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Cyclizine Hydrochloride*

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Abstract. $C_{18}H_{23}N_2^+.Cl^-$, *Pnma*, $a = 11{\cdot}833\ (3)$, $b = 13{\cdot}631\ (3)$, $c = 10{\cdot}023\ (3)$ Å, $Z = 4$, $D_c = 1{\cdot}24$ Mg m^{-3}, μ(Mo $K\alpha$) = 0·191 mm^{-1}. The molecule lies on a crystallographic plane of symmetry and the crystal structure is held together by van der Waals packing of ion pairs linked by hydrogen bonds. The distance of 6·03 Å between the protonated N atom and the centroid of the phenyl ring is close to those observed in other antihistamines belonging to different chemical classes, but does not correspond to that observed in histamine itself. The final R was 0·047.

Introduction. Antihistamines, or, more precisely, H_1 histamine receptor antagonists, are a class of drugs able to antagonize competitively the effects of histamine at the H_1 receptor site. In many cases agonists and their competitive antagonists show remarkable chemical similarities, but this similarity has been questioned (Ariens, 1977) for antihistaminic agents, which do not appear to mimic histamine and its agonists. Nevertheless, chemical and stereochemical similarities can be found among antihistamines themselves, in spite of the fact that they belong to at least five different chemical classes. In general, it is assumed (Witiak, 1970) that the pharmacodynamic part of antihistamines can be reduced to $Ar_2X{-}C{-}C{-}N^+$ (where X = N, C–O or CH). Reports in the literature suggest (Witiak, Muhi-Eldeen, Mahishi, Sethi & Gerald, 1971) that the presence of two aromatic rings is useful for the enhancement of antihistaminic activity but that strongest antagonism occurs only when at least one ring is able to assume a fixed distance from the amino N atom.

From crystal structure determinations of histadyl hydrochloride (Clark & Palenik, 1972), (±)-brompheniramine maleate (James & Williams, 1971), (+)-chlorpheniramine maleate (James & Williams, 1974*a*) and triprolidine hydrochloride (James & Williams, 1974*b*), the distance between the amino N and the centroid of one of the unsaturated rings is found to lie in the range 6–6·40 Å (James & Williams, 1974*b*). In a recent paper (Bertolasi, Borea, Gilli & Sacerdoti, 1980) we have reported the crystal structure of carbinoxamine maleate, which belongs to the class of the aminoethyl ether derivatives, and have shown that a similar distance of 6·30 Å is found in this molecule.

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Hence, the compounds of this chemical class conform to the general scheme, in spite of the different number of atoms in the chain.

In this present paper we report the crystal structure of another antihistamine, cyclizine hydrochloride, which belongs to the chemical class of the piperazino derivatives and contains the pharmacodynamic moiety $Ar_2N\begin{matrix}\swarrow CH_2-CH_2\searrow\\ \searrow CH_2-CH_2\swarrow\end{matrix}N-R$. In this class of compounds another crystal structure has been determined, that of cinnarizine free base (Mouillé, Cotrait, Hospital & Marsau, 1975), and presently our aim is to establish the common stereochemical features between these two compounds and the other antihistamines of different classes previously reported.

The compound, kindly provided by Wellcome Italia, Pomezia (Rome), was recrystallized from ethanol. Intensities were collected from a crystal of dimensions 0·14 × 0·14 × 0·28 mm on an automatic Philips PW 1100 four-circle diffractometer with monochromated Mo $K\alpha$ radiation and the $\omega/2\theta$ scan technique. Of 2029 independent reflections ($\theta \leq 28°$), 884 having $I_o \geq 3\sigma(I_o)$ were considered to be observed. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Most computations were carried out with the *SHELX* 76 system of programs (Sheldrick, 1976). The structure was solved by Patterson and Fourier methods and refined by full-matrix least squares in the anisotropic mode for the non-hydrogen atoms and in the isotropic mode for the H atoms. Weights for the last cycle were calculated as $2/w = \sigma^2(F_o) + 0{\cdot}000127|F_o|^2$. The final discrepancy factors $R = \sum|\Delta|/\sum|F_o|$ and $R_w = (\sum w|\Delta|^2/\sum|F_o|^2)^{1/2}$ were 0·047 and 0·041 respectively. Positional parameters are listed in Table 1.*

Table 1. *Positional* (×10⁴; ×10³ *for* H) *and thermal* (Å² ×10⁴) *parameters with e.s.d.'s in parentheses*

	x	y	z	U or U_{eq}*
Cl	4413 (1)	2500	−3878 (1)	55
C(1)	7396 (3)	5121 (3)	3328 (4)	43
C(2)	8139 (3)	4770 (3)	2381 (4)	40
C(3)	7895 (3)	3924 (3)	1674 (3)	33
C(4)	6898 (2)	3419 (2)	1898 (3)	29
C(5)	6165 (3)	3765 (3)	2878 (4)	41
C(6)	6416 (3)	4610 (3)	3575 (4)	46
C(7)	6628 (4)	2500	1092 (5)	32
N(8)	5429 (3)	2500	670 (3)	30
C(9)	5144 (3)	3363 (3)	−130 (4)	38
C(10)	3884 (3)	3396 (3)	−372 (4)	39
N(11)	3495 (3)	2500	−1089 (4)	32
C(12)	2244 (4)	2500	−1263 (7)	45
H(1)	754 (3)	573 (3)	374 (3)	51
H(2)	884 (3)	511 (2)	224 (3)	50
H(3)	840 (2)	368 (2)	106 (3)	28
H(5)	550 (3)	340 (2)	303 (3)	44
H(6)	591 (3)	483 (3)	423 (3)	52
H(7)	707 (3)	250	32 (4)	32
H(91)	558 (2)	336 (2)	−100 (3)	47
H(92)	532 (3)	397 (3)	34 (3)	45
H(101)	346 (2)	338 (2)	48 (3)	34
H(102)	372 (2)	396 (2)	−91 (3)	44
H(11)	383 (4)	250	−191 (4)	36
H(121)	191 (4)	250	−35 (5)	58
H(122)	204 (3)	310 (2)	−178 (3)	53

* U_{eq} according to Hamilton (1959).

Discussion. A general view of the molecule is shown in Fig. 1; bond lengths and angles are listed in Tables 2 and 3. The structure is built up from ion pairs (cyclizine monocation and chloride anion) linked by a hydrogen

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35220 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Interatomic distances* (Å) *with e.s.d.'s in parentheses*

C(1)–C(2)	1·379 (5)	C(7)–N(8)	1·481 (5)
C(1)–C(6)	1·376 (5)	N(8)–C(9)	1·463 (4)
C(2)–C(3)	1·383 (5)	C(9)–C(10)	1·511 (5)
C(3)–C(4)	1·385 (4)	C(10)–N(11)	1·490 (4)
C(4)–C(5)	1·392 (4)	N(11)–C(12)	1·490 (6)
C(4)–C(7)	1·524 (4)	N(11)–H(11)	0·92 (4)
C(5)–C(6)	1·379 (5)	Cl···H(11)	2·09 (3)

Table 3. *Interatomic angles* (°) *with e.s.d.'s in parentheses*

C(2)–C(1)–C(6)	119·1 (4)	C(4)–C(7)–N(8)	110·6 (2)
C(1)–C(2)–C(3)	120·6 (4)	C(7)–N(8)–C(9)	112·2 (2)
C(2)–C(3)–C(4)	120·6 (3)	C(9)–N(8)–C(9′)	107·0 (4)
C(3)–C(4)–C(5)	118·5 (3)	N(8)–C(9)–C(10)	109·9 (4)
C(3)–C(4)–C(7)	120·1 (3)	C(9)–C(10)–N(11)	110·9 (4)
C(5)–C(4)–C(7)	121·5 (3)	C(10)–N(11)–C(12)	111·3 (3)
C(4)–C(5)–C(6)	120·4 (4)	C(10)–N(11)–C(10′)	110·1 (4)
C(1)–C(6)–C(5)	120·8 (4)	N(11)–H(11)···Cl	173 (2)
C(4)–C(7)–C(4′)	110·5 (4)		

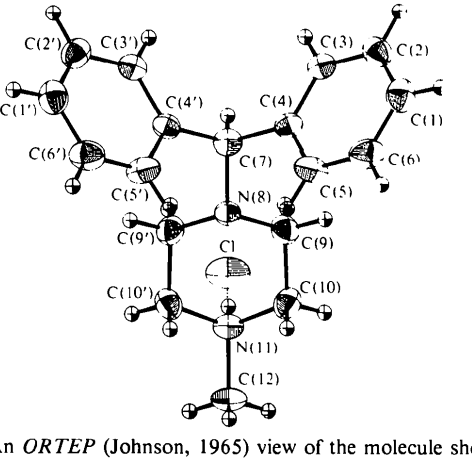

Fig. 1. An *ORTEP* (Johnson, 1965) view of the molecule showing the thermal ellipsoids at 40% probability.

Table 4. *Parameters controlling the overall shape of some antihistamines of known crystal structure (distances in Å)*

Compound	Reference	CG1*	CG2*	d_{N-CG1}	d_{N-CG2}	$d_{CG1-CG2}$
Histadyl hydrochloride	*a*	thenyl	pyridyl	6·48	5·56	5·30
(±)-Brompheniramine maleate	*b*	pyridyl	phenyl	6·21	5·57	4·67
(+)-Chlorpheniramine maleate	*c*	phenyl	pyridyl	6·16	5·41	4·80
Triprolidine hydrochloride	*d*	pyridyl	phenyl	6·01	5·42	4·92
Carbinoxamine maleate	*e*	phenyl	pyridyl	6·30	5·74	4·66
Cinnarizine	*f*	phenyl	phenyl	6·18	6·26	4·81
Cyclizine hydrochloride	*g*	phenyl	phenyl	6·03	6·03	4·82

References: (*a*) Clark & Palenik (1972); (*b*) James & Williams (1971); (*c*) James & Williams (1974*a*); (*d*) James & Williams (1974*b*); (*e*) Bertolasi *et al.* (1980); (*f*) Mouillé *et al.* (1975); (*g*) present work.

* Centroids of the group quoted below.

bond, N(11)–H(11)···Cl [H(11)···Cl = 2·09, N(11)···Cl = 3·00 Å]. The molecule has mirror symmetry with atoms C(7), H(7), N(8), N(11), H(11), C(12), H(121) and Cl lying on a crystallographic symmetry plane. Bond distances and angles are normal. The phenyl group is planar within experimental error and displays approximate *mm* symmetry with the C(3)–C(4)–C(5) and C(2)–C(1)–C(6) angles smaller and the others greater than 120°. The piperazine ring adopts a chair conformation, the relevant torsion angles being C(10′)–N(11)–C(10)–C(9) = 52·8, N(11)–C(10)–C(9)–N(8) = −59·6 and C(10)–C(9)–N(8)–C(9′) = 64·2°. The torsion angles involving the phenyl groups are related by symmetry and are 44 and −44° for N(8)–C(7)–C(4)–C(5) (τ_1) and N(8)–C(7)–C(4′)–C(5′) (τ_2) respectively. Minimization of the non-bonded intramolecular energy of the free monocation, carried out by the steepest-descent method and using semi-empirical atom-pair potentials (Giglio, 1969), shows that this symmetrical conformation is near to the calculated minimum at $\tau_1 = 51$ and $\tau_2 = -45°$.

Table 4 contains some molecular parameters of antihistamines of known crystal structure. It can be seen that the rule proposed by Witiak (1970) and James & Williams (1974*a*,*b*), that in all antihistamines there is an unsaturated ring whose centre of gravity is at a fixed distance from the amino N atom, is reasonably satisfied by all the compounds given in the table, provided that the thenyl group is considered the relevant unsaturated ring for histadyl.

The mean distance d_{N-CG1} is 6·20 ± 0·16 Å, which can be tentatively considered to be the most probable distance between the two centres (protonated N and unsaturated ring) for optimal drug–receptor interaction. This result appears to substantiate the idea (Ariens, 1977) that H_1 receptor agonists and antagonists do not possess common chemical or stereochemical features, unless a flexible receptor protein is proposed (James & Williams, 1974*b*). In fact, histamine itself cannot attain a distance between the aminic N and the centroid of its imidazole ring greater than 4·94 Å in its fully extended conformation.

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