Acta Cryst. (1980). B**36**, 1223–1225

2-Cyano-1-methyl-3-{2-[(5-methyl-1*H*-imidazol-4-yl)methylthio]ethyl}guanidine Monohydrate

BY BISERKA KOJIĆ-PRODIĆ AND ŽIVA RUŽIĆ-TOROŠ

'Rudjer Bošković' Institute, PO Box 1016, 41001 *Zagreb, Yugoslavia*

AND NEVENKA BRESCIANI-PAHOR AND L. RANDACCIO

Istituto di Chimica, Università di Trieste, 34127 *Trieste, Italy*

(*Received* 17 *October* 1979; *accepted* 26 *November* 1979)

Abstract. $C_{10}H_{16}N_6S.H_2O$, $M_r = 270{\cdot}36$, monoclinic, *Cc*, $a = 12{\cdot}632\ (3)$, $b = 7{\cdot}785\ (2)$, $c = 15{\cdot}493\ (4)$ Å, $\beta = 117{\cdot}66\ (2)°$, $Z = 4$, $U = 1349{\cdot}47$ Å^3, $D_c = 1{\cdot}330$ Mg m^{-3}, Mo $K\alpha$ ($\lambda = 0{\cdot}7107$ Å, $\mu = 0{\cdot}991$ mm^{-1}); final $R = 0{\cdot}026$. The interatomic distances and angles are in agreement with the given atom type and hybridization. Molecules are connected by hydrogen bonds, N–H···O, 2·835 (3) and O–H···N, 2·801 (3) Å, acting between water molecules and imidazole moieties, forming an infinite ribbon along **a**.

Introduction. The title compound (without H_2O) named as cimetidine, developed and marketed by Smith Kline & French under the proprietary name Targomet®, is a histamine H_2-receptor antagonist. Black, Duncan, Durant, Ganellin & Parsons (1972) described the first antagonist, burimamide. More than 700 compounds were synthesized before burimamide, as a desirable compound, was obtained. Further studies led to the synthesis of metiamide which had better properties than burimamide. In the synthesis of the H_2 antagonist the imidazole part of histamine is preserved and the side chain is extensively modified, but for the H_1 antihistamines the imidazole ring is modified. Thus cimetidine as the H_2 antagonist was introduced where the thiourea in the side chain is replaced by cyanoguanidine. Cimetidine is an efficient drug; it has caused a significant reduction in diurnal gastric acid secretion but without serious hematologic toxicity. After 6 weeks of treatment most ulcer patients were cured compared with members of the placebo group. By the administration of the drug in doses of 200 mg three times a day, even stimulated gastric secretion was inhibited. Cimetidine was found to be effective even in the Zollinger–Ellison syndrome (Goth, 1978).

Two crystalline phases named cimetidine A and B (Smith Kline & French, 1978) have already been described. Crystallization from various organic solvents always gave the same crystalline form which was recognized as cimetidine (marked as CRC 1820/I in the paper by Kojić-Prodić, Kajfež, Belin, Toso & Šunjić, 1979), whereas crystallization from aqueous solutions of different concentrations gave three more forms (CRC 1820/II-IV). The previously marked cimetidine A is found to be identical with the form CRC 1820/I and cimetidine B with CRC 1820/IV. The crystalline form labeled CRC 1820/I is cimetidine, whose crystal structure was solved by Hädicke, Frickel & Franke (1978). The specimen CRC 1820/II is cimetidine monohydrate and its crystal structure is described in this paper. The crystals for this investigation were prepared at the Department of Biomedical and Biochemical Research, Compagnia di Ricerce Chimice (CRC), San Giovanni al Natisone, Italy, by Dr V. Šunjić and co-workers (CRC, 1977*a*,*b*; Kojić-Prodić, Kajfež, Belin, Toso & Šunjić, 1979).

Preliminary cell dimensions and space group were determined from oscillation and Weissenberg photographs recorded with Cu $K\alpha$ radiation. The cell dimensions given in the *Abstract* were refined from diffractometer measurements. Intensities were collected on a Siemens diffractometer by the $\theta/2\theta$ scan procedure with Mo $K\alpha$ radiation. 1592 independent reflexions in the range $7 < \theta < 28°$ were recorded. 1508 reflexions having $I > 2\sigma(I)$ were used in the calculations. The data were corrected for background, Lorentz and polarization effects but not for absorption. The Patterson method in the space group *Cc* located the S atom on $y = \frac{1}{4}$. As a consequence, only a limited number of reflexions were phased and thus the Fourier synthesis was not successful. *MULTAN* 78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) gave only chicken-wire *E* maps. Among the reflexions phased on the basis of the S atom coordinates, 13 were selected, and used as known phases in the *MULTAN* input. In this way, the solution of the structure was obtained. The *E* map corresponding to the solution with the best figure of merit revealed the positions of 17 non-hydrogen atoms out of 18 in the molecule. The remaining N atom (in the imidazole ring) was located from the resulting Fourier synthesis. Refinement was by the full-matrix least-squares method, minimizing

0567-7408/80/051223-03$01.00

$\sum w||F_o| - |F_c||^2$. The type 3 weighting scheme from the XRAY system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972) was used. The weights were assigned as: $w = w_1 w_2$, where $w_1 = 1$ for $|F_o| \le 25$ and $w_1 = 25/|F_o|$ for $|F_o| > 25$; $w_2 = 1$ for $\sin\theta \ge 0{\cdot}5$ and $w_2 = (\sin\theta)/0{\cdot}5$ for $\sin\theta < 0{\cdot}5$. Anisotropic refinement and a subsequent weighted difference synthesis were performed to locate the H atoms. A scale factor, heavy-atom coordinates and anisotropic thermal parameters (161 variables in all; x and z coordinates of the S atom fixed) were refined. The H atoms were included in the structure factor calculation only. For H atoms the isotropic thermal parameters are those of the bonded atoms plus 1. Anisotropic thermal parameters (of the non-hydrogen atoms) are in the usual range; the maximum value of U_{22} for C(7′) is 0·079 (10) Å^2. The final $R = 0{\cdot}026$ and $R_w = 0{\cdot}031$ for 1508 reflexions having $I > 2\sigma(I)$.

Scattering factors given by Cromer & Mann (1968) and (for H) Stewart, Davidson & Simpson (1965) were used. An anomalous-dispersion correction was included for S (Cromer & Liberman, 1970).

The calculations were carried out on a Univac 1110 computer at the University Computing Centre in Zagreb with the XRAY system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972).

Atom coordinates are listed in Tables 1 and 2.*

Discussion. The structural formula and bond lengths are given in Fig. 1 and the molecular packing is in Fig. 2. Bond angles are listed in Table 3.

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35019 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final atomic coordinates* (×10^5) *for non-hydrogen atoms*

	x	y	z
S	48760 (0)	75769 (7)	40520 (0)
O	30568 (16)	46380 (27)	48426 (14)
N(1)	56357 (19)	31107 (26)	25561 (16)
N(2)	41787 (17)	15973 (25)	28041 (15)
N(3)	39989 (15)	45026 (23)	24745 (14)
N(4)	67907 (21)	5179 (30)	26541 (20)
N(1′)	69294 (20)	23770 (28)	53054 (15)
N(3′)	54132 (19)	38120 (28)	52878 (16)
C(1)	44414 (20)	61164 (28)	22976 (15)
C(2)	54405 (21)	68872 (29)	32183 (17)
C(3)	46136 (20)	30402 (27)	26228 (15)
C(4)	62169 (20)	16901 (29)	26176 (17)
C(5)	30726 (21)	14985 (32)	28764 (19)
C(2′)	58579 (22)	22707 (33)	52997 (20)
C(4′)	62428 (20)	49614 (30)	52764 (15)
C(5′)	71819 (21)	40787 (32)	52847 (16)
C(6′)	60437 (21)	68404 (31)	52283 (17)
C(7′)	83163 (23)	46874 (43)	52928 (22)

Bond lengths and angles are comparable to the values found in cimetidine (Hädicke, Frickel & Franke, 1978); bond-length differences between these two molecules are in the range 0·022 (3)–0·003 (2) Å. There are no significant differences in the lengths

Table 2. *Positional parameters* (×10^3) *for hydrogen atoms*

	x	y	z
H(N′1)	733	140	537
H(2′)	543	100	532
H(6′)1	675	744	534
H(6′)2	580	717	568
H(7′)1	833	420	470
H(7′)2	900	445	580
H(7′)3	817	590	512
H(1)1	471	592	185
H(1)2	378	692	204
H(2)1	610	576	358
H(2)2	583	800	312
H(N2)	477	60	300
H(N3)	317	460	263
H(5)1	250	180	225
H(5)2	300	220	337
H(5)3	283	40	300
H(O1)	283	500	425
H(O2)	377	460	500

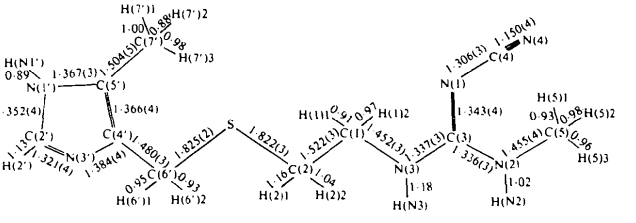

Fig. 1. Structural formula and bond lengths (Å).

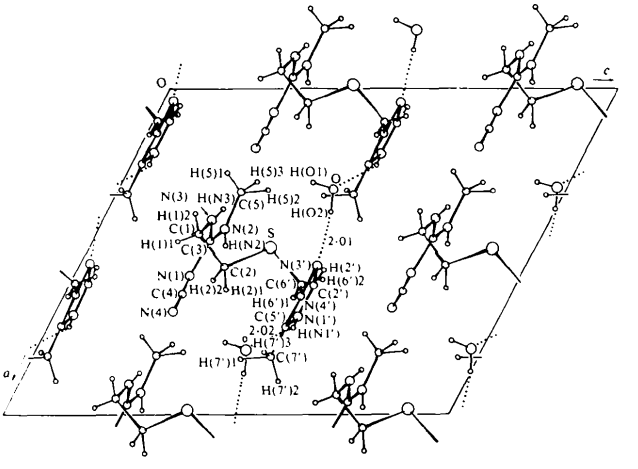

Fig. 2. Molecular packing viewed along **b**. Intermolecular hydrogen bonds, O–H(O2)···N(3′), 2·801 (3) and N(1′)–H(N1′)···O, 2·835 (3) Å, acting between water molecules and imidazole residues, form an infinite ribbon along **a**.

[N(1)–C(3), 1·343 (4), N(2)–C(3), 1·336 (3) and N(3)–C(3), 1·337 (3) Å] of the N–C bonds in the guanidine residue although they should be present due to the hybridization type of the atoms involved. These almost equivalent values of the N–C bond and the planarity of the guanidine moiety (Table 5) can be explained by a delocalized bonding system. Such an effect was also observed in 2-cyano-1,3-dimethylguanidine (Chastain, McCarty & Wieland, 1971) and cimetidine (Hädicke, Frickel & Franke, 1978). The presence of the crystalline water molecule in the structure of the title compound causes a completely different conformation (Table 4) and packing comparing to that of cimetidine (Hädicke, Frickel & Franke, 1978). Molecules are connected by hydrogen bonds [N(1′)–H(N1′)···O, 2·835 (3) and O–H(2)···N(3′), 2·801 (3) Å] acting between water molecules and imidazole moieties, forming an infinite ribbon along **a** (Fig. 2). However, cimetidine (Hädicke, Frickel & Franke, 1978) exhibits an intramolecular hydrogen bond, N(2)–H···N(3′) 2·881 Å, between imidazole and guanidine residues. Intermolecular hydrogen bonds, N(3)–H···N(4) 2·911 Å, between guanidine groups form a twelve-membered ring. A head-to-tail orientation of the molecules results in an intermolecular hydrogen bond, N(1′)–H···N(1) 2·954 Å, between imidazole and guanidine moieties, forming waved layers.

Table 3. *Bond angles* (°)

C(2′)–N(1′)–C(5)	107·6 (2)	C(2)–C(1)–H(1)2	108
C(2′)–N(1′)–H(N1′)	118	N(3)–C(1)–H(1)1	108
C(5′)–N(1′)–H(N1′)	135	N(3)–C(1)–H(1)2	108
N(1′)–C(2′)–N(3′)	111·2 (2)	H(1)–C(1)–H(1)2	110
N(1′)–C(2′)–H(2′)	123	C(1)–C(2)–S	110·7 (2)
N(3′)–C(2′)–H(2′)	126	C(1)–C(2)–H(2)1	105
C(2′)–N(3′)–C(4′)	105·5 (2)	C(1)–C(2)–H(2)2	116
N(3′)–C(4′)–C(5′)	109·5 (2)	S–C(2)–H(2)1	108
N(3′)–C(4′)–C(6′)	121·8 (2)	S–C(2)–H(2)2	103
C(5′)–C(4′)–C(6′)	128·6 (3)	H(2)1–C(2)–H(2)2	115
N(1′)–C(5′)–C(4′)	106·1 (2)	C(3)–N(1)–C(4)	119·2 (2)
N(1′)–C(5′)–C(7′)	122·5 (3)	C(3)–N(2)–C(5)	124·3 (2)
C(4′)–C(5′)–C(7′)	131·4 (3)	C(3)–N(2)–H(N2)	113
C(4′)–C(6′)–S	113·6 (2)	C(5)–N(2)–H(N2)	122
C(4′)–C(6′)–H(6′)1	111	N(1)–C(3)–N(2)	123·7 (2)
C(4′)–C(6′)–H(6′)2	110	N(1)–C(3)–N(3)	117·0 (2)
S–C(6′)–H(6′)1	107	N(2)–C(3)–N(3)	119·3 (3)
S–C(6′)–H(6′)2	106	C(1)–N(3)–C(3)	121·7 (2)
H(6′)1–C(6′)–H(6′)2	110	C(1)–N(3)–H(N3)	116
C(6′)–S–C(2)	102·4 (1)	C(3)–N(3)–H(N3)	121
C(2)–C(1)–N(3)	112·9 (2)	N(1)–C(4)–N(4)	174·4 (3)
C(2)–C(1)–H(1)1	110	H(O1)–O–H(O2)	96·0 (3)

Table 4. *Torsion angles* (°)

N(3′)–C(4′)–C(6′)–S	−70·4 (4)
C(5′)–C(4′)–C(6′)–S	107·4 (3)
C(4′)–C(6′)–S–C(2)	−59·5 (3)
S–C(2)–C(1)–N(3)	−67·7 (3)
C(2)–C(1)–N(3)–C(3)	−75·8 (4)
C(1)–N(3)–C(3)–N(2)	178·5 (3)

Table 5. *Displacements* (Å) *from least-squares planes through the imidazole ring and guanidine residue*

Atoms included in the calculations of the least-squares planes are denoted by asterisks.

Imidazole ring		Guanidine residue	
N(1′)*	0·004 (2)	N(1)*	0·051 (3)
C(2′)*	−0·004 (3)	N(2)*	0·013 (3)
N(3′)*	0·002 (2)	N(3)*	−0·049 (2)
C(4′)*	0·000 (2)	N(4)*	0·038 (3)
C(5′)*	−0·002 (2)	C(3)*	0·017 (3)
C(6′)	−0·040 (3)	C(4)*	0·006 (3)
C(7′)	0·015 (3)	C(5)	−0·027 (3)

The authors thank Dr V. Šunjić for the crystals.

References

Black, J. W., Duncan, W. A. M., Durant, C. J., Ganellin, C. R. & Parsons, E. M. (1972). *Nature (London)*, **236**, 385–390.

Chastain, R. V., McCarty, C. G. & Wieland, D. M. (1971). *Chem. Commun.* pp. 198–199.

Compagnia di Ricerce Chimice (1977*a*). Swiss Pat. Appl. 15 212/77.

Compagnia di Ricerce Chimice (1977*b*). Swiss Pat. Appl. 15 213/77.

Cromer, D. T. & Liberman, D. (1970). *J. Chem. Phys.* **53**, 1891–1898.

Cromer, D. T. & Mann, J. B. (1968). *Acta Cryst.* A**24**, 321–324.

Goth, A. (1978). *Medical Pharmacology*, 9th ed. Saint Louis: C. V. Mosby Co.

Hädicke, E., Frickel, F. & Franke, A. (1978). *Chem. Ber.* **111**, 3222–3232.

Kojić-Prodić, B., Kajfež, F., Belin, B., Toso, R. & Šunjić, V. (1979). *Gazz. Chim. Ital.* In the press.

Main, P., Hull, S. E., Lessinger, L., Germain, G., Declercq, J. P. & Woolfson, M. M. (1978). *MULTAN 78. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

Smith Kline & French (1978). German Pat. Appl. 2 742 531.

Stewart, J. M., Kruger, G. J., Ammon, H. L., Dickinson, C. & Hall, S. R. (1972). The XRAY system – version of June 1972. Tech. Rep. TR-192. Computer Science Center, Univ. of Maryland, College Park, Maryland.

Stewart, R. F., Davidson, E. R. & Simpson, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.