We thank the Graduate School of the University of Minnesota for partial support of this work.

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Structure of *N*-Cyano-*N'*-methyl-*N''*-(2-{[(5-methyl-1*H*-imidazol-4-yl)-methyl]thio}ethyl)guanidine (Cimetidine) Monohydrochloride Monohydrate, $C_{10}H_{17}N_6S^+.Cl^-.H_2O$

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(*Received* 23 *February* 1983; *accepted* 18 *May* 1983)

Abstract. $M_r = 306{\cdot}82$, monoclinic, $P2_1/c$, $a = 11{\cdot}542$ (3), $b = 10{\cdot}859$ (3), $c = 11{\cdot}632$ (3) Å, $\beta = 91{\cdot}09$ (2)°, $V = 1457{\cdot}5$ (7) Å^3, $Z = 4$, $D_m = 1{\cdot}391$ (1), $D_x = 1{\cdot}398$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 2{\cdot}362$ mm^{-1}, $F(000) = 648$, $T = 293$ K, final $R = 0{\cdot}046$ for 2478 independent reflections. Both N atoms of the imidazole ring are protonated and hydrogen-bonded to a Cl^- ion and an N atom of the cyano group of an adjacent molecule, respectively. The Cl^- ion is further linked with the N atom of the neighboring guanidine group by a hydrogen bond, consequently forming a 20-membered ring consisting of two cimetidine molecules and two Cl^- ions related by a center of symmetry, respectively.

Introduction. Cimetidine monohydrochloride is a specific histamine H_2-receptor antagonist which inhibits the secretion of the histamine-stimulated gastric acid. It is utilized in the treatment of peptic ulcer by injection, and has been widely investigated for its stability (Walker *et al.*, 1981; Yuhas, Loften, Baldinus & Mayron, 1981; Rosenberg, Dougherty, Mayron & Baldinus, 1980). Comparing the four kinds of cimetidine crystalline structures (forms *A*, *B*, *C* and *D*) with their inhibitory effects for peptic ulceration in rats, we previously proposed that the relative orientation of the cyanoguanidine group with respect to the imidazole ring is an important factor for the effective binding to the histamine H_2-receptor (Shibata, Kokubo, Morimoto, Morisaka, Ishida & Inoue, 1983). On the other hand, the conformation of cimetidine may change depending upon the environment, acidic or basic, because it has an imidazole ring capable of being isomerized and shows a weak inhibitory effect of peptic ulceration. In order to obtain the conformational characteristics of cimetidine under an acidic environment, we carried out the X-ray analysis of the crystal structure of cimetidine monohydrochloride.

Experimental. Cimetidine monohydrochloride was crystallized as the monohydrate by the slow evaporation of an aqueous solution of 1*M* HCl saturated with cimetidine. D_m measured by flotation in C_6H_6/CCl_4. Single crystal 0·2 × 0·3 × 0·5 mm; cell parameters determined by least-squares methods on the basis of 20 independent 2θ values; intensity data collected on a Rigaku four-circle diffractometer, graphite-monochromated Cu $K\alpha$, $\sin\theta/\lambda \le 0{\cdot}588$ Å^{-1}, $h: -13 \rightarrow 13$, $k: 0 \rightarrow 12$, $l: 0 \rightarrow 13$; four standards measured every 100 reflections: no significant variation; of 2494 reflections measured by ω–2θ scan mode, 2478 had $I \ge 2\sigma(I)$ and were subsequently used for structure refinement; Lorentz and polarization corrections applied, but absorption ignored. Structure solved by direct methods with *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). An *E* map, computed with the 200 phase set ($|E| \ge 1{\cdot}72$) having the highest combined figure of merit, gave reasonable positions for all non-H atoms. Refinement by block-diagonal least squares with anisotropic thermal parameters for all non-H atoms. Positional parameters of all H atoms obtained from a difference Fourier map and refined with isotropic thermal parameters. The quantity minimized was $\sum w(|F_o| - |F_c|)^2$; $w = 1{\cdot}0$ for $0 < F_o \le 15{\cdot}0$ and $w = 1{\cdot}0/[1{\cdot}0 + 0{\cdot}398\ (F_o - 15{\cdot}0)]$ for $F_o > 15{\cdot}0$; final $R = 0{\cdot}046$, $R_w = 0{\cdot}059$. Ratio of maximum least-squares shift to error: for non-H atoms ~0·008, for H atoms ~0·06. Maximum and minimum

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heights in final difference Fourier map: 0·3 and −0·3 e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974). No correction for secondary extinction. All numerical calculations made on the ACOS-900 computer at the Computation Center of Osaka University using *The Universal Crystallographic Computing System* (1979).

Discussion. The final coordinates are listed in Table 1.* The bond lengths and angles of the non-H atoms are given in Fig. 1. Most of the bond lengths and angles are in agreement with those of three different cimetidine crystals: forms *A* (Hädicke, Frickel & Franke, 1978), *C* and *D* (Shibata, Kokubo, Morimoto, Morisaka, Ishida & Inoue, 1983). However, the bond length N(1)–C(1) [1·322 (3) Å] is shorter than those of form *A* (1·332 Å), form *C* (1·362 Å) and form *D* (1·346 Å). The imidazole ring is almost planar and the C(4) atom lies almost on this plane. The dihedral angle between this ring and the side chain [C(5)–S–C(6)–C(7)] is 61·2 (1)°, and the cyanoguanidine group takes a *gauche* orientation with respect to the imidazole ring viewed along atoms C(5) to C(7) (see Fig. 2).

Based on Kier's (1968) proposal for the histamine molecule, Shibata *et al.* (1983) previously proposed two conditions for the conformation of cimetidine necessary for binding to the H_2-receptor: (1) the distance of ~3·6 Å between the N(2) atom of the imidazole ring and either N atom [N(3) or N(4)] of the guanidine group; (2) a *gauche* orientation of this group

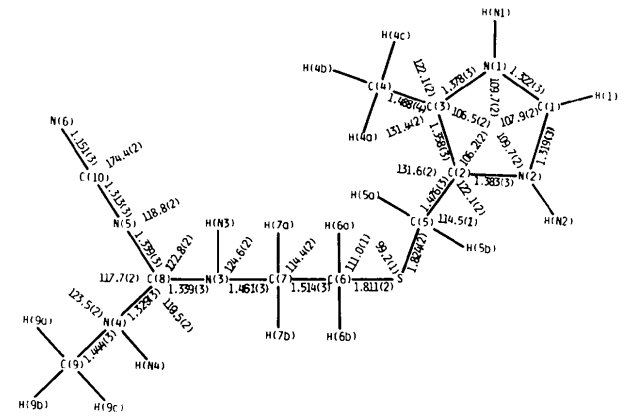

Fig. 1. Bond lengths (Å), bond angles (°) and atom numbering.

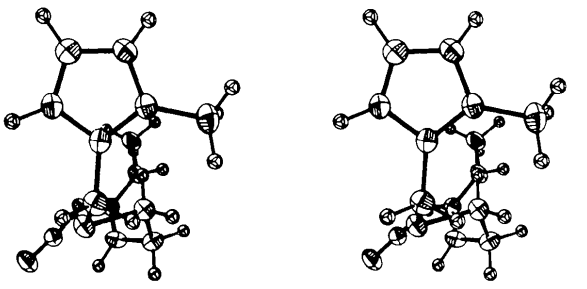

Fig. 2. Stereoview of a molecule of the title compound.

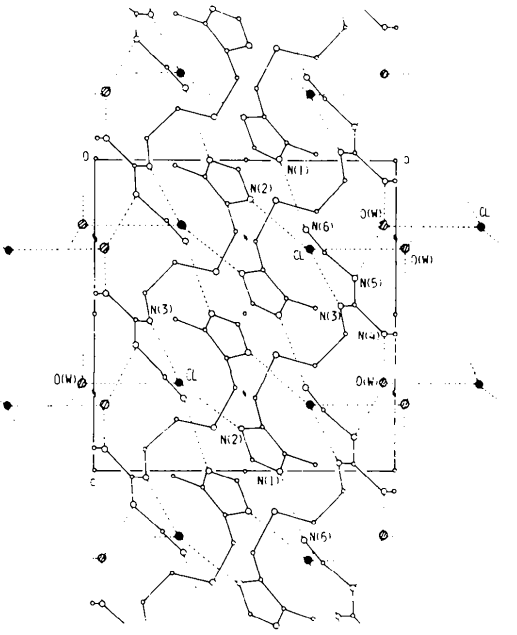

Fig. 3. The molecular arrangement viewed along **b**.

* Lists of structure factors, H-atom coordinates, anisotropic thermal parameters for non-H atoms, selected torsion angles, and the equations of the least-squares planes of the imidazole ring and the guanidine group, and the atomic displacements from them have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38601 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional* (×10^4) *and equivalent isotropic thermal parameters of non-*H *atoms with their standard deviations*

$B_{eq} = \frac{1}{4}(a^2B_{11} + b^2B_{22} + c^2B_{33} + 2acB_{12}\cos\beta)$.
W represents water of crystallization.

	x	*y*	*z*	B_{eq}(Å^2)
O(*W*)	10232 (2)	5817 (2)	2801 (1)	3·5
Cl	2822 (1)	6656 (1)	2024 (1)	2·4
S	6074 (0·4)	5019 (1)	1340 (0·4)	2·5
N(1)	6148 (1)	6638 (2)	5127 (1)	2·6
N(2)	4911 (1)	6574 (2)	3739 (2)	2·7
N(3)	8232 (2)	5411 (2)	−211 (1)	2·6
N(4)	9462 (1)	6822 (2)	651 (1)	2·6
N(5)	8683 (1)	7282 (2)	−1118 (1)	2·7
N(6)	7311 (2)	6903 (2)	−2724 (2)	3·8
C(1)	5250 (2)	7212 (2)	4650 (2)	3·0
C(2)	5607 (2)	5547 (2)	3625 (2)	2·4
C(3)	6391 (2)	5590 (2)	4610 (2)	2·4
C(4)	7361 (2)	4751 (2)	4840 (2)	3·4
C(5)	5411 (2)	4631 (2)	2704 (2)	2·7
C(6)	7584 (2)	4849 (2)	1760 (2)	2·5
C(7)	8314 (2)	4528 (2)	734 (2)	2·6
C(8)	8780 (2)	6497 (2)	−233 (2)	2·3
C(9)	10031 (2)	8003 (2)	739 (2)	3·5
C(10)	7944 (2)	7029 (2)	−1957 (2)	2·7

Table 2. *Hydrogen bonds and short contacts* (<3·5 Å) *with their standard deviations*

(*a*) Hydrogen bonds

Donor (*D*)	Acceptor (*A*)	*D*—*A* (Å)	H···*A* (Å)	∠*D*—H···*A* (°)
N(2)	Cl	3·101 (2)	2·13 (3)	167 (3)
N(4)	O(*W*)	2·856 (3)	1·89 (3)	157 (2)
O(*W*)	Cl^{i}	3·270 (2)	2·44 (3)	162 (3)
O(*W*)	N(5^{ii})	3·020 (3)	2·11 (4)	167 (3)
N(1)	N(6^{iii})	2·830 (3)	1·95 (3)	164 (3)
N(3)	Cl^{iv}	3·297 (2)	2·47 (2)	146 (2)

(*b*) Short contacts (Å) (<3·5 Å)

O(*W*)—C(6)	3·431 (3)	N(1)—C(5^{v})	3·417 (3)
O(*W*)—C(9)	3·380 (3)	N(2)—C(3^{v})	3·471 (3)
N(1)—N(5^{ii})	3·492 (3)	N(2)—C(4^{v})	3·442 (4)
N(4)—N(6^{ii})	3·440 (3)	C(2)—C(3^{v})	3·426 (3)
N(1)—C(2^{v})	3·457 (3)	N(4)—C(7^{vi})	3·390 (3)

Roman-numeral superscripts denote the following equivalent positions relative to the reference molecule at *x*,*y*,*z*.

(i) $1+x, y, z$ (iv) $1-x, 1-y, -z$
(ii) $x, \frac{3}{2}-y, \frac{1}{2}+z$ (v) $1-x, 1-y, 1-z$
(iii) $x, y, 1+z$ (vi) $2-x, 1-y, -z$

with respect to the imidazole ring. Although the observed conformation in the cimetidine monohydrochloride satisfies the latter condition, the N(2)···N(3) or N(2)···N(4) distance is significantly longer than 3·6 Å [N(2)···N(3) = 6·170 (3); N(2)···N(4) = 6·426 (3) Å]; this situation in cimetidine monohydrochloride may be in part responsible for its rather weak inhibitory effect of peptic ulceration (Kokubo, Morimoto & Morisaka, in preparation).

Fig. 3 shows the crystal packing viewed along the *b* axis. The water molecules and the Cl^- ions lie between neighboring guanidine groups and between neighboring imidazole and guanidine moieties, respectively. Hydrogen bonds and short contacts less than 3·5 Å are listed in Table 2. The O atom of the water molecule is hydrogen-bonded to N(4) and N(5) of the neighboring guanidine groups [N(4)—H(N4)···O(*W*) = 2·856 (3), O(*W*)—H(*Wb*)···N(5) = 3·020 (3) Å], and to the neighboring Cl^- ion [O(*W*)—H(*Wa*)···Cl = 3·270 (2) Å]. These hydrogen bonds stabilize the molecular arrangement along the *c* axis (Fig. 3). The Cl^- ion is further hydrogen-bonded to the N(3) atom of the neighboring guanidine group [Cl···N(3) = 3·297 (2) Å] and to the N(2) atom of the neighboring imidazole ring [Cl···N(2) = 3·101 (2) Å]; a cyclic dimer of cimetidine involving a 20-membered ring system *via* two Cl^- ions is thereby formed (see Fig. 3). In this dimer formation, the two head-to-tail-arranged cimetidine molecules are related to each other by a center of symmetry.

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Acta Cryst. (1983). C**39**, 1257–1259

1,2-*O*-Isopropylidene-α-D-glucofuranurono-6,3-lactone, $C_9H_{12}O_6$

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(*Received* 3 *March* 1983; *accepted* 18 *May* 1983)

Abstract. $M_r = 216·19$, monoclinic, $P2_1$, $a = 7·647$ (1), $b = 6·162$ (1), $c = 11·227$ (3) Å, $\beta = 105·63$ (1)°, $Z = 2$, $V = 509·5$ Å^3, $D_x = 1·41$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ(Cu $K\alpha$) = 1·024 mm^{-1}, $F(000) = 228$, $T = 293$ K, $R = 0·0487$ for 779 unique observed reflections [$F \geq 3\sigma(F)$]. The material was prepared by Mackie & Perlin [*Can. J. Chem.* (1965), **43**, 2921–2924] and recrystallized from $CHCl_3$/petroleum ether. The analysis has confirmed the structure of the title compound.

Introduction. The title compound and 5-hydroxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranurono-6,3-lactone (see following paper, Sheldrick, Mackie & Akrigg, 1983) were investigated to confirm their synthesis and to clarify the structure of the *gem* diol.

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