3)	5201 (3)	6947 (6)	3227 (3)	38 (2)	227 (10)	48 (3)	−13 (4)	1 (2)	22 (4)
C(4)	4652 (3)	5907 (5)	3578 (3)	36 (2)	159 (7)	39 (2)	−3 (3)	−3 (2)	9 (3)
Si(5)	3234 (1)	4863 (1)	4575 (1)	33 (1)	84 (2)	34 (1)	−2 (1)	−1 (1)	−1 (1)
C(6)	2629 (2)	3741 (5)	6217 (3)	33 (2)	140 (7)	44 (2)	0 (3)	−2 (2)	19 (4)
C(7)	2428 (3)	3654 (6)	7138 (3)	43 (2)	192 (9)	47 (3)	0 (4)	2 (2)	27 (4)
C(8)	2577 (3)	4846 (7)	7703 (3)	43 (2)	260 (11)	36 (2)	15 (5)	1 (2)	16 (5)
C(9)	2907 (3)	6121 (6)	7349 (3)	41 (2)	215 (10)	35 (2)	11 (4)	−4 (2)	−12 (4)
C(10)	3480 (3)	7692 (5)	6123 (3)	61 (3)	127 (7)	52 (3)	−11 (4)	7 (2)	−27 (4)
C(11)	3278 (3)	8224 (5)	5129 (3)	53 (2)	95 (6)	58 (3)	4 (3)	−2 (2)	−11 (3)
C(12)	2974 (2)	5019 (4)	5834 (2)	27 (2)	112 (6)	37 (2)	0 (3)	−5 (1)	5 (3)
C(13)	3112 (2)	6241 (5)	6415 (3)	30 (2)	135 (7)	40 (2)	6 (3)	−4 (2)	−14 (3)
C(14)	3941 (2)	7768 (5)	4454 (3)	34 (2)	102 (6)	40 (2)	0 (3)	−9 (2)	10 (3)
C(15)	4011 (2)	6288 (4)	4190 (3)	30 (2)	106 (6)	33 (2)	2 (3)	−1 (2)	6 (3)
C(16)	3691 (3)	3001 (4)	4362 (3)	51 (2)	102 (6)	49 (2)	6 (3)	−3 (2)	−6 (3)
C(17)	2222 (2)	5046 (4)	3859 (2)	36 (2)	113 (6)	38 (2)	−6 (3)	−5 (2)	4 (3)
C(18)	1543 (2)	3898 (4)	4084 (3)	34 (2)	108 (6)	38 (2)	−7 (3)	−5 (2)	5 (3)
C(19)	744 (2)	4087 (4)	3487 (3)	35 (2)	103 (6)	40 (2)	0 (3)	−6 (2)	−1 (3)
N(20)	68 (2)	2976 (3)	3699 (2)	32 (2)	109 (5)	36 (2)	0 (2)	0 (1)	0 (3)
C(21)	276 (3)	1519 (5)	3301 (3)	59 (3)	101 (6)	55 (3)	−12 (4)	3 (2)	−15 (3)
C(22)	−791 (3)	3461 (6)	3359 (3)	31 (2)	217 (9)	77 (3)	6 (4)	−7 (2)	23 (5)
Cl(23)	−143 (1)	2273 (1)	5755 (1)	113 (1)	125 (2)	47 (1)	20 (1)	26 (1)	−3 (1)
O(24)	1448 (3)	171 (5)	5298 (4)	67 (2)	301 (9)	203 (5)	31 (4)	5 (3)	32 (5)

radiation. During data collection, the intensities of three standard reflections were measured every 97 reflections with no significant variation in intensity observed. The data were reduced to F^2 and $\sigma(F^2)$ by procedures similar to those previously described (Schmonsees, 1974). Standard deviations were assigned as follows:

Fig. 2. Interatomic bond distances; primed atoms are related by the transformation: $-x, -y, 1-z$.

Fig. 3. Interatomic bond angles.

$$\sigma(I) = [\sigma_{counter}(I)^2 + (0.03I)^2]^{1/2},$$

where $\sigma_{counter} = (I + K^2 B)^{1/2}$, $I =$ net intensity, $B =$ total background counts and $K =$ ratio of scan time to background time. No corrections were made for absorption, extinction and anomalous dispersion. The 1896 data with $F^2 > 3\sigma(F^2)$ from 3932 data scanned were used in the structure solution and refinement.

Structure solution and refinement

The structure was solved by an iterative application of the $\sum_2$ relationship (Long, 1965; Sayre, 1952) using 150 normalized structure factors of magnitude 1·5 or greater. An E map based on the set of phases for the solution with the largest consistency index (0·96) yielded the positions of 23 of the nonhydrogen atoms. Least-squares refinement (Busing, Martin & Levy, 1962) with isotropic thermal parameters gave a discrepancy value $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.140$. A difference Fourier map indicated the presence of an additional nonhydrogen atom (3·4 e Å^{-3}) which was included in subsequent calculations as the oxygen atom of a water molecule. The inclusion of a water molecule in the crystal structure is consistent with the chemical analysis. Refinement was completed with anisotropic thermal parameters for nonhydrogen atoms and the inclusion of hydrogen atoms at ideal locations (Zalkin, 1974) with fixed hydrogen distances of 1·0 Å. Isotropic thermal parameters for the hydrogen atoms were fixed at values 10% larger than the equivalent isotropic B of the atom to which they are bonded. Tables 2 and 3 give positional and thermal parameters with associated estimated standard deviations. Final discrepancy values were $R_1 = 0.046$ and $R_2 = [\sum w(|F_o| - |F_c|)^2 / \sum w F_o^2]^{1/2} = 0.052$.[*] The largest parameter shift in the final cycle of full matrix refinement was 9% of its standard deviation; the error of fit was 1·55. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The highest residual electron density in the final difference map was 0·26 e Å^{-3}.

Discussion

One molecular formula unit of silipramine hydrochloride and one water of hydration comprise the asymmetric part of the structure. A view of the asymmetric unit is shown in Figs. 2 and 3 with the values of interatomic bond distances and angles indicated (Busing, Martin & Levy, 1964). The values are similar to those reported for related heterocycles (Post, Kennard & Horn, 1975; Corey, Corey & Glick,
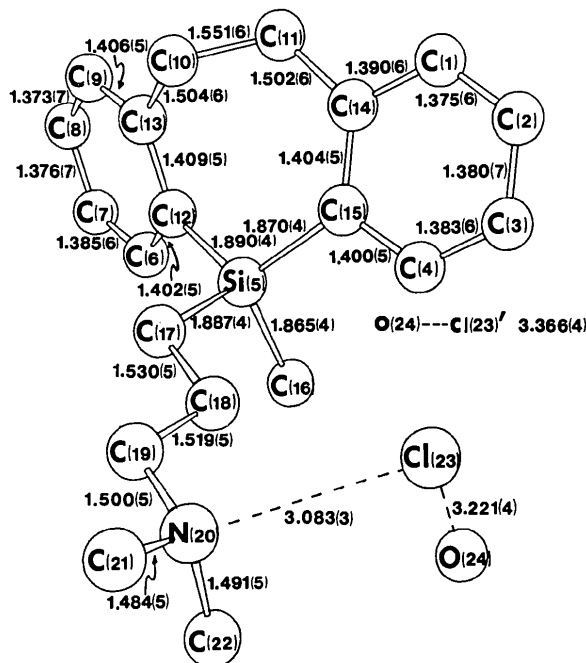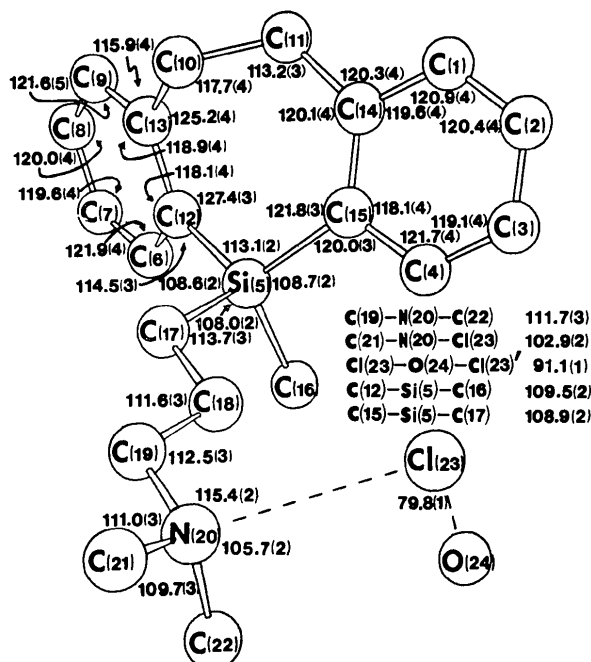
Table 3. *Hydrogen atom positional parameters* $(\times 10^3)$
with thermal parameters

Isotropic thermal parameters have been assigned fixed values
10 % greater than the equivalent B of the atom bonded to the
hydrogen atom.

	x	y	z	B (Å²)
H(Cl)	445	986	429	4·6
H(C2)	552	916	325	5·4
H(C3)	565	665	279	5·2
H(C4)	471	486	339	4·3
H(C6)	252	287	581	4·1
H(C7)	218	273	739	5·1
H(C8)	244	478	837	5·2
H(C9)	300	698	776	4·7
H'(C10)	328	861	643	5·0
H''(C10)	412	771	609	5·0
H'(C11)	340	928	528	4·7
H''(C11)	265	810	500	4·7
H'(C16)	420	284	478	4·5
H''(C16)	385	277	372	4·5
H'''(C16)	328	223	457	4·5
H'(C17)	228	524	319	3·8
H''(C17)	194	590	416	3·8
H'(C18)	130	388	472	3·7
H''(C18)	168	287	389	3·7
H'(C19)	46	495	378	3·7
H''(C19)	81	428	282	3·7
H(N20)	5	289	438	3·6
H'(C21)	78	112	365	4·8
H''(C21)	39	147	263	4·8
H'''(C21)	−18	80	345	4·8
H'(C22)	−84	385	272	5·6
H''(C22)	−96	425	380	5·6
H'''(C22)	−122	270	351	5·6
H'(O24)	95	82	544	11·2
H''(O24)	106	−56	499	11·2

1975). The 118·1 (4)° angles in the benzo rings at C(12)
and C(15) follow the trend associated with such angles
for second-row element substituents on benzene rings
(Domenicano, Vaciago & Coulson, 1975). The tri-
cyclic framework of the molecule exhibits a folded
boat conformation with an extended dimethylamino-
propyl side chain occupying the pseudoaxial position
on the silicon heteroatom. Least-squares planes for the

Table 4. *Equations of least-squares planes of the benzo*
groups and deviations (Å) *of atoms from these planes*

X, Y, Z are orthogonal unit vectors defined by the equations:
$$X = \mathbf{a}, \quad Y = \mathbf{b}, \quad Z = \mathbf{a} \times \mathbf{b}.$$
Plane 1: $-0\cdot620X + 0\cdot163Y - 0\cdot768Z = -7\cdot565$

C(1)	0·00	C(12)*	0·98
C(2)	0·00	C(13)*	1·58
C(3)	0·00	C(14)	0·00
C(4)	0·00	C(15)	0·00
Si(5)*	−0·12	C(16)*	0·36
C(10)*	1·40	C(17)*	−1·92
C(11)*	0·03		

Plane 2: $-0\cdot919X + 0\cdot333Y - 0\cdot210Z = -4\cdot390$

Si(5)*	0·07	C(10)*	0·01
C(6)	0·00	C(11)*	−0·72
C(7)	0·01	C(14)*	0·18
C(8)	−0·01	C(15)*	0·66
C(9)	0·00	C(16)*	1·24
C(12)	0·00	C(17)*	−1·64
C(13)	0·00		

* Atoms not included in least-squares plane calculation.

Table 5. *Torsion angles* (°) *about the seven-membered*
central ring

Si(5)—C(12)	17·6 (4)	C(11)–C(14)	71·2 (5)
C(12)–C(13)	1·8 (6)	C(14)–C(15)	5·6 (5)
C(13)–C(10)	32·9 (6)	C(15)–Si(5)	−43·9 (4)
C(10)–C(11)	−92·4 (5)		

benzo groups are given in Table 4. Torsion angles
about the central ring are presented in Table 5.

A stereoscopic view of the nonhydrogen atoms in
the asymmetric unit is given in Fig. 4; the numbering
scheme is the same as that of Figs. 2 and 3. Inter-
molecular packing distances are normal. The water
molecules and chloride ions form Cl–H₂O hydrogen-
bonded dimers [Cl(23)···O(24), 3·221 (4); Cl(23)'···
O(24), 3·366 (4) Å; Cl(23)···O(24)···Cl(23)', 91·1 (1);
O(24)···Cl(23)···O(24)' 88·9 (1)°] located about a
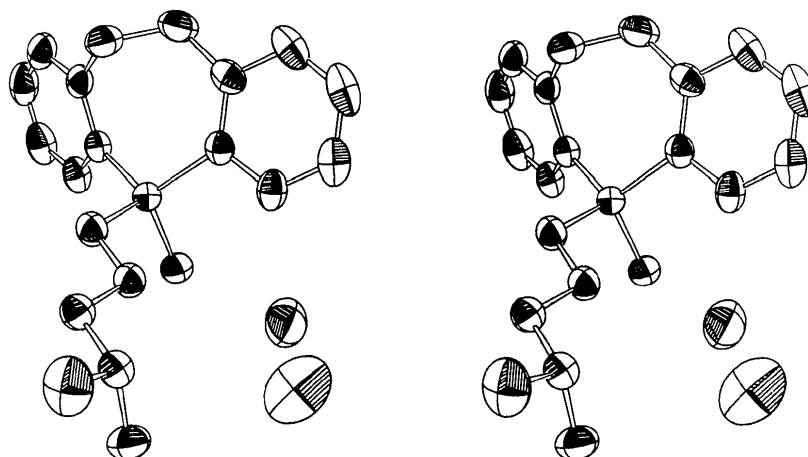crystallographic center of symmetry. The chloride

Fig. 4. A stereoscopic view of silipramine hydrochloride hydrate. The atoms are represented by 50 % probability thermal ellipsoids.

ions of the dimer are also hydrogen bonded to the nitrogen atom of the dimethylamino group [N(20)··· Cl(23), 3·083 (3) Å; N(20)···Cl(23)···O(24), 79·8 (1); N(20)···Cl(23)···O(24)', 76·8 (1)°].

With the aid of Dreiding models, Wilhelm & Kuhn (1970) and Wilhelm (1975) have identified steric parameters to describe the tricyclic skeleton in polycyclic p ychoactive drugs. A preliminary account of structure–activity correlations in psychoactive drugs has been presented (Kennard, Post, Rodgers & Horn, 1975). The tricyclic framework may be described by a generalized set of structural parameters which include: (1) a bend angle, (2) the distance between centers of benzo groups, (3) a skew distance and (4) a twist angle (Corey, Corey & Glick, 1975).

The bend angle is defined as the dihedral angle between the planes of the benzo group atoms. The skew distance is the difference between nonbonded benzo carbon distances across the central ring, i.e. in silipramine the difference between the C(13)···C(14) and C(12)···C(15) distances. The twist angle is the mean value of the torsion angles about the same pair of nonbonding vectors, i.e. in silipramine, the mean

value for torsion angles C(12)–C(13)···C(14)–C(15) and C(13)–C(12)···C(15)–C(14).

The values of the four parameter for silipramine and for imipramine, are given in Table 6. These four structural parameters have been calculated for related dibenzoheteroepins and carbocycles which contain saturated ethano bridges at the 10,11-positions and for which structural data have been published* (Corey,

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* These data are deposited with the structure factors; see previous footnote.

Table 6. *Comparison of dibenzotricyclic structural parameters for silipramine and imipramine*
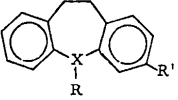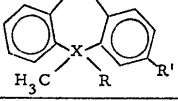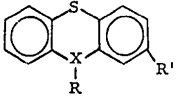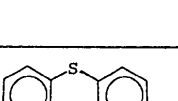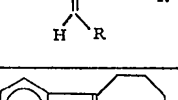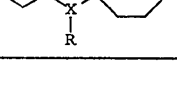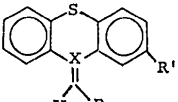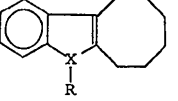
	Silipramine*	Imipramine†	
Bend angle (°)	141·8	130·3	123·0
Distance between benzo centers (Å)	5·61	4·96	4·79
Skew distance (Å)	0·31	0·67	0·61
Twist angle (°)	22·9	17·2	8·4

* This work.
† Two molecules per asymmetric unit (Post, Kennard & Horn, 1975).

Table 7. *Torsion angles (°) in propyl side chains on tricyclic frameworks*

Torsion angles have been calculated from the published atomic coordinates; calculations in right-handed reference system. The benzo carbon atom used for the torsion angle calculation is in the ring bonded to the ethano carbon which is on the same side of the framework as X or the benzo carbon atom on the substituted benzo ring.

Compound	X	R	R'	Torsion angles				Reference
				$X–C_\alpha$	$C_\alpha–C_\beta$	$C_\beta–C_\gamma$	$C_\gamma–N$	
	N	$(CH_2)_3N(CH_3)_2 \cdot HCl$	H	A: 137 B: 59	-180 160	173 61	169 64	Post, Kennard & Horn (1975)
	Si	$(CH_2)_3N(CH_3)_2 \cdot HCl \cdot H_2O$	H	-178	-180	-180	161	Corey, Corey & Glick, this work
	N	$(CH_2)_3N(CH_3)_2$	Cl	69	-164	75	74	McDowell (1969)
	N	$(CH_2)_3N(CH_3)_2 \cdot HCl$	Cl	-129	-152	-127	4	Dorignac-Calas & Marsau (1972)
	N	$(CH_2)_3N(CH_3)_2 \cdot HCl$	CF_3	A: -149 B: -69	-142 -178	58 -179	67 172	Phelps & Cordes (1974)
	N	$(CH_2)_3N(CH_3)_2 \cdot H_4C_4O_4$	OCH_3	80	-176	170	63	Marsau & Gauthier (1973)
	N	$(CH_2)_3N\!\!\diagup\!\!\diagdown\!\!N–CH_3$	SCH_2CH_3	-142	175	-55	164	McDowell (1970)
	C	$(CH_2)_2N(CH_3)_2 \cdot HCl$	Cl	3	151	-173	-61	Post, Kennard & Horn (1974)
	N	$(CH_2)_3N(CH_3)_2 \cdot HCl \cdot H_2O$	–	-83	-177	-167	-58	Rodgers, Kennard, Horn & Riva di Sanseverino (1974).

Corey & Glick, 1975). These derivatives may be grouped according to the atom which occupies the 5-position: (1) tetrahedral atom (Ge, Corey, Corey, Glick & Dueber, 1972; Si, this report; Si, Corey, Corey & Glick, 1975), (2) approximately planar three-coordinate atoms (N, Post, Kennard & Horn, 1975; C, Larsson, 1970; C, Tokuma, Nojima & Morimoto, 1970), and (3) a divalent two-coordinate atom (S, Koch & Evrard, 1974). The value of the bend angle decreases through the series Ge > Si > N > C > S and ranges from 156·4 to 103·7°. The distance between centers of the benzo rings decreases as the bend angle decreases (from 5·74 Å for the Ge heterocycle to 4·79 Å for the sulfur heterocycle). The magnitude of the skew distance is primarily a function of the covalent radius of the atom in the 5-position of the ring system (0·19 for the Ge heterocycle to 0·67 Å for the N heterocycle).

In addition to the tricyclic skeleton described in the previous paragraph, a characteristic of compounds which exhibit psychotropic activity is the presence of a side chain terminated by a nitrogen functional group. The most common side chain bonded to the central ring is a N,N-dimethylaminopropyl group. It has been proposed that maximum transmission of psychotropic activity involves a side chain that is folded back over the tricyclic framework, i.e. a side-chain conformation which requires a gauche distribution about the C_α–C_β bond (Wilhelm & Kuhn, 1970; Wilhelm, 1975). Table 7 summarizes the torsional angles associated with this side chain in the solid state for pharmaceutically active compounds and closely related systems. A fully extended side chain corresponds to torsion angles of $\pm 180°$ (ideal value) for C_α–C_β and C_β–C_γ bonds. An examination of Table 7 shows that for the nine derivatives there are two general conformations observed for the C_α–C_β and C_β–C_γ bonds: trans–trans and trans–gauche. At this time there is no evidence in the solid state for a gauche distribution about the C_α–C_β bond which would be required for the side chain to fold back over the tricyclic framework. Theoretical calculations on phenothiazine derivatives suggested that the conformation of the side chain was related to the degree of folding (bend angle) (Coubeils & Pullman, 1972). Data recently reported for the phenothiazine derivative, triflupromazine (Phelps & Cordes, 1974), do not fit the model proposed by Coubeils & Pullman, nor can they be extended to the other derivatives cited in Table 7. The conformation of the side chain determines the relative distance between the terminal basic group and the tricyclic framework. An attempt has been made to relate this distance of the side chain nitrogen atom from the geometric center of the benzene rings in the tricyclic system to neuroleptic activity (Horn, Post & Kennard, 1975).

The energy difference between rotamers is probably small since both trans–trans and trans–gauche conformers are present in the same unit cell in two of the cases cited in Table 7. In solution, NMR studies show

that there is apparently no conformational preference for the dimethylaminopropyl side chain in imipramine (the free base) in CDCl₃ (Abraham, Kricka & Ledwith, 1974) nor for chlorpromazine (free base) in $(CD_3)_2SO$ (Barbe & Chauvet-Monges, 1974). The side chain in imipramine hydrochloride exists predominantly in the gauche–trans conformation in CDCl₃ (this conformation is still preferred but favored less in D₂O) (Abraham, Kricka & Ledwith, 1974), a conformer thus far not reported in the solid state. The fully extended (or nearly so) protonated side chain may be favored in the solid state by packing and hydrogen-bonding interactions. Thus, calculations relating psychotropic activity to distances obtained for side chains in the solid state may not be meaningful.

It has been proposed that psychotropic activity in tricyclic pharmaceuticals is related to the bend angle (Wilhelm & Kuhn, 1970; Wilhelm, 1975). Neuroleptic (tranquilizing) activity has been associated with larger bend angles and antidepressant activity with smaller bend angles. The parent phenothiazine molecule exhibits a bend angle of 153° (Bell, Blount, Briscoe & Freeman, 1968). When the N-substituent is bulkier than methyl (Wakayama, 1971) with one exception (Marsau & Gauthier, 1973), the bend angle falls in the range 134–146° (Chu & van der Helm, 1975; Marsau, 1971; McDowell, 1969, 1970, 1975; Dorignac-Calas & Marsau, 1972; Phelps & Cordes, 1974; Marsau & Gauthier, 1973).* The nitrogen atom in the central ring of phenothiazine derivatives, as for imipramine, is approximately planar. Although the bend angles for the two independent molecules of the asymmetric unit for imipramine hydrochloride are 123 and 130°, these values do not differ greatly from those derivatives which contain a central six-membered ring. The range of bend angles for tricyclic systems with central seven-membered rings is 103–156°. It should be noted, however, that the system with the smallest bend angle is a strong neuroleptic (Koch & Evrard, 1974) which is contrary to the published hypothesis (Wilhelm & Kuhn, 1970; Wilhelm, 1975).

Predictions of neuroleptic vs antidepressant activity based on bend angles determined from solid state diffraction studies or measured from models should be made with caution because room temperature NMR measurements have revealed that the tricyclic framework undergoes rapid ring inversion (Abraham, Kricka & Ledwith, 1974; Corey, 1975).

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* A table with these data has been deposited with the structure factors. See footnote on p. 2027.

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