Acta Cryst. (1980). B**36**, 2287–2291

Crystallographic and Conformational Studies on Histamine H_1 Receptor Antagonists. I. Structure of Carbinoxamine Maleate

BY V. BERTOLASI

Istituto Chimico, Università di Ferrara, Italy

P. A. BOREA

Istituto di Farmacologia, Università di Ferrara, Italy

AND G. GILLI AND M. SACERDOTI

Centro di Strutturistica Diffrattometrica, Università di Ferrara, Italy

(*Received* 23 *November* 1979; *accepted* 28 *May* 1980)

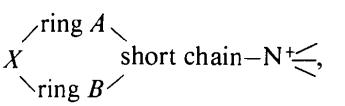
Abstract

Carbinoxamine maleate, $C_{16}H_{20}ClN_2O^+.C_4H_3O_4^-$, crystallizes in space group $P2_12_12_1$ with a = 10·527 (3), b = 11·151 (3), c = 17·626 (4) Å and Z = 4. Diffractometer data were collected with Cu $K\alpha$ radiation and the structure was refined to an R value of 0·045 using 1448 observed reflections. The compound crystallizes with spontaneous resolution of the enantiomers and the absolute configuration of carbinoxamine was determined to be S in the crystal under investigation. The crystal is built by ion pairs linked by an intermolecular hydrogen bond. The five-membered aminoethyl chain assumes a conformation such as to reproduce the distance between the amino N and the centroid of an aromatic ring already observed in other antihistamines with different chains. Conformational-energy calculations suggest that the conformation found in the crystal corresponds to a minimum for the free ion.

Introduction

Histamine H_1 receptor antagonists (hereafter antihistamines) are a class of drugs of widespread use which antagonize to varying degrees most of the physiological effects of histamine, 4-(2-aminoethyl)imidazole, on different organs or systems of the body. The effects antagonized are those of histamine on smooth muscle, capillary permeability, exocrine glandular secretion and cardiovascular effects. Antihistamines are believed to compete with histamine at its specific H_1 receptor site and are unable to antagonize other effects of histamine, such as the increase of gastric secretion and uterus contraction, which are inhibited by another class of drugs, the H_2 receptor antagonists, not discussed in the present paper.

A relevant number of studies have been carried out in the past in an attempt to define the pharmacodynamic moieties of antihistamines and the results of these investigations can be summarized (Horn, 1975) by saying that all the most active antihistamines are characterized by two unsaturated, usually aromatic, rings connected by a short chain to an amino N protonated at the physiological pH (7·4), according to the general scheme



where X represents an –S–, $-CH_2-$ or –CH=CH– group bridging sometimes the *ortho* positions of rings A and B.

From a chemical point of view, antihistamines can be divided (Melville, 1973) into ethylenediamine, aminoethyl ethers, propylamine, phenothiazine, piperidine and piperazine derivatives. All these classes are represented by at least one crystal structure determination with the exception of the aminoethyl ethers, and the present paper reports the first structure determination of a derivative of this class, namely carbinoxamine maleate.

Experimental

Crystals of racemic carbinoxamine maleate have been kindly provided by Cilag-Chemie Italiana, Milan, Italy, and were recrystallized from ethyl acetate. Intensity data were collected on an automatic Siemens AED diffractometer from a crystal of dimensions 0·2 × 0·3 × 0·4 mm using Ni-filtered Cu $K\alpha$ radiation. Of 1507 reflections collected ($\theta \leq 55°$), 1448 having $I_o \geq 3\sigma(I_o)$ were used in the refinement.

0567-7408/80/102287-05$01.00

The crystal data are: $C_{16}H_{20}ClN_2O^+.C_4H_3O_4^-$, 2-[*p*-chloro-α-(2-dimethylammonioethoxy)benzyl]-pyridine maleate, orthorhombic, $P2_12_12_1$ (No. 19), $a = 10{\cdot}527$ (3), $b = 11{\cdot}151$ (3), $c = 17{\cdot}626$ (4) Å, $Z = 4$, $D_c = 1{\cdot}31$ Mg m^{-3}, μ(Cu $K\alpha$) = 1·81 mm^{-1}.

The space group and the presence of an asymmetric C atom [C(7)] in the molecule indicate that the racemic compound crystallizes with spontaneous resolution of the enantiomers. The determination of the absolute configuration was not relevant in view of the racemic nature of the compound under investigation. However, both enantiomorphous structures have been refined and found to correspond, as discussed later, to different values of the discrepancy indices. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The structure was solved by direct methods (*MULTAN* 74; Main, Woolfson, Lessinger, Germain & Declercq, 1974) and the remaining calculations were carried out by means of the *SHELX* 76 system of programs (Sheldrick, 1976). Most H atoms were found in the difference map made after the isotropic refinement; however, only H(17) and H(2*A*), involved in hydrogen bonds, were actually refined isotropically; the others were given calculated positions (C–H distance 1·08Å). Both enantiomorphous structures were refined by full-matrix least squares using anisotropic temperature factors for all the non-hydrogen atoms. Final disagreement factors $R = \sum|\Delta|/\sum|F_o|$ and $R_2 = (\sum w|\Delta|^2/\sum w|F_o|^2)^{1/2}$ were $R = 0{\cdot}045$ and 0·052 and $R_w = 0{\cdot}050$ and 0·058, respectively, for the two enantiomers. Atomic coordinates for the structure corresponding to the lowest R value are reported in Table 1.* Weights for the last cycle were given according to the formula $k/w = \sigma^2(F_o) + 0{\cdot}00017|F_o|^2$.

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

The isotropic temperature factor is of the form $\exp(-8\pi^2 U \sin^2\theta/\lambda^2)$; U_{eq} is according to Hamilton (1959).

	x	*y*	*z*	*U* or U_{eq}
Cl	−9670 (1)	1956 (1)	−7340 (1)	107
C(1)	−8500 (4)	844 (4)	−7319 (3)	71
C(2)	−8397 (5)	62 (6)	−7899 (3)	88
C(3)	−7491 (5)	−839 (5)	−7859 (3)	80
C(4)	−6659 (4)	−933 (4)	−7263 (2)	58
C(5)	−6776 (5)	−98 (5)	−6683 (2)	75
C(6)	−7691 (6)	799 (4)	−6707 (3)	76
C(7)	−5645 (5)	−1877 (4)	−7248 (2)	65
C(8)	−4394 (4)	−1368 (4)	−7523 (2)	62
C(9)	−3604 (6)	−715 (5)	−7053 (3)	87
C(10)	−2523 (6)	−194 (7)	−7333 (4)	104
C(11)	−2256 (6)	−359 (6)	−8098 (3)	98
C(12)	−3047 (6)	−1024 (5)	−8518 (3)	88
N(13)	−4131 (4)	−1550 (4)	−8251 (2)	74
O(14)	−5546 (3)	−2326 (2)	−6488 (1)	68
C(15)	−4856 (6)	−3404 (4)	−6446 (2)	81
C(16)	−5100 (5)	−3953 (4)	−5683 (3)	82
N(17)	−4508 (3)	−3304 (3)	−5031 (2)	65
C(18)	−4997 (7)	−3832 (5)	−4330 (3)	103
C(19)	−3110 (5)	−3327 (5)	−5051 (4)	110
H(17)	−4838 (42)	−2479 (44)	−5004 (26)	64
C(1*A*)	−3589 (4)	2539 (4)	−5263 (2)	62
C(2*A*)	−4813 (4)	2111 (3)	−4963 (3)	63
C(3*A*)	−5233 (4)	1009 (3)	−4821 (2)	60
C(4*A*)	−4608 (4)	−176 (4)	−4917 (2)	56
O(1*A*)	−3373 (3)	3617 (3)	−5266 (2)	83
O(2*A*)	−2755 (3)	1775 (3)	−5515 (2)	76
O(3*A*)	−5247 (3)	−1062 (3)	−4729 (2)	82
O(4*A*)	−3497 (3)	−247 (3)	−5184 (2)	71
H(2*A*)	−2916 (48)	987 (43)	−5423 (24)	71

Discussion

The crystal structure, shown in Fig. 1, is built up by the van der Waals packing, without significant short contacts, of ion pairs (carbinoxamine monocation and maleate monoanion) linked by an intermolecular hydrogen bond [O(3*A*)···H(17) and O(3*A*)···N(17) distances of 1·72 and 2·67 Å respectively].

Views of the carbinoxamine and maleate ions are shown in Fig. 2(*a*,*b*) and their bond distances and angles are given in Tables 2 and 3. The molecular parameters of carbinoxamine do not show unusual features. The distortion of the phenyl angles [C(2)–C(1)–C(6) = 121·4 and C(3)–C(4)–C(5) = 117·1°] is congruent with what is known of the inductive effects of the substituents (Domenicano, Vaciago & Coulson, 1975) and the C(8)–N(13)–C(12) angle of 116·2° is close to that of 116·9° determined for pyridine by microwave spectroscopy (Sørensen, Mahler & Rastrup-Andersen, 1974). Both phenyl and pyridyl groups are planar within experimental error (χ^2 of 2·9 and 2·5 respectively). The molecule has the absolute configuration *S*, according to the convention of Cahn, Ingold & Prelog (1966).

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35286 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

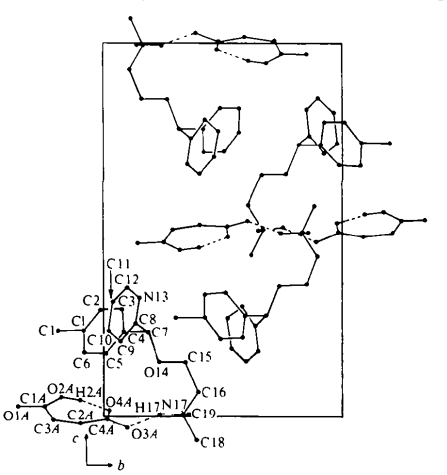


Fig. 1. The packing of the molecules in the crystal.

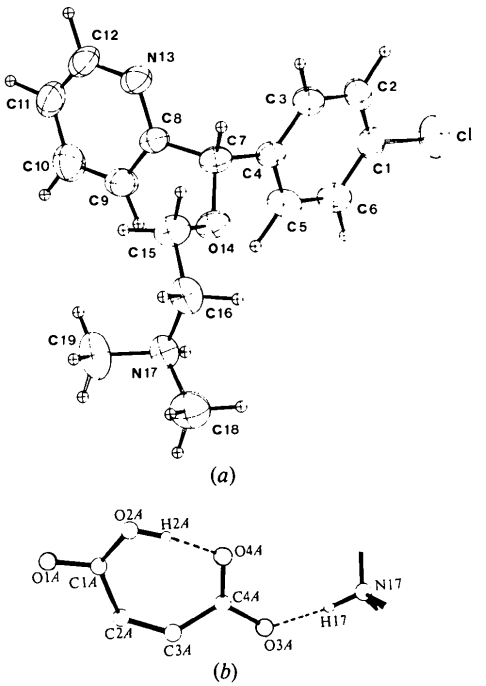


Fig. 2. (*a*) An *ORTEP* (Johnson, 1965) view of the molecule displaying the thermal ellipsoids at 40% probability. (*b*) Schematic drawing of the maleate anion showing the hydrogen bonds.

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

C(1)–Cl	1·749 (5)	C(15)–C(16)	1·501 (7)
C(1)–C(2)	1·347 (7)	C(16)–N(17)	1·493 (6)
C(1)–C(6)	1·375 (7)	N(17)–C(18)	1·464 (6)
C(2)–C(3)	1·387 (8)	N(17)–C(19)	1·472 (7)
C(3)–C(4)	1·372 (6)	N(17)–H(17)	0·98 (5)
C(4)–C(5)	1·387 (6)		
C(4)–C(7)	1·500 (6)	C(1*A*)–C(2*A*)	1·472 (6)
C(5)–C(6)	1·389 (7)	C(1*A*)–O(1*A*)	1·223 (5)
C(7)–C(8)	1·514 (6)	C(1*A*)–O(2*A*)	1·302 (6)
C(7)–O(14)	1·434 (5)	C(2*A*)–C(3*A*)	1·329 (5)
C(8)–C(9)	1·381 (7)	C(3*A*)–C(4*A*)	1·486 (6)
C(8)–N(13)	1·328 (5)	C(4*A*)–O(3*A*)	1·241 (5)
C(9)–C(10)	1·370 (8)	C(4*A*)–O(4*A*)	1·263 (5)
C(10)–C(11)	1·389 (8)	O(2*A*)–H(2*A*)	0·91 (5)
C(11)–C(12)	1·338 (8)		
C(12)–N(13)	1·367 (7)	O(3*A*)···H(17)	1·71
O(14)–C(15)	1·406 (6)	O(4*A*)···H(2*A*)	1·56

The maleate monoanion, besides being hydrogen linked through the oxygen O(3*A*) to the amino N, contains an intramolecular hydrogen bond: O(2*A*)–H(2*A*)···O(4*A*). This bond is very short [H(2*A*)···O(4*A*) and O(2*A*)···O(4*A*) distances of 1·56 and 2·46 Å respectively] and its length lies in a range where symmetrical hydrogen bonding may be observed. In the present case, however, it is asymmetric, the asymmetry being confirmed by the pattern of the C–O bond distances at the two ends of the maleate ion.

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

Cl–C(1)–C(2)	119·9 (4)	C(8)–N(13)–C(12)	116·2 (5)
Cl–C(1)–C(6)	118·6 (4)	C(7)–O(14)–C(15)	112·7 (3)
C(2)–C(1)–C(6)	121·4 (5)	O(14)–C(15)–C(16)	107·9 (4)
C(1)–C(2)–C(3)	119·0 (4)	C(15)–C(16)–N(17)	114·8 (4)
C(2)–C(3)–C(4)	122·2 (4)	C(16)–N(17)–C(18)	107·9 (4)
C(3)–C(4)–C(5)	117·1 (5)	C(16)–N(17)–C(19)	113·0 (4)
C(3)–C(4)–C(7)	121·4 (4)	C(16)–N(17)–H(17)	110 (3)
C(5)–C(4)–C(7)	121·5 (4)	C(18)–N(17)–C(19)	111·3 (5)
C(4)–C(5)–C(6)	121·5 (4)	C(18)–N(17)–H(17)	102 (3)
C(1)–C(6)–C(5)	118·6 (4)	C(19)–N(17)–H(17)	112 (3)
C(4)–C(7)–C(8)	110·5 (3)		
C(4)–C(7)–O(14)	108·2 (3)	C(2*A*)–C(1*A*)–O(1*A*)	118·9 (4)
C(8)–C(7)–O(14)	111·5 (3)	C(2*A*)–C(1*A*)–O(2*A*)	120·1 (4)
C(7)–C(8)–C(9)	122·0 (4)	O(1*A*)–C(1*A*)–O(2*A*)	121·0 (4)
C(7)–C(8)–N(13)	115·6 (4)	C(1*A*)–C(2*A*)–C(3*A*)	131·2 (4)
C(9)–C(8)–N(13)	122·3 (4)	C(2*A*)–C(3*A*)–C(4*A*)	130·7 (4)
C(8)–C(9)–C(10)	120·5 (5)	C(3*A*)–C(4*A*)–O(3*A*)	115·9 (4)
C(9)–C(10)–C(11)	117·5 (6)	C(3*A*)–C(4*A*)–O(4*A*)	120·6 (4)
C(10)–C(11)–C(12)	119·0 (6)	O(3*A*)–C(4*A*)–O(4*A*)	123·5 (4)
C(11)–C(12)–N(13)	124·5 (5)	C(1*A*)–O(2*A*)–H(2*A*)	117 (3)
		N(17)–H(17)···O(3*A*)	164
		O(2*A*)–H(2*A*)···O(4*A*)	172

The values of the torsion angles defining the conformation of the carbinoxamine cation are reported in Table 4. The aminoethyl chain adopts a *t*, *t*, *g* conformation, as determined by the values of the torsion angles τ_0, τ_1 and τ_2. Such a conformation controls the overall geometry of the molecule and, in particular, the distances between the amino nitrogen, N(17), and the centroids, CG1 and CG2, of the phenyl [atoms C(1)–C(6)] and pyridyl [atoms N(13), C(8)–C(12)] groups. As these distances have been used as a criterion of comparison among different classes of antihistamines, it is of particular interest to check whether or not the crystallographically observed conformation corresponds to a conformational minimum of the free cation. Accordingly, all the torsion angles, τ_0–τ_5, have been estimated by minimizing the non-bonded intramolecular potential energy U of the free ion using semi-empirical atom–atom potentials (Giglio, 1969) and the steepest-descent method. The results are shown in Table 4. The average value of the absolute differences between observed and calculated torsion angles is 12° and their maximum is 28°, while the distance d_1 between N(17) and CG1 (see Table 4) does not change in practice. Making allowance for the rather crude force field used in the computations, this result could be considered to indicate that the preferred conformation of the free cation is not far from that found in the crystal. On the other hand, more sophisticated INDO calculations have already been carried out by Pullman, Courrière & Berthod (1975) on a model molecule of carbinoxamine and these authors were able to show that, for assigned values of τ_0, τ_4 and τ_5 and for two different preselected values of τ_3, the energy minimum was associated with a *t*, *g* conformer as far as τ_1 and τ_2 were concerned. The $U(\tau_1,\tau_2)$ map of Fig. 3, produced for τ_0, τ_3, τ_4 and τ_5 values cor-

Table 4. *Observed and calculated torsion angles* (°) *and observed and calculated values* (Å) *of the distances controlling the overall shape of the molecule for carbinoxamine maleate*

E.s.d.'s are in parentheses.

		Observed value	Calculated value	$\lvert\Delta\rvert$
τ_3	H(17)–N(17)–C(16)–C(15)	51 (2)	52	2
τ_2	N(17)–C(16)–C(15)–O(14)	−71 (1)	−62	9
τ_1	C(16)–C(15)–O(14)–C(7)	−166 (1)	−194	28
τ_0	C(15)–O(14)–C(7)–C(4)	166 (1)	152	14
τ_4	O(14)–C(7)–C(4)–C(5)	41 (1)	21	20
τ_5	O(14)–C(7)–C(8)–C(9)	−39 (1)	−39	0
		Observed value	Calculated value	$\lvert\Delta\rvert$
d_1	N(17)–CG1*	6·30 (1)	6·28	0·02
d_2	N(17)–CG2*	5·74 (1)	4·92	0·82
d_3	CG1–CG2*	4·66 (1)	4·66	–

* CG1 and CG2 are the centroids of the phenyl and pyridyl groups.

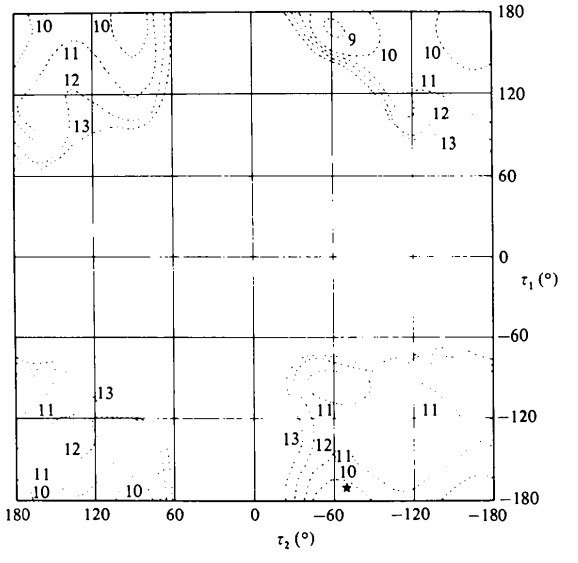


Fig. 3. Intramolecular potential energy (kcal mol^{-1}; 1 kcal mol^{-1} ≡ 4·2 kJ mol^{-1}) calculated for the carbinoxamine monocation as a function of the torsion angles τ_1 = C(16)–C(15)–O(14)–C(7) and τ_2 = N(17)–C(16)–C(15)–O(14).

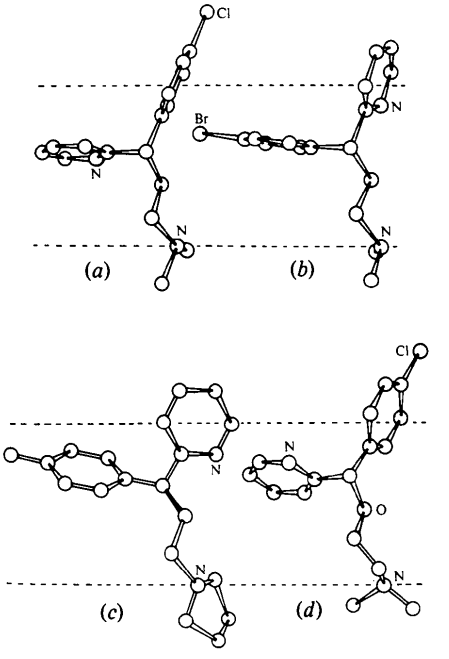


Fig. 4. Comparison of the molecular structures of four antihistamines projected on the plane defined by the amino N and the centres of gravity of the aromatic rings. The two dashed lines are 6 Å apart. (*a*) (+)-Chlorpheniramine (James & Williams, 1974*a*); (*b*) (±)-brompheniramine (James & Williams, 1971); (*c*) triprolidine (James & Williams, 1974*b*); (*d*) (+)-carbinoxamine (present work).

responding to the calculated minimum, shows that our results are in agreement with the previous theoretical calculations and fit the experimental findings reasonably well.

The present molecular structure has been compared with that of other compounds having antihistaminic activity with the aim of identifying common stereochemical features. Such a comparison has been carried out with the two propylamino derivatives of known structure, (±)-brompheniramine maleate (James & Williams, 1971) and (+)-chlorpheniramine maleate (James & Williams, 1974*a*), both containing the four-membered chain =CH–CH_2–CH_2–$N^+\lesssim$ instead of the five-atom chain =CH–O–CH_2–CH_2–$N^+\lesssim$ of the present compound. Moreover, the comparison has been extended to the only known propenylamino derivative, triprolidine hydrochloride (James & Williams, 1974*b*), displaying the chain =C=CH–CH_2–$N^+\lesssim$, this latter compound being probably the most useful for determining the drug-receptor topography owing to its semi-rigid structure.

Fig. 4 shows a view of the four molecules, all projected on the plane defined by the amino N and the centroids of the two aryl or heteroaryl rings. The H atoms (including the proton at the aminic N) have been omitted for the sake of clarity. Apart from the evident steric similarities among the four molecules, the most striking common feature appears to be the constancy of the distance, d_1, between the amino N and the centroid (CG1) of the aromatic ring lying on its vertical in Fig. 4, this distance being 6·30, 6·01, 6·21 and 6·01 Å in carbinoxamine, triprolidine, brompheniramine and chlorpheniramine respectively.

The constancy of the distance d_1 in antihistamines was originally pointed out by James & Williams (1974*b*) on the basis of the crystal structure determinations of compounds (*a*), (*b*) and (*c*) of Fig. 4 and of histadyl hydrochloride (Clark & Palenik, 1972), not reported in the figure. The present findings that the five-membered aminoethyl ether chain assumes a

conformation such as to reproduce the 6–6·20 Å distance observed for the derivatives of the four-membered propylamino and propenylamino chains and that its conformation is weakly affected by the crystal forces confirm the results of James & Williams (1974*b*) and support the idea that a distance of 6–6·30 Å between the protonated N and the centroid of an unsaturated ring is relevant to the antihistaminic activity. Also, this hypothesis is confirmed, from a completely different point of view, by the structure–activity studies on substituted propenylamines (Casy & Ison, 1970; Ison Franks & Soh, 1973). 1-Aryl-1-benzylprop-1-en-3-amines have been synthetized and biologically tested for the *cis* and *trans* (H/phenyl) isomers and the first has been found to be two hundred times more active than the second. As the distance between the amino N and the centroid of the phenyl ring is fixed at about 6 Å for the isomer having the phenyl group *cis* to the H atom, while such a distance lies in the range 3·4 to 5·4 Å, depending on τ_2, for the *trans* isomer (for comparison, see Fig. 4*c*), the different activities of the two isomers can be explained by stating that maximum antihistaminic activity is associated with a N—centroid distance not shorter than 6·0 Å.

It should be noted, however, that other important factors contribute to the antihistaminic activity of a given compound, in particular its pK_a value (Barlow, 1968), its lipophilicity and the presence or absence of another unsaturated ring in the molecule. As regards, in particular, this latter factor, all the experimental data agree in indicating that the presence of two unsaturated rings produces compounds which are most potent as antihistamines (Witiak, Muhi-Eldeen, Mahishi, Sethi & Gerald, 1971; Ariens, 1977) and, moreover, the different activities observed for the two enantiomers of chiral antihistamines seem to imply the need for at least three sites, most probably the amino N and the two unsaturated rings, in the drug-receptor interaction (Witiak *et al.*, 1971).

References

ARIENS, E. J. (1977). *Biological Activity and Chemical Structure*, edited by J. A. KEVERLING BUISMAN, pp. 1–35. Amsterdam: Elsevier.

BARLOW, R. B. (1968). *Introduction to Chemical Pharmacology*, pp. 344–377. London: Methuen.

CAHN, R. S., INGOLD, C. K. & PRELOG, V. (1966). *Angew. Chem. Int. Ed. Engl.* **5**, 385–415.

CASY, A. F. & ISON, R. R. (1970). *J. Pharm. Pharmacol.* **22**, 270–278.

CLARK, G. R. & PALENIK, G. J. (1972). *J. Am. Chem. Soc.* **94**, 4005–4009.

DOMENICANO, A., VACIAGO, A. & COULSON, C. A. (1975). *Acta Cryst.* B**31**, 221–234.

GIGLIO, G. (1969). *Nature (London)*, **222**, 339–341.

HAMILTON, W. C. (1959). *Acta Cryst.* **12**, 609–610.

HORN, A. S. (1974). *Handbook of Psychopharmacology*, Vol. 2, edited by L. L. IVERSEN, D. S. IVERSEN & S. H. SNYDER, pp. 179–243. New York: Plenum.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press.

ISON, R. R., FRANKS, F. M. & SOH, K. S. (1973). *J. Pharm. Pharmacol.* **25**, 887–894.

JAMES, M. N. G. & WILLIAMS, G. J. B. (1971). *J. Med. Chem.* **14**, 670–675.

JAMES, M. N. G. & WILLIAMS, G. J. B. (1974*a*). *Can. J. Chem.* **52**, 1872–1879.

JAMES, M. N. G. & WILLIAMS, G. J. B. (1974*b*). *Can. J. Chem.* **52**, 1880–1888.

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794, revised. Oak Ridge National Laboratory, Tennessee.

MAIN, P., WOOLFSON, M. M., LESSINGER, L., GERMAIN, G. & DECLERCQ, J. P. (1974). *MULTAN* 74. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

MELVILLE, K. I. (1973). *Histamine and Antihistamines*, Vol. I. Oxford: Pergamon Press.

PULLMAN, B., COURRIÈRE, P. & BERTHOD, H. (1975). *Mol. Pharmacol.* **11**, 268–279.

SHELDRIK, G. M. (1976). *SHELX* 76. A program for crystal structure determination. Univ. of Cambridge, England.

SØRENSEN, G. O., MAHLER, L. & RASTRUP-ANDERSEN, N. (1974). *J. Mol. Struct.* **20**, 119–126.

WITIAK, D. T., MUHI-ELDEEN, Z., MAHISHI, N., SETHI, O. P. & GERALD, M. C. (1971). *J. Med. Chem.* **14**, 24–30.