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2-(4-Imidazolyl)ethylammonium Bromide (Histamine Monohydrobromide)

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Abstract. $C_5H_{10}N_3Br$, monoclinic, $P2_1/a$ [non-standard setting of No. 14. C_{2h}^5, equivalent positions $\pm(x,y,z)$, $\pm(\frac{1}{2}+x,\frac{1}{2}-y,z)$], $a=18{\cdot}273$ (9), $b=9{\cdot}385$ (5), $c=4{\cdot}688$ (2) Å, $\beta=104{\cdot}34$ (3)°, $Z=4$, $D_m=1{\cdot}63$ (mean), $D_c=1{\cdot}636$ g ml^{-1}, $\mu=54{\cdot}99$ cm^{-1} (Mo $K\alpha$ radiation). The histamine monocation is found to exist in the conformation with the alkyl chain extended (*trans*) and perpendicular to the plane of the imidazole ring. The imidazole residue exists in the N^{τ}–H tautomeric form, different from that of crystalline histamine base.

Introduction. Histamine monohydrobromide was prepared by Mr W. Tertiuk (Smith, Kline and French Laboratories Ltd.) from histamine base and an equivalent of hydrogen bromide in anhydrous ethanol. Two recrystallizations from ethanol gave a product, m.p. 184–185°, with satisfactory C, H, N and Br analyses (reported m.p. 182–183°: Pyman, 1912).

Weissenberg photographs gave the systematic absences *h*0*l*, *h* odd, 0*k*0, *k* odd, which uniquely determine the space group. A crystal ($0{\cdot}2\times0{\cdot}2\times0{\cdot}4$ mm) was mounted on a Hilger and Watts four-circle diffractometer fitted with a monochromator. Accurate cell dimensions and orientation matrix were obtained by a least-squares fit to the setting angles of 26 reflexions (M. Dobler & B. Dürr, personal communication) and a complete intensity data set was collected with Mo $K\alpha$ radiation to $2\theta\leq61°$ by an $\omega/2\theta$ scan, ordinate analysis method (Watson, Shotton, Cox & Muirhead, 1970) with 50 steps of 0·02°. 2272 independent reflexions were measured of which 1661 were considered to be observed ($I>3\sigma$). Lorentz and polarization corrections were applied, as was an empirical absorption correction by the method of North, Phillips & Mathews (1968).

The position of the bromine atom was found, from an unsharpened Patterson synthesis, to be very close to $x,\frac{1}{2},\frac{1}{2}$ so that the space group of the bromine atoms alone is $A2/m$. The heavy-atom-phased F_o synthesis is therefore pseudo-symmetric but reasonable positions for C(4), C(5) and N(3) could be found. Inclusion of these atoms in phasing gave the full non-hydrogen atom skeleton. This model was refined by full-matrix least-squares calculations to $R=0{\cdot}106$ with isotropic temperature factors when it was realized that carbon and nitrogen atoms in the imidazole ring had been wrongly assigned. Further least-squares refinement of the corrected model, with anisotropic thermal motion, led to the location of all the hydrogen atoms from a difference synthesis. A final blocked-matrix least-squares refinement, with hydrogen atoms included with individual isotropic temperature factors and reflexion weights of the form $w=1$ if $|F_o|\leq70$ or $w=490/|F_o|^2$ if $|F_o|>70$, gave a final $R=0{\cdot}066$.

Table 1. *Final atomic coordinates with standard deviations in parentheses*

	x/*a*	*y*/*b*	*z*/*c*
Br	0·3852 (1)	0·5110 (1)	0·5058 (2)
N(1)	0·2761 (4)	−0·0053 (9)	0·2775 (15)
N(2)	0·3835 (4)	−0·0741 (7)	0·1924 (16)
N(3)	0·5204 (4)	0·2946 (8)	−0·0707 (16)
C(1)	0·3297 (5)	−0·1076 (10)	0·3260 (19)
C(2)	0·2974 (5)	0·1002 (11)	0·1153 (20)
C(3)	0·3634 (4)	0·0569 (8)	0·0617 (16)
C(4)	0·4121 (5)	0·1318 (9)	−0·1054 (18)
C(5)	0·4694 (5)	0·2256 (9)	0·0967 (19)
H(1)	0·225 (6)	−0·011 (12)	0·272 (23)
H(2)	0·319 (5)	−0·186 (10)	0·423 (21)
H(3)	0·265 (5)	0·179 (10)	0·070 (19)
H(4)	0·437 (5)	0·049 (9)	−0·206 (19)
H(5)	0·380 (5)	0·180 (10)	−0·246 (20)
H(6)	0·505 (4)	0·180 (9)	0·268 (17)
H(7)	0·444 (5)	0·305 (10)	0·165 (19)
H(8)	0·553 (5)	0·349 (19)	0·084 (20)
H(9)	0·550 (5)	0·227 (10)	−0·109 (19)
H(10)	0·498 (6)	0·347 (11)	−0·208 (23)

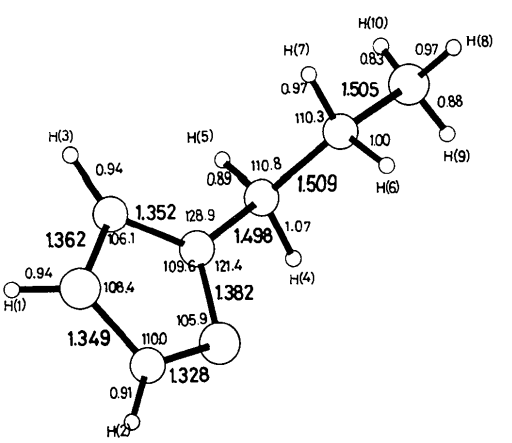

Fig. 1. Bond lengths and angles in histamine monohydrobromide.

Final atomic coordinates are listed in Table 1, thermal parameters in Table 2* and bond lengths and angles are illustrated in Fig. 1.

Discussion. Histamine stimulates the contraction of smooth muscle from various organs, such as the gut and bronchi: the H_1 responses (Ash & Schild, 1966). It also stimulates the secretion of acid by the stomach, increases the heart rate and inhibits contractions in the rat uterus: the H_2 responses (Black, Duncan, Durant, Ganellin & Parsons, 1972). At a *p*H of 7·4 (*i.e.* at the *p*H generally taken to be that of the extracellular fluids in a physiological environment) the monocation of histamine predominates to the extent of 96% and even at *p*H 6·0 is the single most important species (Ganellin, Pepper, Port & Richards, 1973). Kier (1968) suggested that the dual activity of histamine is a consequence of the ability of its monocation to adopt two distinct preferred conformations, *viz. trans* and *gauche* rotamers, and he assigned H_1-receptor activity to the *trans* rotamer and provisionally associated H_2 activity with the *gauche* rotamer. More recently (Ganellin, Pepper Port & Richards, 1973; Ganellin, Port & Richards, 1973; Ganellin, 1973*a*), it was proposed that the fully extended *trans* conformation of the monocation where $\theta_1=0$ and $\theta_2=180°$ (Fig. 2) may be needed for H_1 activity. The crystal structure of histamine monohydrobromide was investigated for information regarding the preferred conformations of the histamine monocation in the solid state.

The crystal is found to contain independent histamine cations and bromine anions. The cations are linked by linear hydrogen bonds (Fig. 3) between N(2) and N(3) [N(2)–H(12)–N(3) angle of 179·4°] with the nitrogen atoms 2·86 Å apart.

The histamine molecule can be described in terms of two planes, those of the imidazole ring and the ethylammonium side chain. The carbon and nitrogen atoms of the former are planar to ±0·01 Å and the hydrogen atoms lie close to this plane. The dihedral angle (θ_1) between the planes is 89·7° and can be compared with that found in other histamine derivatives (Table 3); this value is in the range predicted to be at an energy minimum by EHT molecular-orbital calculations (Ganellin, Port & Richards, 1973). The side chain is in the *trans* configuration in which the torsion angle θ_2 is 177·3°. So far, histamine and its salts are only known to have been obtained as the *trans* form in crystals, although in solution both *trans* and *gauche* forms have comparable stabilities.

* This table and a list of structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30587 (15 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

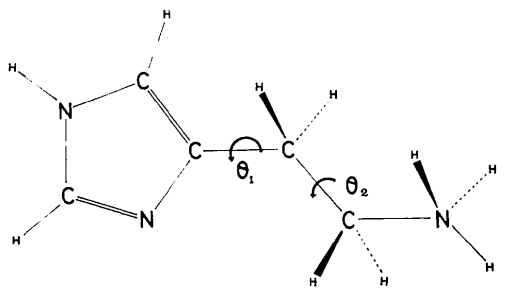

Fig. 2. Torsion angles of the histamine skeleton.

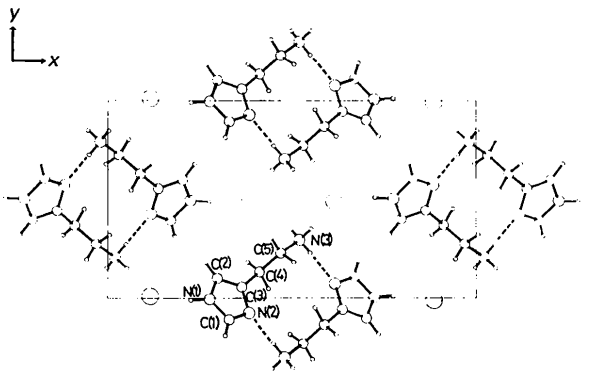

Fig. 3. Histamine monohydrobromide: the crystal structure seen in projection down **c**.

Table 3. *Dihedral angle* (θ_1) *in histamine entities*

	θ_1(°)
Neutral species	
Histamine	66·3[a]
6-Histaminopurine	63·0[b]*
Monocation	
Bromide	89·7[c]
Dication	
Bromide	30[d]
Phosphate	82·5[e]
Sulphate	4·4[f](Molecule I)
	9·2 (Molecule II)
Tetrachlorocobaltate	7[g]

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a. Bonnet & Ibers (1973). *b*. Thewalt & Bugg (1972). *c*. This work. *d*. Decou (1964). *e*. Veidis, Palenik, Schaffrin & Trotter (1969). *f*. Yamane, Ashida & Kakudo (1973). *g*. Bonnet & Jeannin (1972).

* We have computed this value from the published atomic coordinates.

Bonnet & Jeannin (1972) have suggested that, in the absence of interactions of a hydrogen-bonding or ion–dipole nature between hydrogen atoms of the terminal $-NH_3^+$ group and solvate molecules or anions, the dication will take up a *trans* planar conformation ($\theta_1=0$; $\theta_2=180°$). However, it seems more probable that the dihedral angle (θ_1) in histamine, whether protonated or not, is determined by the type of hydrogen-bond scheme rather than its existence or non-existence alone.

The imidazole residues exist in the N^{τ}–H tautomeric form* in which the non-protonated nitrogen (N^{π}) is adjacent to the side chain. This differs from histamine base (as recrystallized from benzene) (Bonnet & Ibers, 1973) but is the same form as found in the crystal of L-histidine (Madden, McGandy, Seeman, Harding & Hoy, 1972; Madden, McGandy & Seeman, 1972), *O*-methyl-L-pyroglutamyl-L-histidine (Cotrait & Allard, 1973), 6-histaminopurine dihydrate (Thewalt & Bugg, 1972) and the H_2-receptor antagonists, burimamide (Kamenar, Prout & Ganellin, 1973) and *N*-methyl-*N'*-{2-(5-methylimidazol-4-yl)methylthioethyl}-thiourea (Critchley, S. R., Prout, K. & Ganellin, C. R. unpublished work).

The N^{τ}–H tautomer is generally regarded as being the biologically active (H_1-receptor) species of histamine and is the preferred form in aqueous solution, although, at 37 °C the free-energy difference between the two tautomers is less than 1 kcal mol^{-1} (Ganellin, 1973*b*).

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* Following the IUPAC–IUB Commission on Biochemical Nomenclature 1972 recommendations for histidine, the imidazole N nearer the side chain is designated N^{π}, and the one farther is N^{τ} (Black & Ganellin, 1974).

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Jujubogenin *p*-Bromobenzoate

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Abstract. $C_{37}H_{51}O_5Br.\frac{1}{2}AcOEt$, m.p. 256–258 °C, triclinic, space group $P1$, with $a=16{\cdot}74$ (1), $b=15{\cdot}29$ (1), $c=7{\cdot}486$ (5) Å, $\alpha=94{\cdot}25$ (1), $\beta=102{\cdot}00$ (1), $\gamma=100{\cdot}98$ (1)°, $Z=2$, $D_x=1{\cdot}268$ g cm^{-3}, μ(Cu $K\alpha$)= 22 cm^{-1}. The structure was solved by the heavy-atom anomalous dispersion method and refined to an R value of 0·076 for 1725 observed reflexions. The chemical structure of jujubogenin has been established as 3β,20*S*-dihydroxy-16β(23*R*),16α(30)-dioxidodammar-24-ene. The dimensions and conformations of the two crystallographically independent molecules involved in the asymmetric unit generally agree with each other.

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Introduction. Jujubogenin, $C_{30}H_{48}O_4$, is the main sapogenin obtained by periodate oxidation of jujuboside B isolated from *Zizyphus jujuba* Mill. and hovenoside G from *Hovenia dulcis* Thunb. (Kawai, Akiyama, Ogihara & Shibata, 1974). The *p*-bromobenzoate was recrystallized from ethyl acetate solution as colourless