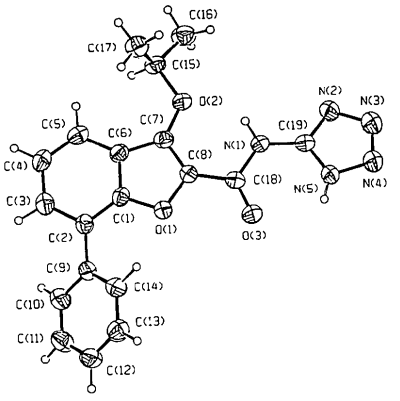

Fig. 1. *ORTEP* drawing of the title compound showing numbering scheme.

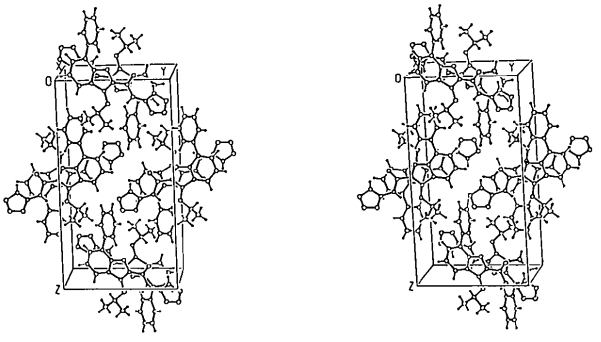

Fig. 2. Stereoview of a unit cell showing molecular packing.

within 0·004 (2) Å and is linked to the benzofuran moiety through a fully extended carboxamide group which exhibits a C(8)C(18)—N(1)C(19) torsion angle of 177·7 (2)°. The mean planes of the benzofuran moiety and the tetrazole ring are oriented at 8·1 (2)°. The corresponding torsion and mean-planes angles in (1) were 174·9 (3) and 10·8 (4)°, respectively (Parvez, Unangst, Connor & Mullican, 1991).

The bond distances and angles in the benzofuran moiety and its substituents, phenyl, methylethoxy, and carboxamide groups, are unexceptional. In the tetrazole ring, the N(3)—N(4) distance [1·285 (2) Å] is clearly indicative of a double bond, which is significantly shorter than N(2)—N(3) and N(4)—N(5) single bonds [1·361 (2) and 1·349 (2) Å, respectively]. There are no unusual intermolecular distances less than van der Waals contacts. However, H atoms on the N(1) and N(5) atoms are directed towards O(2) and O(3), respectively, resulting in intramolecular contacts of 2·058 and 2·236 Å, respectively.

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Structure and Absolute Configuration of an Antihistaminic Drug, Clemastine Hydrogen Fumarate

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Abstract. 2-{2-[1-(4-Chlorophenyl)-1-phenylethoxy]-ethyl}-1-methylpyrrolidinium hydrogen fumarate, $C_{21}H_{27}ClNO^+.C_4H_3O_4^-$, $M_r = 459{\cdot}97$, orthorhombic, $P2_12_12_1$, $a = 9{\cdot}414$ (2), $b = 13{\cdot}154$ (1), $c = 19{\cdot}535$ (2) Å, $V = 2419{\cdot}1$ Å^3, $Z = 4$, $D_x = 1{\cdot}263$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 1{\cdot}684$ mm^{-1}, $F(000) = 976$, $T = 293$ (1) K, $R = 0{\cdot}0564$ for 2130 observed reflections with $I > 3\sigma(I)$. Both six-membered rings are individually planar with their mean planes almost perpendicular to each other [angle 88·0 (1)°]. The pyrrolidine ring exhibits an envelope conformation and is protonated at the N

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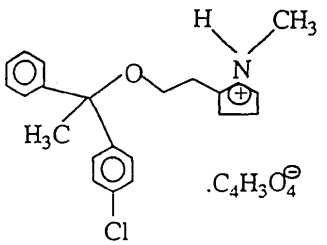
atom which is hydrogen bonded to one of the O atoms of the fumarate anion with N···O = 2·71 Å and N—H···O = 175·8°.

Introduction. Clemastine is an antihistamine affecting the histamine H_1-receptor site, which is most often employed in pharmacology to treat allergic rhinitis (AMA Division of Chicago, 1983). It is a member of the ethanolamine class of antihistamines and hence its most prevalent side effects are drowsiness and dizziness. Generally, this drug is only given to adults in the tablet form in amounts of 2·68 mg, ranging from one to three times daily (Albanese, 1982). Clemastine hydrogen fumarate exhibits a remarkable similarity to (+)-chloropheniramine hydrogen maleate, which is actually a member of the alkylamine class of H_1-antihistamines. The crystal structure of clemastine hydrogen fumarate has been determined to established its conformation and absolute configuration as part of a program correlating biological activity and molecular structure of antihistaminic drugs.



Experimental. Colorless prismatic crystals of the hydrogen fumarate (Sigma, Inc.) were obtained from a solution of methanol by slow evaporation at room temperature (293 K) under normal lighting conditions. A suitable crystal of approximate dimensions 0·20 × 0·45 × 0·60 mm was chosen for data collection. Unit-cell constants and a crystal orientation matrix were determined on an Enraf–Nonius CAD-4 diffractometer by a least-squares refinement of the setting angles of 25 reflections with $20 < \theta < 40°$. Intensity data were collected by the $\omega/2\theta$ scan method using variable scan speed (0·92–5·50° min^{-1}), scan width $(0{\cdot}60 + 0{\cdot}14\tan\theta)°$ and monochromated Cu $K\alpha$ radiation in the range $5 < \theta < 65°$ with h 0 to 11, k 0 to 15 and l 0 to 22. Three reflections were monitored every two hours of exposure time and showed insignificant variations. The intensities of 2345 unique reflections were measured, of which 2130 had $I > 3\sigma(I)$, where $\sigma^2(I) = S + 2B + [0{\cdot}04(S - B)]^2$, with S = scan count and B = time-averaged background count extended 25% on each side. Data were corrected for Lorentz, polarization and absorption effects (North, Phillips & Mathews, 1968); the max. and min. relative transmission coefficients were 1·000 and 0·821, respectively.

The structure was solved by direct methods with *MULTAN*82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982) and refined by full-matrix least-squares calculations employing F's, initially with isotropic and finally with anisotropic temperature factors for the non-H atoms. A difference Fourier synthesis calculated at an intermediate stage of the refinement revealed all H atoms. These were included in the refinement with idealized geometry (C—H and O—H 0·95 Å) and overall isotropic temperature factors for the different types of H atoms in the subsequent refinement. Atomic scattering factors for non-H atoms were taken from Cromer & Mann (1968) and those for H atoms were taken from Stewart, Davidson & Simpson (1965). At this point parallel and independent refinement calculations were carried out on the two stereoisomers of the molecule and anomalous-dispersion corrections for chlorine (Cromer & Liberman, 1970) were applied to both. After six cycles of full-matrix refinement, convergence was reached and one configuration gave $R = 0{\cdot}0601$ and $wR = 0{\cdot}0887$, whereas the other gave $R = 0{\cdot}0564$ and $wR = 0{\cdot}803$, where $w = \{[\sigma^2(F_o) + 0{\cdot}50F_o]^2\}^{-1}$. A statistical test on the wR-factor ratio (Hamilton, 1965) indicated that the former stereoisomer could be rejected at the 0·005 significance level as being the configuration present in the crystal. Accordingly, all coordinates reported herein refer to the statistically favored configuration, the R enantiomer. At the conclusion of the refinement, $(\Delta/\sigma)_{max} < 0{\cdot}14$, the difference electron density map was essentially featureless with $\Delta\rho = -0{\cdot}41$ to $0{\cdot}30$ e Å^{-3} and $S = 2{\cdot}774$. Atomic parameters are given in Table 1,* intramolecular bond distances and angles in Table 2. Fig. 1 shows the molecular structure.

Discussion. Bond lengths and angles in clemastine do not differ significantly from the expected values. The C—C aromatic bond lengths range from 1·358 (7) to 1·398 (7) Å, while the angles range from 117·1 (4) to 121·8 (4)°, the mean distance being 1·378 (7) Å and the mean angle 120·0 (4)°. The C—Cl bond distance 1·740 (5) Å does not differ from the expected value. The two C_{sp^3}—C_{sp^2} bond distances in the molecule are 1·533 (5) and 1·511 (5) Å. The C_{sp^3}—C_{sp^3} bond lengths range from 1·498 (6) to 1·530 (5) Å, the two C—O bonds are 1·434 (5) and 1·452 (4) Å and the C—N bonds range from 1·481 (6) to 1·510 (5) Å. All the aforementioned values are within 4σ of the expected bond lengths.

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and least-squares planes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53386 (32 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final fractional coordinates and equivalent isotropic thermal parameters* (Å^2), *with e.s.d.'s in parentheses*

$$B_{eq} = (1/3)\sum_i \sum_j B_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
Cl	1·0280 (2)	0·7523 (1)	0·9686 (1)	9·07 (4)
O1	0·7173 (3)	1·1620 (2)	1·1014 (1)	3·97 (5)
O2	0·8518 (3)	0·8203 (2)	0·2172 (2)	4·60 (6)
O3	0·7305 (3)	0·6783 (2)	0·2064 (2)	5·46 (7)
O4	0·3591 (3)	0·9404 (2)	0·2801 (2)	6·54 (8)
O5	0·4919 (3)	1·0779 (2)	0·2742 (1)	4·04 (5)
N	0·9094 (3)	1·2088 (2)	1·3011 (2)	3·55 (5)
C1	0·7711 (4)	1·0332 (3)	1·0160 (2)	3·54 (7)
C2	0·7718 (5)	0·9507 (3)	1·0603 (2)	4·46 (8)
C3	0·8512 (5)	0·8651 (3)	1·0462 (2)	4·87 (9)
C4	0·9309 (5)	0·8613 (4)	0·9874 (2)	5·33 (9)
C5	0·9336 (6)	0·9418 (4)	0·9433 (2)	6·1 (1)
C6	0·8522 (5)	1·0275 (4)	0·9576 (2)	5·11 (9)
C7	0·6770 (4)	1·1243 (3)	1·0342 (2)	3·84 (7)
C8	0·5253 (4)	1·0886 (3)	1·0417 (2)	3·94 (7)
C9	0·4541 (5)	1·0464 (4)	0·9870 (2)	5·37 (9)
C10	0·3157 (6)	1·0124 (4)	0·9927 (3)	6·5 (1)
C11	0·2456 (5)	1·0178 (4)	1·0535 (3)	6·1 (1)
C12	0·3130 (5)	1·0588 (4)	1·1084 (3)	6·2 (1)
C13	0·4516 (5)	1·0961 (4)	1·1032 (2)	5·18 (9)
C14	0·6830 (5)	1·2112 (3)	0·9822 (2)	4·89 (8)
C15	0·8593 (4)	1·2009 (3)	1·1057 (2)	4·59 (8)
C16	0·8782 (4)	1·2433 (3)	1·1763 (2)	4·35 (8)
C17	0·8657 (4)	1·1647 (3)	1·2330 (2)	3·55 (7)
C18	0·9645 (4)	1·0728 (3)	1·2280 (2)	4·43 (8)
C19	0·9797 (5)	1·0336 (3)	1·2997 (2)	5·00 (9)
C20	0·9398 (5)	1·1193 (3)	1·3472 (2)	4·94 (9)
C21	0·8060 (5)	1·2807 (4)	1·3314 (3)	5·8 (1)
C22	0·7404 (4)	0·7709 (3)	0·2210 (2)	3·73 (7)
C23	0·6071 (4)	0·8255 (3)	0·2423 (2)	4·09 (7)
C24	0·6006 (4)	0·9237 (3)	0·2505 (2)	3·95 (7)
C25	0·4713 (4)	0·9795 (3)	0·2699 (2)	3·82 (7)

Table 2. *Intramolecular distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

Cl—C4	1·740 (5)	C7—C8	1·511 (5)
O1—C7	1·452 (4)	C7—C14	1·530 (5)
O1—C15	1·434 (5)	C8—C9	1·378 (6)
O2—C22	1·236 (4)	C8—C13	1·390 (6)
O3—C22	1·254 (4)	C9—C10	1·382 (7)
O4—C25	1·191 (5)	C10—C11	1·360 (8)
O5—C25	1·312 (4)	C11—C12	1·358 (7)
N—C17	1·508 (5)	C12—C13	1·398 (7)
N—C20	1·510 (5)	C15—C16	1·498 (6)
N—C21	1·481 (6)	C16—C17	1·521 (5)
C1—C2	1·388 (5)	C17—C18	1·528 (5)
C1—C6	1·374 (5)	C18—C19	1·499 (6)
C1—C7	1·533 (5)	C19—C20	1·508 (6)
C2—C3	1·378 (6)	C22—C23	1·504 (5)
C3—C4	1·373 (6)	C23—C24	1·304 (5)
C4—C5	1·365 (7)	C24—C25	1·471 (5)
C5—C6	1·391 (7)		

C7—O1—C15	114·7 (3)	C9—C8—C13	117·1 (4)
C17—N—C20	106·1 (3)	C8—C9—C10	121·8 (4)
C17—N—C21	114·8 (3)	C9—C10—C11	120·7 (5)
C20—N—C21	112·5 (3)	C10—C11—C12	118·9 (4)
C2—C1—C6	118·1 (4)	C11—C12—C13	121·2 (4)
C2—C1—C7	118·0 (3)	C8—C13—C12	120·2 (4)
C6—C1—C7	123·9 (3)	O1—C15—C16	107·3 (3)
C1—C2—C3	121·1 (4)	C15—C16—C17	114·1 (3)
C2—C3—C4	119·5 (4)	N—C17—C16	111·1 (3)
Cl—C4—C3	119·6 (4)	N—C17—C18	101·2 (3)
Cl—C4—C5	119·8 (4)	C16—C17—C18	116·4 (3)
C3—C4—C5	120·7 (4)	C17—C18—C19	105·7 (3)
C4—C5—C6	119·4 (4)	C18—C19—C20	107·1 (3)
C1—C6—C5	121·1 (4)	N—C20—C19	105·2 (3)
O1—C7—C1	109·0 (3)	O2—C22—O3	124·1 (3)
O1—C7—C8	105·4 (3)	O2—C22—C23	118·3 (3)
O1—C7—C14	109·6 (3)	O3—C22—C23	117·6 (3)
C1—C7—C8	109·0 (3)	C22—C23—C24	123·1 (3)
C1—C7—C14	114·1 (3)	C23—C24—C25	124·4 (4)
C8—C7—C14	109·4 (3)	O4—C25—O5	123·1 (3)
C7—C8—C9	120·7 (4)	O4—C25—C24	124·2 (3)
C7—C8—C13	122·2 (3)	O5—C25—C24	112·7 (3)

The chloro-substituted phenyl moiety is inclined 88·0 (1)° with respect to the other phenyl moiety. The pyrrolidine ring exhibits a C17 envelope conformation with C17 0·573 (4) Å out of the plane of the other ring atoms. The unsubstituted phenyl moiety is inclined only 30·3 (2)° with respect to the pyrrolidine ring, while the chloro-substituted phenyl moiety is almost perpendicular to the pyrrolidine ring with a dihedral angle of 84·9 (2)°. The nitrogen-containing side chain from C7 is also not fully extended. The torsion angles about O1, C15 and C16 indicate that those atoms do not have fully extended bonds, suggesting important aspects of the receptor site of H_1-histamine.

The stereoview of the unit cell (Fig. 2) shows the hydrogen bond which binds the clemastine cationic

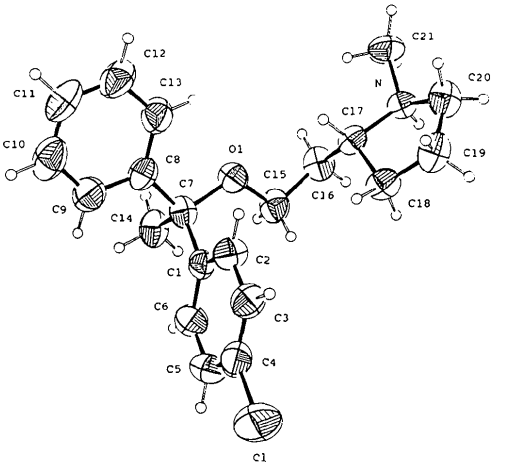


Fig. 1. *ORTEP* (Johnson, 1976) drawing of the clemastine cation with numbering scheme.

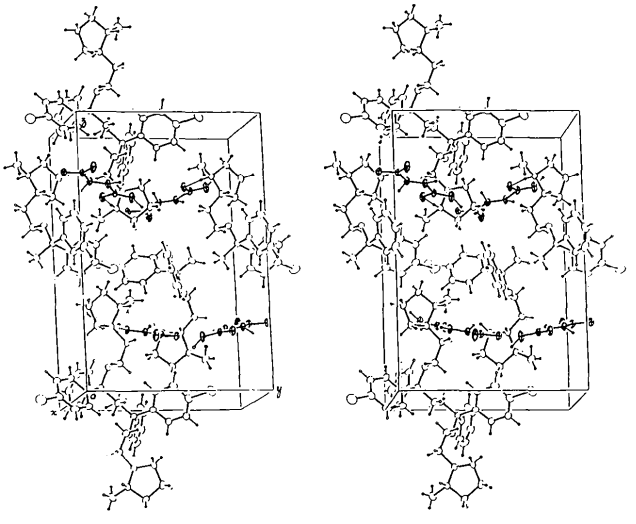


Fig. 2. Stereoview of the unit cell of clemastine hydrogen fumarate.

species to the anionic fumarate. The hydrogen bond extends from the H atom bonded to the N atom to O2 of the fumarate species. The N—H···O bond angle is 175·8°, and the H(N)···O2 bond length is 1·76 Å, while the total separation between N and O2 is 2·70 Å. Besides this hydrogen bond, there are no intermolecular forces which can be singled out for mention. Finally, there are no detectable unusual van der Waals distances in the crystal.

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Structures of 2-Chloro-4-cyclohexylamino-6-methoxy-1,3,5-triazine and 2-Chloro-4-methoxy-6-piperidino-1,3,5-triazine

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Abstract. $C_{10}H_{15}ClN_4O$, triclinic, $P\bar{1}$, $M_r = 242·7$, a = 6·817 (1), b = 7·967 (1), c = 12·018 (1) Å, α = 85·01 (1), β = 73·80 (1), γ = 69·65 (1)°, V = 587·6 Å^3, $Z = 2$, $D_x = 1·372$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 2·8$ mm^{-1}, $F(000) = 256$, $T = 295$ K, $R = 0·056$ for 1416 observed reflections. $C_9H_{13}ClN_4O$, monoclinic, $P2_1/n$, $M_r = 228·7$, $a = 6·571$ (1), b = 13·090 (1), $c = 12·855$ (2) Å, $\beta = 95·07$ (2)°, V = 1101·4 Å^3, $Z = 4$, $D_x = 1·379$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 3·0$ mm^{-1}, $F(000) = 480$, $T = 295$ K, $R = 0·076$ for 1299 observed reflections. The molecules of the two compounds show similar types of stacking, with triazine ring separations of 3·84 and 3·28 Å, respectively. The study shows the dependence of ring geometry not only upon the types and positions of substituents but also upon the Cl—C(ring) bond length.

Introduction. Although triazine molecules form a flat benzene-like aromatic system, their properties differ considerably from those of benzene due to the different atomic types in the ring. The most common triazines are 1,3,5-triazines (*s*-triazines), which are produced commercially from 2,4,6-trichloro-1,3,5-triazine. This compound easily exchanges its Cl atoms and is therefore a very reactive chlorination agent. The partial substitution of Cl atoms by alkoxy group(s) changes the course of reaction and, for example, 2-chloro-4,6-dialkoxy-1,3,5-triazines and carboxylic acids give reactive 2-alkanoyloxy intermediates, which under further treatment with alcohols or amines yield appropriate esters or amides (Kamiński, 1985, 1987).

To date we know of only two reports of crystal structures containing Cl—triazine bonds: 2-chloro-4-dimethylamino-6-triphenylphosphoranylidene-amino-1,3,5-triazine (Cameron, Mannan, Biddlestone & Shaw, 1975) and 2-(*N'*-acetylhydrazino)-4,6-dichloro-1,3,5-triazine (Reck & Jankowsky, 1981). These reports, together with the structures reported here, provide an opportunity for studying the influence of chlorine substitution on the *s*-triazine ring.

Experimental. Prismatic crystals of 2-chloro-4-cyclohexylamino-6-methoxy-1,3,5-triazine (CCMT) and 2-chloro-4-methoxy-6-piperidino-1,3,5-triazine (CMPT) were obtained from methanol solutions by slow evaporation of the solvent. Crystals of dimensions 0·17 × 0·16 × 0·11 (CCMT) and 0·33 × 0·26 × 0·21 mm (CMPT) were used for data collection and unit-cell determination. Diffraction data were collected on a CAD-4 diffractometer with Cu $K\alpha$ radiation up to $\theta = 75$ and 65° for CCMT and CMPT, respectively. The unit-cell parameters were calculated from 25 reflections in the θ range 16–32° (CCMT)

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