

The Structure of a Degradation Product of 2-Mercaptopurine: 5-Amino-2-thiocytosine Dihydrochloride Dihydrate

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Abstract. $C_4H_8N_4S^{2+} \cdot 2Cl^- \cdot 2H_2O$ ($M_r = 251.136$) is orthorhombic, $P2_12_12_1$, with $a = 6.2236$ (7), $b = 10.8285$ (10), $c = 15.3729$ (14) Å ($V = 1036.0$ Å³), $Z = 4$, $d_c = 1.610$, d_o (flotation) = 1.62 Mg m⁻³. Full-matrix least-squares refinement using 2507 observed reflections [$I > 3\sigma(I)$] with $2\theta < 90^\circ$ converged at $R = R_w = 0.029$ and $S = 1.4$. Average e.s.d.'s in bonding are 0.0018 Å and 0.12° (non-hydrogen atoms) except for values involving S, for which they are 0.0014 Å and 0.11°. The molecular structure of the cytosine moiety is very similar to that of cytosine hydrochloride [Mandel, N. S. (1977). *Acta Cryst.* B33, 1079–1082]. The crystal structure consists of an extensive three-dimensional hydrogen-bonding network, with chains of 5-amino-2-thiocytosine molecules along the [010] direction linked through hydrogen bonds to the two Cl⁻ ions and one of the water molecules. Two of the H atoms of the $-NH_3^+$ group are involved in bifurcated hydrogen bonds.

Introduction. When commercially available (Sigma Chemical Co.) 2-mercaptopurine was dissolved in 1 M hydrochloric acid, a white precipitate was formed (not further analysed). The filtrate yielded yellow, prismatic crystals of the title compound by evaporation at room temperature. A specimen of good quality was ground to a sphere of radius 0.19 mm and used throughout the experiments. The space group was uniquely determined from the systematic extinctions. The cell parameters were determined from a least-squares fit to 34 reflections with $25^\circ < 2\theta < 53^\circ$, measured on an automated Syntex P1 diffractometer at 292 K (graphite-monochromated Mo $K\alpha$ radiation, $\lambda = 0.71069$ Å). The conditions for data collection were as described by Nordenson & Hvoslef (1981). The total number of reflections considered was 2671, of which 2507 had $I > 3\sigma(I)$ and were treated as observed. The data were converted to relative structure amplitudes in the usual way using computer programs adapted to a CDC 6600 computer by Groth (1973). This reference covers all programs used unless otherwise stated. The data were corrected for absorption by the method of Palm (1964).

The structure was solved by direct methods (Germain, Main & Woolfson, 1971) and refined by

full-matrix least-squares techniques. The H atoms were located from a difference Fourier synthesis and included in the refinement with isotropic thermal parameters. Final atomic coordinates and B_{eq} values (Willis & Pryor, 1975) are given in Table 1.* A final

* A list of observed and calculated structure factors, with e.s.d.'s of the observations, thermal parameters corresponding to the coordinates in Table 1, data concerning rigid-body-motion corrections and atomic parameters obtained from the refinement with $\sin \theta/\lambda > 0.7$ Å⁻¹ have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36068 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional atomic coordinates for 5-amino-2-thiocytosine dihydrochloride dihydrate, and isotropic B values*

The e.s.d.'s in the last figure are given in parentheses. The B value for a non-hydrogen atom (B_{eq}) is the average value of the three main anisotropic vibration axes. Its e.s.d. is ~ 0.02 Å² for Cl⁻ and S and ~ 0.04 – 0.05 Å² for C, N and O. These values were

calculated by $\sigma^2(B_{eq}) = \sum_i \sum_j \left(\frac{\delta B_{eq}}{\delta U_{ij}} \sigma_{U_{ij}} \right)^2$, where $B_{eq} = \frac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$.

	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}/B
S	0.31433 (9)	-0.21710 (4)	0.64484 (2)	2.75 Å ²
C(2)	0.32851 (25)	-0.13786 (13)	0.55304 (9)	1.78
C(4)	0.35134 (25)	0.05815 (12)	0.47802 (8)	1.60
C(5)	0.35459 (26)	-0.00703 (12)	0.39757 (8)	1.60
C(6)	0.34485 (26)	-0.13179 (13)	0.39811 (8)	1.83
N(1)	0.33206 (26)	-0.19411 (11)	0.47406 (8)	1.98
N(3)	0.33725 (23)	-0.01124 (11)	0.55109 (8)	1.73
N(7)	0.36813 (29)	0.05928 (13)	0.31566 (8)	2.15
N(9)	0.36123 (31)	0.17845 (12)	0.48487 (10)	2.36
Cl(1)	0.41209 (7)	0.37038 (4)	0.32773 (3)	2.46
Cl(2)	0.36160 (7)	0.37314 (4)	0.64479 (3)	2.54
OW(1)	0.32731 (30)	-0.44295 (12)	0.48100 (11)	3.09
OW(2)	0.41104 (28)	0.09595 (14)	0.71009 (9)	2.58
H(1)	0.328 (6)	-0.273 (3)	0.472 (2)	4.4 (7)
H(3)	0.344 (4)	0.025 (2)	0.596 (2)	2.3 (4)
H(6)	0.350 (3)	-0.177 (2)	0.347 (1)	1.4 (3)
H(N7)1	0.378 (5)	0.007 (2)	0.276 (2)	3.2 (5)
H(N7)2	0.485 (5)	0.108 (3)	0.316 (2)	3.3 (6)
H(N7)3	0.244 (8)	0.105 (4)	0.309 (3)	7.3 (10)
H(N9)1	0.373 (4)	0.219 (2)	0.442 (2)	2.2 (4)
H(N9)2	0.354 (5)	0.206 (3)	0.528 (2)	3.0 (5)
H(OW1)1	0.343 (5)	-0.486 (3)	0.449 (2)	3.2 (6)
H(OW1)2	0.345 (8)	-0.484 (5)	0.521 (3)	7.2 (11)
H(OW2)1	0.521 (7)	0.083 (4)	0.721 (2)	5.2 (9)
H(OW2)2	0.405 (6)	0.163 (4)	0.707 (2)	4.2 (7)

difference Fourier synthesis had no regions of electron density larger than $0.27 \text{ e } \text{Å}^{-3}$, except for a single peak of $0.38 \text{ e } \text{Å}^{-3}$ at the position expected for the bonding electrons of the C(5)–C(6) bond. The atomic scattering factors used were those of Doyle & Turner (1968) for C, N, and O, those of Stewart, Davidson & Simpson (1965) for H, and those from *International Tables for X-ray Crystallography* (1962) for S and Cl^- .

Extinction corrections were not applied.

Discussion. The effect of sulphur-containing analogues of purine and pyrimidine in cancer chemotherapy is well known (Roy-Burman, 1979). Possible similarities between some enzymatic reactions and reactions in the solid state due to ionizing radiation (Miyagawa, Tamura & Cook, 1969) have initiated ESR and ENDOR studies on several mercaptopurine compounds (Alexander & Sagstuen, 1979, and references cited therein). Attempts to make crystals of 2-mercaptapurine, as a hydrochloride, led to the C(8)-degraded species 5-amino-2-thiocytosine. IR spectra show that the degradation takes place upon dissolving 2-mercaptapurine in hydrochloric acid. This was unexpected, as the electrochemical degradation of purine compounds is believed to occur at C(6) in the six-membered ring of the molecule (Dryhurst, 1977). The present observation may thus have relevance to the interpretation of electrochemical data.

The pyrimidine moiety of the title compound is shown in Fig. 1, with thermal ellipsoids, atomic notation, bond lengths and angles included. The torsional angles are given in Table 2.

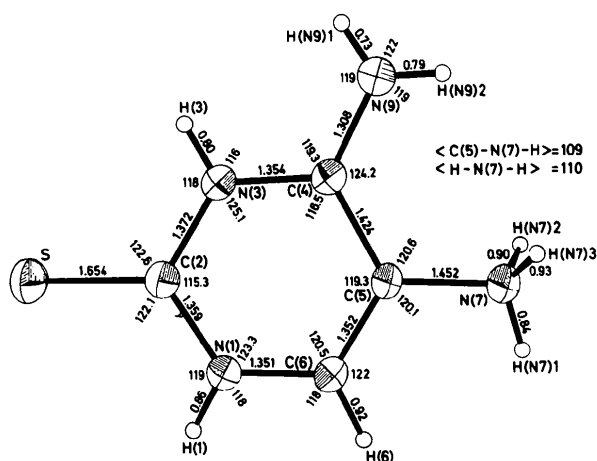


Fig. 1. The 5-amino-2-thiocytosine molecule with atomic notation and thermal ellipsoids scaled to include 50% probability (Johnson, 1976). Bonding distances (Å) and angles ($^\circ$) are included. E.s.d.'s in bonding (non-hydrogen atoms) are 0.0017–0.0019 Å, except for the C(2)–S bond where the e.s.d. is 0.0014 Å. E.s.d.'s in angles are 0.11–0.13 $^\circ$. Libration correction gives an average lengthening of 0.004 Å. Further details of libration corrections and the rigid-body-model approximation are given in the deposited material.

The bonding distances and angles correspond closely to those of cytosine hydrochloride (Mandel, 1977), the largest difference being 0.011 Å for the C(4)–C(5) bond. The average difference is 0.005 Å, and the r.m.s. difference 0.0065 Å. The additional C(5)–N(7) bond is a normal single bond, and the C(2)–S bond length is within the range normally found for C–S double bonds in similar compounds (Shefter & Mautner, 1967; Sletten, Sletten & Jensen, 1969; Furberg & Jensen, 1970).

The thermal motion is reasonably well approximated by a rigid-body model (Schomaker & Trueblood, 1968), which gives an average lengthening of the bonding distances of 0.0037 (7) Å. The two largest libration axes are along N(3)–N(1) and C(5)–C(2) and have r.m.s. amplitudes of 3.3 and 4.4 $^\circ$, respectively. The third libration axis is perpendicular to the ring and has an r.m.s. amplitude of 1.8 $^\circ$. Further data regarding the rigid-body model are given in the deposited material.

The thermal vibrations are rather small for a room-temperature structure determination. This is most probably a result of the extensive hydrogen-bonding network. A stereoview of the unit-cell content and some neighbouring molecules is given in Fig. 2, and details of

Table 2. Torsional angles ($^\circ$), not involving hydrogen atoms

The e.s.d.'s are in the range 0.13 to 0.25 $^\circ$. The torsional angles for the H atoms do not deviate more than 5 $^\circ$ (2.5σ) from the expected values of 0 or 180 $^\circ$, except for H(N7)2 and H(N7)3, which are staggered with respect to C(4).

C(6)–N(1)–C(2)–N(3)	0.5	S–C(2)–N(1)–C(6)	–179.6
N(1)–C(2)–N(3)–C(4)	–0.8	S–C(2)–N(3)–C(4)	179.2
C(2)–N(3)–C(4)–C(5)	0.8	N(9)–C(4)–N(3)–C(2)	–179.2
N(3)–C(4)–C(5)–C(6)	–0.3	N(9)–C(4)–C(5)–C(6)	179.6
C(4)–C(5)–C(6)–N(1)	0.0	N(9)–C(4)–C(5)–N(7)	–0.4
C(5)–C(6)–N(1)–C(2)	–0.1	N(7)–C(5)–C(4)–N(3)	179.6
		N(7)–C(5)–C(6)–N(1)	–180.0

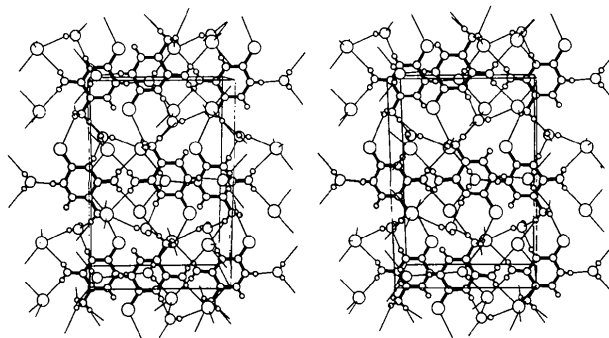


Fig. 2. Stereodrawing of the crystal packing and unit-cell content. The view is approximately towards the *a* axis (at an angle of 10 $^\circ$), with the *c* axis pointing down and the *b* axis pointing to the left. Hydrogen bonds are drawn as single lines. The different atoms are indicated by circles of different sizes, with $\text{Cl} = \text{S} > \text{O} > \text{N} = \text{C} > \text{H}$.

Table 3. *Details of hydrogen bonding*

The e.s.d.'s in bond lengths are about 0.02 Å for bonds involving H, and 0.002 Å for other distances. The e.s.d.'s of the angles are 1–3°. The $A \cdots H \cdots A$ angles for the bifurcated bonds are 81° for H(N7)1 and 95° for H(N7)3.

$D-H \cdots A$	Distance (Å)			Angle (°)
	$D-H$	$D \cdots A$	$H \cdots A$	$D-H \cdots A$
N(1)–H(1)···OW(1)	0.86	2.697	1.85	173
N(3)–H(3)···OW(2)	0.80	2.745	1.96	169
N(9)–H(N9)1···Cl(1)	0.79	3.203	2.42	171
N(9)–H(N9)2···Cl(2)	0.73	3.239	2.55	159
N(7)–H(N7)1···Cl(1 ⁱ)	0.84	3.304	2.53	153
N(7)–H(N7)1···OW(2 ⁱⁱ)	0.84	2.912	2.34	125
N(7)–H(N7)2···Cl(2 ⁱⁱ)	0.90	3.216	2.43	146
N(7)–H(N7)3···Cl(2 ^{iv})	0.93	3.294	2.49	145
N(7)–H(N7)3···S ⁱⁱ	0.93	3.333	2.82	116
OW(1)–H(OW1)1···Cl(1 ^v)	0.69	3.149	2.46	176
OW(1)–H(OW1)2···Cl(2 ^v)	0.77	3.218	2.45	173
OW(2)–H(OW2)1···Cl(1 ⁱⁱⁱ)	0.72	3.194	2.60	143
OW(2)–H(OW2)2···Cl(2)	0.73	3.180	2.48	161

Symmetry code: None x, y, z ; (i) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (ii) $\frac{1}{2}-x, -y, z-\frac{1}{2}$; (iii) $\frac{1}{2}+x, \frac{1}{2}-y, 1-z$; (iv) $x-\frac{1}{2}, \frac{1}{2}-y, 1-z$; (v) $x, y-1, z$.

Table 4. *Coordination angles (°) around the Cl⁻ ions and the water molecules*

The e.s.d.'s for angles involving Cl⁻ are ~1° and for those involving water molecules ~3°.

H(N7)1···Cl(1)···H(N9)1	155	H(N7)···Cl(2)···H(N7)3	147
H(N7)1···Cl(1)···H(OW1)1	101	H(N7)2···Cl(2)···H(N9)2	103
H(N7)1···Cl(1)···H(OW2)1	101	H(N7)2···Cl(2)···H(OW1)2	96
H(N9)1···Cl(1)···H(OW1)1	104	H(N7)2···Cl(2)···H(OW2)2	95
H(N9)1···Cl(1)···H(OW2)1	82	H(N7)3···Cl(2)···H(N9)2	107
H(OW1)1···Cl(1)···H(OW2)2	86	H(N7)3···Cl(2)···H(OW1)2	102
H(OW2)1–OW(2)–H(OW2)2	105	H(N7)3···Cl(2)···H(OW2)2	83
H(OW2)1–OW(2)···H(3)	109	H(N9)2···Cl(2)···H(OW1)2	84
H(OW2)1–OW(2)···H(N7)1	123	H(N9)2···Cl(2)···H(OW2)2	68
H(OW2)2–OW(2)···H(3)	108	H(OW1)2···Cl(2)···H(OW2)2	152
H(OW2)2–OW(2)···H(N7)1	117	H(OW1)1–OW(1) H(OW1)2	100
H(3)···OW(2)···H(N7)1	92	H(OW1)1–OW(1)···H(1)	128
		H(OW1)2–OW(1)···H(1)	130

the hydrogen bonds and the Cl⁻ ion coordination are given in Tables 3 and 4. Except for the two bifurcated hydrogen bonds, all such bonds are of intermediate

strengths. The four atoms involved in each bifurcated bond are located almost exactly in the same plane. Both Cl⁻ ions have a coordination leaving one side open, and may be derived from slightly distorted octahedral coordinations lacking two and one of the corners, respectively. The water molecules have different coordinations. OW(1) participates in the hydrogen bonding in a planar, trigonal fashion, whereas the coordination of OW(2) is clearly tetrahedral.

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