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The Crystal and Molecular Structure of 9-Methyl-8-phenyl-6-thiopurine Hemihydrate

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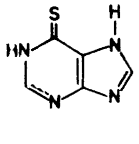
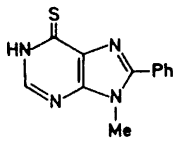
The structure of 9-methyl-8-phenyl-6-thiopurine hemihydrate, $(C_{12}N_4SH_{10})\cdot\frac{1}{2}H_2O$, has been solved by X-ray crystallographic methods. The crystals are monoclinic, space group $C2/c$, with $a = 16.046$ Å, $b = 7.071$ Å, $c = 21.784$ Å and $\beta = 104.79°$. 2116 reflections were measured on a four-circle diffractometer using Mo$K\alpha$ radiation. The structure was refined to $R = 0.044$. Standard deviations in bond lengths and angles involving non-hydrogen atoms are in the range 0.003 – 0.006 Å and 0.2 – 0.3°, respectively. The phenyl group is twisted 28.5° relative to the purine ring. The molecules are piled on top of one another along the *b*-axis with alternate purine and phenyl rings in the stack. The interplanar spacing is 3.53 Å.

The present structure investigation was carried out to study the steric interactions in substituted purine bases. The structure of the unsubstituted 6-thiopurine molecule (I) has already been determined to high accuracy in two independent X-ray investigations.[1,2]



(I)



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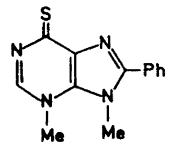

(III)

In the present paper the structure of II is reported. Further studies will include molecule III. F. Bergmann and co-workers have synthesized several compounds of this type and the results of UV, NMR and mass spectrometric measurements [3] will be discussed in relation to the structure obtained. Experimental dipole moments have also been obtained for some of the compounds [4] and will be correlated with theoretical calculations.[5]

EXPERIMENTAL

A sample of 9-methyl-8-phenyl-6-thiopurine (MPTP) was kindly supplied by F. Bergmann, the Hebrew University of Jerusalem. The crystals were grown from a 20 % solution of acetic acid in water by slow evaporation.

Weissenberg photographs showed the space group to be either $C2/c$ or Cc. The distribution of normalized structure factors indicated that $C2/c$ was the correct one. Cell parameters were determined by least-squares treatment of the 2θ settings for 12 reflections measured on the diffractometer. The density of the crystals was measured by flotation in a mixture of tetrachloromethane and benzene and the obtained value agreed satisfactorily with that calculated for the hemihydrate.

The crystal data are as follows:

$(C_{12}N_4SH_{10}).\frac{1}{2}H_2O$ M.W. = 251.31
Crystal system: monoclinic, space group $C2/c$.
$a = 16.046(5)$ Å, $b = 7.071(2)$ Å, $c = 21.784(4)$ Å, $\beta = 104.79(2)°$
$V = 2389(1)$ Å^3, $F_{000} = 524$, $Z = 8$
$D_m = 1.397$ g cm^{-3}, $D_x = 1.38$ g cm^{-3}
Linear absorption coefficient: $\mu = 2.57$ cm^{-1}.

Data were collected on a tape-operated four-circle diffractometer with niobium filtered Mo$K\alpha$ radiation. The crystal used had dimensions 0.65 mm × 0.10 mm × 0.07 mm, and was mounted along [010] which coincides with the needle axis. Integrated intensities were measured with the $\theta - 2\theta$ scan technique, the scan ranges being calculated as $\Delta\theta_1 = a_1 + b_1 \tan\theta$ and $\Delta\theta_2 = a_2 + b_2 \tan\theta$. Suitable scan ranges were obtained with $a_1 = 0.30°$, $b_1 = 0.20°$, $a_2 = 0.32°$ and $b_2 = 0.20°$. Both the peak and the background were measured twice and the net count was derived by subtracting the background counts from the peak counts. The error in the net intensity of each reflection was derived as

$$\sigma(I) = [\sigma_c^2 + (k\sigma_c^2)^2]^{\frac{1}{2}}$$

where σ_c is the error due to counting statistics. The factor k was set equal to 0.01 to include the error caused by electronic instability and misalignment of the crystal as reflected in the plot of standard reflections. Of the 2116 reflections measured in the interval $1° < \theta < 25°$, 678 were less than $2\sigma_c$. These reflections were set equal to the threshold value of $2\sigma_c$ and included in the refinement only if $F_{calc} > F_{threshold}$.

The structure was solved by a symbolic addition procedure and refined by full-matrix least-squares on an IBM 360/50 computer. The quantity minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = 1/\sigma_F^2$. The atomic scattering factors for the heavier atoms were obtained from *International Tables for X-Ray Crystallography* (1962),[6] and those for the hydrogen atoms were from Stewart *et al.*[7] In the three initial cycles of refinement isotropic temperature parameters were used. Later the non-hydrogen atoms were included with anisotropic parameters. All the hydrogen parameters in the MPTP-molecule were well determined. However, some difficulties were encountered in refining the hydrogen atoms of the water molecule. The difference map indicated some kind of disorder in the orientation of the water hydrogens. Further refinement did not completely resolve this problem.

The refinement was terminated when all shifts were less than 0.1σ. The residual $R = (\sum||F_o| - |F_c||)/\sum|F_o|$ omitting unobserved reflections was 0.044. Final coordinates and temperature factors are listed in Tables 1 and 2, respectively. The thermal ellipsoids as shown in Fig. 3 seem to be physically meaningful. The phenyl group is seen to have an in-plane movement rather than an expected rotational movement around C(8)–C(10).

A rigid-body motion analysis [8] was carried out where the purine part of the molecule was treated separately. The r.m.s. deviation calculated between observed and calculated U_{ij}'s is 2.1×10^{-4} Å^2. The estimated standard deviation in U_{ij}'s from the full-matrix refinement is on the average 2.7×10^{-4} Å^2. The libration tensor were used to correct bond lengths between non-hydrogen atoms. The corrections are in the range 0.006 – 0.003 Å and are all less than 2σ.

Table 1. Final positional parameters with the corresponding standard deviations in parentheses.

Atom	*X/a*	*Y/b*	*Z/c*
S	0.51309(5)	0.02758(15)	0.39788(4)
O	0.50000(0)	0.27141(73)	0.25000(0)
N(1)	0.38878(16)	0.08445(37)	0.45727(11)
N(3)	0.24075(15)	0.14804(37)	0.41662(11)
N(7)	0.33271(15)	0.08282(34)	0.28474(10)
N(9)	0.20250(14)	0.14271(35)	0.30195(10)
C(2)	0.30879(20)	0.12170(48)	0.46341(14)
C(4)	0.25981(18)	0.12877(41)	0.36001(13)
C(5)	0.33917(17)	0.09161(42)	0.34883(12)
C(6)	0.41112(18)	0.06746(42)	0.40043(13)
C(8)	0.25023(18)	0.11371(40)	0.25790(13)
C(9)	0.11198(21)	0.19762(62)	0.29290(18)
C(10)	0.21485(19)	0.11256(42)	0.18819(13)
C(11)	0.13142(22)	0.05716(50)	0.15951(15)
C(12)	0.10301(25)	0.05725(55)	0.09358(17)
C(13)	0.15851(28)	0.10656(54)	0.05736(17)
C(14)	0.24190(27)	0.15824(53)	0.08600(16)
C(15)	0.27052(23)	0.16031(47)	0.15140(14)
H(0)	0.4805(30)	0.2008(61)	0.2708(21)
H(1)	0.4304(20)	0.0558(46)	0.4935(15)
H(2)	0.3071(17)	0.1406(42)	0.5076(13)
H(11)	0.0918(18)	0.0223(42)	0.1824(13)
H(12)	0.0440(19)	0.0120(44)	0.0754(13)
H(13)	0.1391(22)	0.1113(48)	0.0109(17)
H(14)	0.2818(20)	0.1976(46)	0.0611(14)
H(15)	0.3304(19)	0.1989(43)	0.1737(13)
H(91)	0.0796(21)	0.0667(52)	0.2890(14)
H(92)	0.1056(18)	0.2604(43)	0.3306(14)
H(93)	0.0946(18)	0.2803(44)	0.2547(15)

RESULTS AND DISCUSSION

Planarity of the molecule. The accumulation of accurate structural information on purines has revealed that the molecules are slightly bent around the conjugated bond C(4) – C(5).[9] In MPTP which has fairly large substituents, this feature is still present as shown in Fig. 1. The dihedral angle between the pyrimidine ring and the imidazole ring is 1.0°. In addition to the bending the purine part of the molecule is also slightly twisted around C(4) – C(5).

The phenyl group is rotated around C(8) – C(10) making a dihedral angle of 28.5° with the imidazole plane. In this conformation nearly symmetric short contacts appear between the *ortho*-hydrogen H(11) and the adjacent methyl hydrogen atoms. The lengths of the contacts H(11)···H(91) and H(11)···H(93) are 2.36(4) Å and 2.38(4) Å, respectively.

Methylation at N(7) or N(9) in 8-phenyl purines produces a large hypsochromic shift in contrast to the behaviour of the non-phenylated analogues, indicating a twist of the phenyl group.[3] The introduction of a second methyl

Table 2. Thermal parameters with the corresponding standard deviations in parentheses. The anisotropic thermal parameters are defined by the expression $T_i = \exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$ and the isotropic parameters by $T_i = \exp[-8\pi^2U \sin^2\theta/\lambda^2]$. For non-hydrogen atoms the values are multiplied by a factor of 10^4, for hydrogen atoms by 10^3.

	U_{11}	U_{22}	U_{33}	U_{12}	U_{23}	U_{13}
S	379(4)	955(8)	389(4)	149(5)	59(5)	141(3)
O	1018(34)	637(30)	890(31)	0	0	538(27)
N(1)	424(15)	533(18)	300(13)	95(13)	1(12)	104(12)
N(3)	437(15)	527(18)	353(13)	58(13)	14(12)	187(12)
N(7)	422(14)	444(17)	300(12)	55(12)	2(11)	132(10)
N(9)	326(12)	415(16)	361(13)	17(11)	−1(11)	107(10)
C(2)	524(20)	531(22)	313(17)	80(17)	−5(15)	170(15)
C(4)	382(16)	353(18)	325(15)	20(14)	1(13)	109(13)
C(5)	369(16)	372(18)	303(15)	24(14)	−1(13)	131(12)
C(6)	375(16)	428(20)	347(15)	48(14)	15(14)	132(12)
C(8)	374(15)	349(18)	356(16)	4(14)	−5(13)	134(13)
C(9)	369(18)	632(27)	480(21)	73(18)	6(20)	144(16)
C(10)	475(18)	347(18)	339(15)	46(15)	−9(14)	96(14)
C(11)	525(20)	479(23)	460(19)	−14(17)	−46(16)	93(16)
C(12)	595(24)	642(28)	506(21)	33(21)	−74(19)	−61(19)
C(13)	906(30)	601(26)	343(19)	96(23)	25(18)	74(21)
C(14)	791(28)	543(25)	393(19)	62(20)	7(17)	210(20)
C(15)	566(21)	432(21)	379(18)	38(17)	−9(15)	163(16)
	U		U		U	
H(1)	73(11)	H(13)	88(12)	H(92)	58(10)	
H(2)	58(9)	H(14)	65(10)	H(93)	55(10)	
H(11)	46(8)	H(15)	52(9)	H(0)	124(19)	
H(12)	63(10)	H(91)	73(12)			

group at N(3) is accompanied by a bathochromic shift of $\Delta\lambda_{max}$ +5 nm. N(3) methylation without the presence of Me N(9) gives a much larger shift, $\Delta\lambda_{max}$ +12. This is ascribed to an increased steric interference between 9-methyl and 8-phenyl substituents, when a methyl group is introduced at N(3). Further details of the stereochemistry have to await the structure determination of III.

Bond lengths and angles. The molecular dimensions are shown in Fig. 2. There is no known purine type tautomer directly comparable to the present

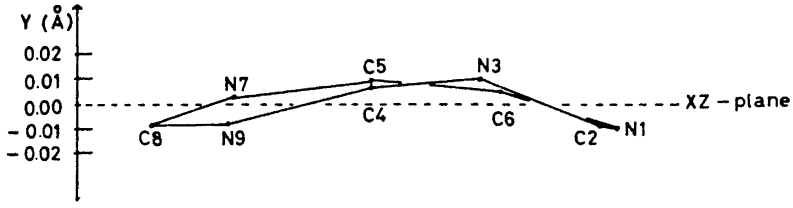

Fig. 1. The puckering of the purine ring. The scale of the ordinate is expanded relative to the abscissa.

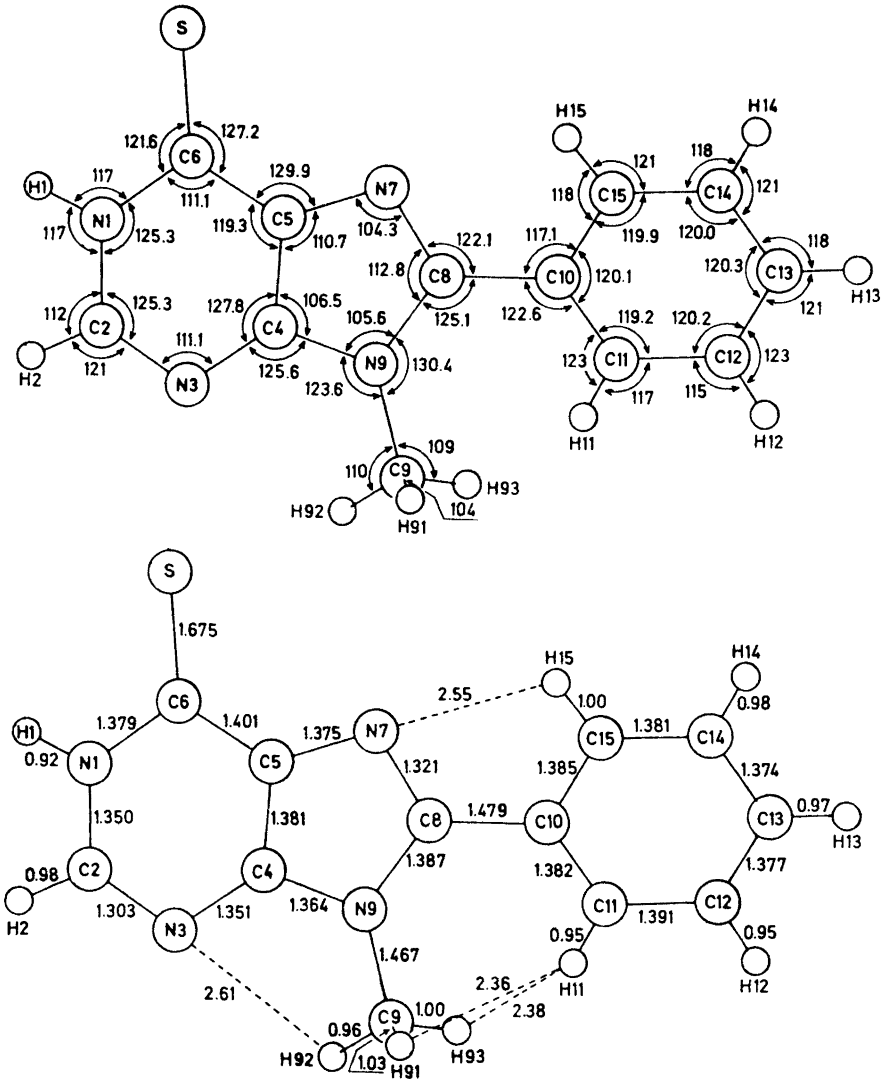

Fig. 2. Bond lengths and angles in 9-methyl-8-phenyl-6-thiopurine.

structure. The 6-thiopurine molecule [1,2] is a N(7) – H tautomer, thus only the pyrimidine parts in I and II are chemically equivalent. The structure of 1,3,9-trimethyl-xanthine (TMX) has recently been determined [10] and there the imidazole part may be compared to the present structure. In Table 3 pertinent bond lengths and angles in the three structures are listed. The dimensions of 6-thiopurine are most precise having been determined twice independently.[1,2] The pyrimidine parts in MPTP and 6-thiopurine, excluding

Table 3. Comparison of bond lengths (Å) and angles(°) in the purine part of 9-methyl-8-phenyl-6-thiopurine (MPTP), 6-thiopurine (TP)[1,2] and 1,3,9-trimethylxanthine (TMX).[19] The values of TP are the average of two independent determinations.

Bond	MPTP	TP	TMX
N(1) – C(2)	1.350	1.354	1.389
C(2) – N(3)	1.301	1.308	1.382
N(3) – C(4)	1.352	1.362	1.374
C(4) – C(5)	1.380	1.395	1.366
C(5) – C(6)	1.401	1.401	1.417
C(6) – N(1)	1.379	1.378	1.408
C(6) – S, (O)	1.676	1.677	1.216
C(5) – N(7)	1.375	1.371	1.384
N(7) – C(8)	1.321	1.349	1.299
C(8) – N(9)	1.387	1.329	1.376
N(9) – C(4)	1.365	1.365	1.365
Angles			
C(5) – C(6) – N(1)	111.1	110.8	112.9
C(5) – C(6) – S, (O)	127.2	126.8	126.9
N(1) – C(6) – S, (O)	121.6	122.4	120.2
C(6) – N(1) – C(2)	125.3	125.0	126.2
N(1) – C(2) – N(3)	125.3	125.0	117.6
C(2) – N(3) – C(4)	111.1	113.2	118.4
N(3) – C(4) – C(5)	127.8	124.1	123.5
C(4) – C(5) – C(6)	119.3	121.8	121.4
C(4) – C(5) – N(7)	110.7	105.9	110.7
C(6) – C(5) – N(7)	129.9	132.3	128.0
C(5) – N(7) – C(8)	104.3	106.1	103.7
N(7) – C(8) – N(9)	112.8	113.6	114.0
C(8) – N(9) – C(4)	105.6	104.3	105.0
N(9) – C(4) – C(5)	106.5	110.1	106.6

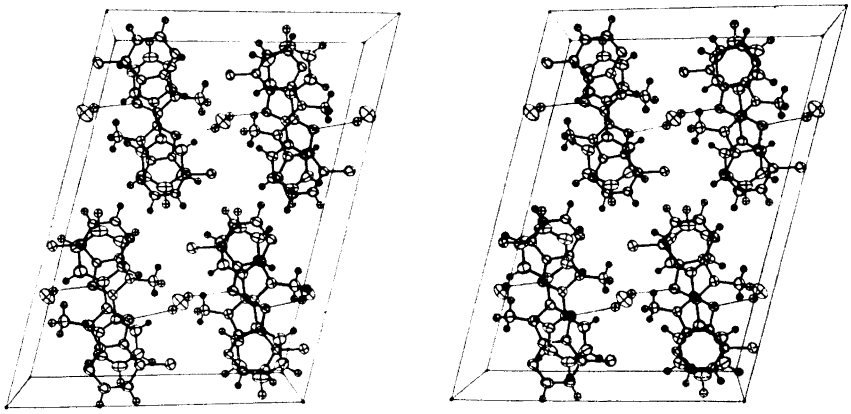

Fig. 3. Stereoscopic drawing of the contents of the unit cell viewed along the *b*-axis.

atoms C(4) and C(5) are identical within standard deviations. The effect of introducing a phenyl group in the imidazole ring is also apparently minor. The lengthenings of bonds N(7) – C(8) and C(8) – N(9) adjacent to the substitution site are probably significant. The steric interaction between methyl and phenyl has increased the external angles C(9) – N(9) – C(8) and N(9) – C(8) – C(10) though without significantly altering the internal angles at N(9) and C(8).

Molecular packing and hydrogen bonding. A stereoscopic drawing of the unit cell is shown in Fig. 3. The usual stacking pattern observed in purine structures is here replaced by alternate purine – phenyl stacking for molecules related by screw axis. The interplanar distance purine – phenyl is 3.53 Å and thus appreciably less than the van der Waals distance of 4.00 Å between aromatic rings. In the crystalline complex of 1,3,7,9-tetramethyluric acid and the carcinogene 3,4-benzpyrene the corresponding distance is 3.48 Å.[11] According to spectroscopic evidence the association between purines and aromatic hydrocarbons is not of the π-complex type but may be described as weak polarization-bonding interaction.[12]

The water molecule situated on the two-fold axis links the stacks together in the direction of the *a*-axis through weak hydrogen bonds to N(7), O – H··· N(7) = 3.255 Å. A normal oxygen-nitrogen hydrogen bond is in the range 2.7 – 2.9 Å. The loose hydrogen bonding found in the present structure may account for the apparent disorder of the water molecule.

Molecules related by a center of symmetry are connected by hydrogen bond N(1) – H···S = 3.24 Å, $\angle$N(1) – H – S = 143°. In thioguanine N – H···S distances are found slightly larger, 3.30 and 3.33, Å respectively.[13]

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