Crystal Structures of Azathioprine Dihydrate and 6-Methylmercaptopurine Trihydrate

WILLIAM J. COOK and CHARLES E. BUGG ˣ

Abstract □ The crystal and molecular structures of 6-methylmercaptopurine trihydrate and of azathioprine dihydrate were determined by the use of three-dimensional, X-ray diffractometer data and were refined by least squares. Both molecules crystallize in the N(9)-H tautomer form, in contrast to the N(7)-H tautomer form found in crystals of 6-mercaptopurine. Unlike 6-mercaptopurine, or other thiopurines that have unsubstituted thio groups, the sulfur atoms of 6-methylmercaptopurine and azathioprine do not act as hydrogen-bond acceptors in the crystal structures. These two derivatives of 6-mercaptopurine assume a conformation in which the substituents on the sulfur atom are directed away from the imidazole moiety of the purine.

Keyphrases □ Azathioprine dihydrate—crystal and molecular structures □ 6-Methylmercaptopurine trihydrate—crystal and molecular structures □ Mercaptopurine derivatives—crystal and molecular structures of azathioprine dihydrate and 6-methylmercaptopurine trihydrate □ Crystallography—determination of structures of azathioprine dihydrate and 6-methylmercaptopurine trihydrate

A number of synthetic purine and pyrimidine analogs are useful chemotherapeutic agents (1–3). Of the purine analogs that are effective in cancer chemotherapy, mercaptopurine is one of the most widely used (3–5). However, its effectiveness is limited by its rapid degradation *in vivo* (6), and derivatives have been synthesized with the intent of preventing this *in vivo* degradation. A particularly effective derivative is azathioprine[1], 6-[(1-methyl-4-nitroimidazol-5-yl)mercapto]purine, in which the protective group is a nitroimidazolyl moiety (7). Azathioprine reacts with sulfhydryl groups, resulting in the slow liberation of free 6-mercaptopurine.

Acquired resistance to mercaptopurine represents the second major obstacle to its successful use (2, 8). For *in vivo* activation, mercaptopurine must be first converted to its ribonucleotide (by the enzyme inosinic-guanylic pyrophosphorylase) and then to 6-methylmercaptopurine ribonucleotide (1, 2). When administered as the ribonucleoside, 6-methylmercaptopurine is capable of inhibiting the growth of cells that have acquired resistance to mercaptopurine by loss of inosinic-guanylic pyrophosphorylase (1). This analog ribonucleoside, mistaken for adenosine by the enzyme adenosine kinase, is converted directly to the ribonucleotide, thus bypassing the pathway responsible for resistance to mercaptopurine (1).

This paper describes the crystal structures of azathioprine dihydrate and 6-methylmercaptopurine trihydrate and discusses some apparent structural effects produced by the addition of substituents to the sulfur atom of mercaptopurine.

[1] Imuran, Burroughs Wellcome Co.; preferred chemical name is 6-[(1-methyl-4-nitroimidazol-5-yl)thio]purine.

Table I—Crystal Data[a]

	Azathioprine Dihydrate	6-Methylmercaptopurine Trihydrate
Stoichiometry	$C_9H_7N_7O_2S \cdot 2H_2O$	$C_6H_6N_4S \cdot 3H_2O$
Z	4	4
Space Group	$P2_1/c$	$P2_1/c$
a	4.560 (1) Å	10.721 (1) Å
b	15.491 (1)	6.976 (2)
c	19.447 (3)	15.027 (2)
β	93.61 (1)°	115.04 (1)°
ρ (calculated)	1.518 g cm^{-3}	1.437 g cm^{-3}
ρ (observed)	1.51 g cm^{-3}	1.43 g cm^{-3}
μ (CuK$\bar{\alpha}$)	22.8 cm^{-1}	27.0 cm^{-1}

[a] The density was measured by flotation in a mixture of benzene and carbon tetrachloride.

EXPERIMENTAL

Yellow crystals of azathioprine were obtained by slowly evaporating a water–ethanol solution; colorless crystals of 6-methylmercaptopurine were grown from a solution of water and dimethylamine. Weissenberg and oscillation photographs showed the crystals to be monoclinic, space group $P2_1/c$, as indicated by the systematic absence of reflections h0l with l odd and 0k0 with k odd.

Data for azathioprine were obtained from a crystal fragment with approximate dimensions of 0.30, 0.20, and 0.03 mm. Data for 6-methylmercaptopurine were obtained from a crystal fragment with approximate dimensions of 0.30, 0.20, and 0.10 mm. All angular and intensity data were collected with an X-ray diffractometer[2], by use of a scintillation counter and nickel-filtered copper radiation.

Cell parameters were measured before and after intensity data were collected. Approximate cell parameters for use in collection of intensity data were calculated by a least-squares analysis of the angular settings for several medium-angle reflections (CuK$\bar{\alpha}$, λ = 1.5418 Å). Accurate values for the cell parameters were determined immediately after data collection by a least-squares analysis of 2θ values for high angle reflections (CuKα_1, λ = 1.54051 Å). The final cell parameters were based on nine reflections from each compound; these parameters were not significantly different from those obtained prior to data collection. Crystal data, including the final cell parameters, are given in Table I.

Intensity data were measured by use of a 2θ scanning technique. The scanning speed was 1°/min, and a 20-sec background measurement was performed at each terminus of the scans. All unique reflections with $2\theta < 128°$ were measured, including 2279 reflections for azathioprine and 1697 reflections for 6-methylmercaptopurine. Those reflections with scan counts below background levels were given their calculated negative intensity values and were retained in all subsequent calculations.

The intensities were assigned variances, $\sigma^2(I)$, according to counting statistics plus a correctional term $(0.03S)^2$, S being the scan count. The intensities and their variances were corrected for Lorentz and polarization effects, and absorption corrections were applied by using the program ORABS (9). The data sets were scaled using Wilson (10) plots.

The trial structure of azathioprine was obtained by the heavy atom method, using sulfur as the heavy atom, and the trial structure for 6-methylmercaptopurine was obtained by direct methods, with the use of the computer program MULTAN (11). A modified version of the full-matrix least-squares program ORFLS was used

[2] Picker FACS-1.

Table II—Heavy Atom Parameters and Their Standard Deviations[a]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Azathioprine Dihydrate									
S	7467 (2)	2359 (1)	2230 (1)	684 (7)	41 (1)	24 (1)	49 (2)	41 (1)	7 (1)
N(1)	4199 (7)	3781 (2)	1949 (1)	439 (18)	38 (2)	20 (1)	16 (4)	16 (3)	5 (1)
C(2)	3293 (9)	4427 (2)	1533 (2)	407 (23)	40 (2)	23 (1)	4 (6)	17 (4)	1 (1)
N(3)	4123 (6)	4608 (2)	904 (1)	444 (18)	38 (2)	19 (1)	−7 (4)	4 (3)	3 (1)
C(4)	6072 (8)	4037 (2)	693 (2)	393 (21)	38 (2)	18 (1)	−26 (5)	8 (4)	0 (1)
C(5)	7167 (8)	3330 (2)	1072 (2)	402 (21)	35 (2)	20 (1)	−10 (5)	6 (4)	1 (1)
C(6)	6144 (8)	3236 (2)	1719 (2)	388 (21)	35 (2)	20 (1)	−10 (5)	−2 (4)	3 (1)
N(7)	9171 (7)	2874 (2)	705 (2)	500 (19)	45 (2)	21 (1)	14 (5)	22 (4)	−1 (1)
C(8)	9212 (9)	3308 (3)	126 (2)	468 (25)	49 (2)	22 (1)	−1 (6)	24 (4)	−5 (1)
N(9)	7442 (7)	4018 (2)	87 (2)	514 (21)	44 (2)	18 (1)	−3 (5)	10 (4)	4 (1)
C(10)	6080 (8)	2590 (2)	3021 (2)	454 (22)	31 (2)	20 (1)	18 (5)	10 (4)	4 (1)
C(11)	4253 (8)	2138 (2)	3424 (2)	467 (23)	32 (2)	20 (1)	7 (5)	2 (4)	5 (1)
N(12)	3919 (7)	2517 (2)	4041 (2)	603 (22)	47 (2)	23 (1)	4 (5)	22 (4)	3 (1)
C(13)	5568 (10)	3204 (3)	4023 (2)	660 (29)	42 (2)	22 (1)	1 (7)	9 (5)	−1 (1)
N(14)	6918 (7)	3282 (2)	3422 (2)	452 (19)	38 (2)	26 (1)	−6 (5)	12 (4)	4 (1)
C(15)	8877 (13)	3997 (3)	3249 (3)	598 (33)	46 (2)	38 (2)	−26 (8)	7 (7)	7 (2)
N(16)	2772 (8)	1344 (2)	3248 (2)	602 (23)	36 (2)	32 (1)	5 (5)	−1 (4)	7 (1)
O(17)	3382 (8)	959 (2)	2731 (2)	1056 (27)	41 (2)	34 (1)	−24 (5)	26 (4)	−4 (1)
O(18)	914 (7)	1093 (2)	3639 (2)	778 (23)	58 (2)	51 (1)	−73 (5)	70 (4)	6 (1)
O(W1)	1203 (14)	1165 (3)	822 (4)	2018 (65)	94 (4)	241 (6)	153 (12)	236 (16)	64 (4)
O(W2)	6145 (17)	340 (5)	685 (8)	1899 (77)	130 (6)	546 (16)	−23 (16)	−86 (25)	137 (8)
6-Methylmercaptopurine Trihydrate									
S	7926 (1)	2332 (1)	741 (1)	49 (1)	215 (1)	49 (1)	−5 (1)	22 (1)	−23 (1)
N(1)	5284 (1)	1946 (2)	−577 (1)	64 (1)	137 (2)	35 (1)	−4 (1)	19 (1)	0 (1)
C(2)	3928 (1)	2075 (2)	−823 (1)	64 (2)	140 (3)	34 (1)	−4 (2)	13 (1)	4 (1)
N(3)	3293 (1)	2636 (2)	−278 (1)	52 (1)	136 (2)	40 (1)	−2 (1)	14 (1)	5 (1)
C(4)	4189 (1)	3137 (2)	631 (1)	56 (1)	102 (3)	38 (1)	1 (2)	21 (1)	9 (1)
C(5)	5611 (1)	3100 (2)	983 (1)	52 (1)	114 (3)	34 (1)	−3 (2)	17 (1)	4 (1)
C(6)	6152 (1)	2462 (2)	338 (1)	54 (1)	102 (3)	38 (1)	−1 (1)	21 (1)	5 (1)
N(7)	6214 (1)	3711 (2)	1953 (1)	63 (1)	178 (3)	35 (1)	−6 (2)	20 (1)	−4 (1)
C(8)	5159 (1)	4084 (2)	2152 (1)	78 (2)	184 (3)	37 (1)	−8 (2)	29 (1)	−4 (1)
N(9)	3917 (1)	3765 (2)	1390 (1)	59 (1)	164 (3)	44 (1)	2 (2)	29 (1)	5 (1)
C(10)	8109 (2)	1489 (3)	−325 (1)	85 (2)	242 (5)	57 (1)	0 (2)	44 (1)	−10 (2)
O(W1)	375 (1)	3198 (2)	−1444 (1)	60 (1)	184 (3)	57 (1)	−6 (1)	16 (1)	2 (1)
O(W2)	1432 (1)	3908 (2)	1426 (1)	115 (2)	222 (3)	154 (2)	38 (2)	102 (1)	54 (2)
O(W3)	8956 (1)	5272 (2)	2916 (1)	67 (1)	197 (2)	46 (1)	−13 (1)	20 (1)	−2 (1)

[a] Values were multiplied by 10^4. Temperature factors are coefficients in the expression $T = \exp(-\beta_{11}h^2 - \beta_{22}k^2 - \beta_{33}l^2 - 2\beta_{12}hk - 2\beta_{13}hl - 2\beta_{23}kl)$. The values of the isotropic extinction parameter are $g = 0.040$ (6) for azathioprine dihydrate and $g = 0.079$ (3) for 6-methylmercaptopurine trihydrate.

to refine the trial structures (12, 13). The quantity minimized was $\Sigma w(F_0^2 - F_c^2/k^2)^2$, with k as a scale factor and the weight w equal to $1/\sigma^2(F_0^2)$. Scattering factors for the nonhydrogen atoms were from the "International Tables for X-ray Crystallography" (14), anomalous dispersion correction factors for these atoms were from Cromer and Liberman (15), and hydrogen-atom scattering factors were from Stewart *et al.* (16).

All hydrogen atoms except those bonded to the two water molecules in azathioprine dihydrate, which exhibited excessive thermal motion, were located in difference Fourier maps, which were calculated during the latter stages of refinement. Final cycles of refinement included all positional parameters, anisotropic temperature factors for the nonhydrogen atoms, isotropic temperature factors for the hydrogen atoms, and Zachariasen's (17) isotropic extinction parameter g [as formulated by Coppens and Hamilton (18)]. The final R index ($\Sigma||F_0| - |F_c||/\Sigma|F_0|$) is 0.079 for azathioprine dihydrate and 0.029 for 6-methylmercaptopurine trihydrate.

During the last cycle of refinement, no parameter shifted more than one-fifth of its estimated standard deviation. Final three-dimensional electron-density difference maps showed no peaks or troughs that exceeded 0.53 e/Å^3 for azathioprine dihydrate and 0.19 e/Å^3 for 6-methylmercaptopurine trihydrate.

RESULTS[3]

Table II lists the final heavy atom parameters and their estimated standard deviations. Table III gives the hydrogen atom parameters and their estimated standard deviations. For nonhydrogen atoms of azathioprine and 6-methylmercaptopurine, the estimated errors in positional coordinates are about 0.004 and 0.002 Å, respectively; for hydrogen atoms of the two purines, these errors are 0.05 and 0.03 Å, respectively.

Figure 1 shows the conformations, thermal ellipsoids, and bond lengths for azathioprine and 6-methylmercaptopurine. Bond angles are listed in Table IV. Both molecules crystallize in the N(9)-

Table III—Hydrogen Atom Parameters and Their Standard Deviations[a]

Atom	x	y	z	B, Å^2
Azathioprine Dihydrate				
H(C2)	200 (7)	481 (2)	171 (1)	2.6 (0.7)
H(C8)	1032 (8)	318 (2)	−22 (2)	4.3 (0.9)
H(N9)	710 (9)	441 (2)	−26 (2)	6.0 (1.1)
H(C13)	577 (8)	364 (2)	436 (2)	4.3 (0.9)
H(C15)	1047 (10)	382 (3)	293 (2)	6.6 (1.2)
H′(C15)	959 (10)	421 (3)	366 (2)	7.1 (1.5)
H″(C15)	770 (10)	441 (3)	301 (2)	7.4 (1.4)
6-Methylmercaptopurine Trihydrate				
H(C2)	335 (2)	167 (2)	−148 (1)	3.5 (0.3)
H(C8)	524 (1)	454 (2)	278 (1)	3.2 (0.3)
H(N9)	310 (2)	391 (3)	139 (1)	4.6 (0.4)
H(C10)	906 (2)	156 (4)	−17 (2)	7.0 (0.5)
H′(C10)	768 (2)	228 (3)	−89 (2)	6.7 (0.6)
H″(C10)	777 (2)	23 (4)	−49 (2)	7.2 (0.6)
H(W1)	3 (2)	210 (3)	−159 (1)	4.8 (0.5)
H′(W1)	110 (2)	303 (3)	−106 (2)	5.3 (0.5)
H(W2)	123 (2)	290 (3)	154 (2)	6.3 (0.6)
H′(W2)	91 (2)	469 (3)	138 (2)	6.6 (0.6)
H(W3)	818 (2)	484 (3)	264 (1)	5.0 (0.5)
H′(W3)	914 (2)	569 (3)	247 (1)	5.0 (0.5)

[a] Positional parameters were multiplied by 10^3.

[3] Tables of observed and calculated structure factors will be furnished by the authors upon request.

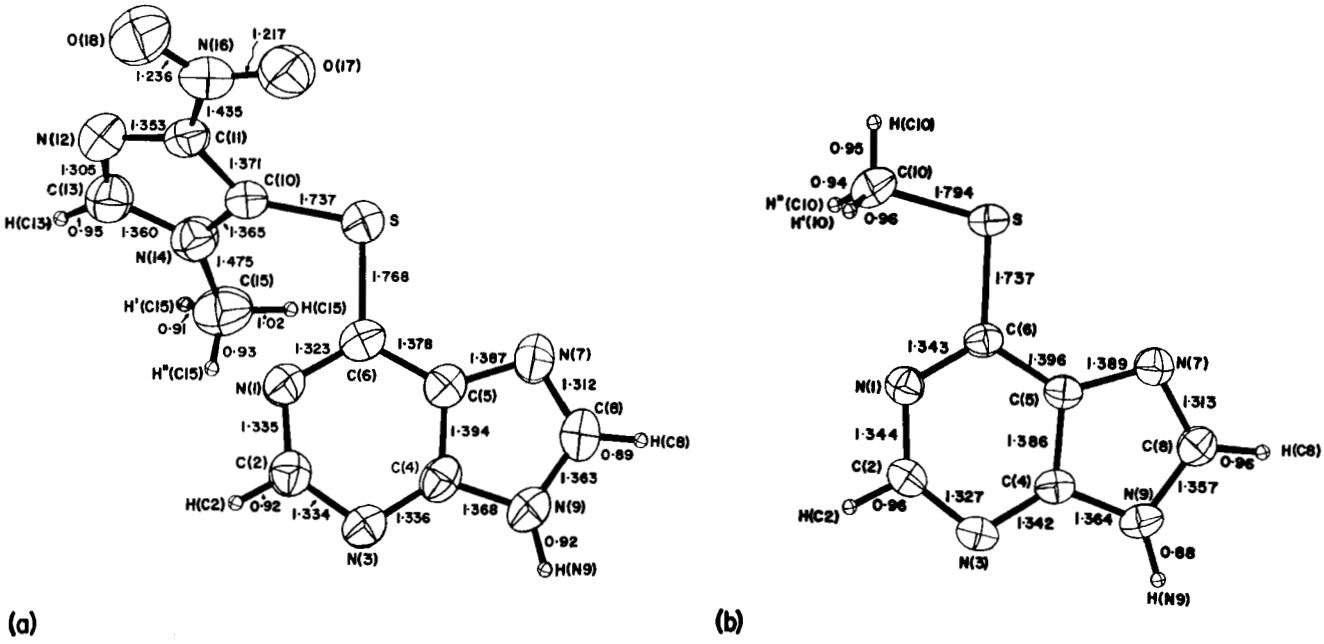


Figure 1—*Perspective view of the molecules, including bond lengths: (a) azathioprine, and (b) 6-methylmercaptopurine. Estimated standard deviations in bond lengths between nonhydrogen atoms are about 0.006 and 0.003 Å for the azathioprine and 6-methylmercaptopurine structures, respectively. Estimated standard deviations in bond lengths involving hydrogen atoms are about 0.06 and 0.03 Å in the azathioprine and 6-methylmercaptopurine structures, respectively. Nonhydrogen atoms are represented by thermal ellipsoids defined by the principal axes of thermal vibration and scaled to include 50% probability. Hydrogen atoms are represented by spheres of 0.07 Å radius. This drawing, as well as Figs. 2 and 4, was prepared by using the computer program ORTEP (32).*

H tautomer form and display a conformation in which the substituents bonded to the sulfur atom (nitroimidazolyl and methyl groups) are directed away from the imidazole moiety of the base [the S-C(10) bond is *trans* to the C(5)-C(6) bond]. It appears that nitroimidazolyl and methyl substituents exert different influences on the geometry of the purine moieties. The most significant differences between corresponding bond lengths and angles in the two structures involve the sulfur atom and/or atom C(6), and it is likely that they are due to inductive effects of the substituents.

Table IV—Bond Angles Involving Nonhydrogen Atoms[a]

	Azathioprine Dihydrate	6-Methylmercaptopurine Trihydrate
C(6)-N(1)-C(2)	117.6°	117.6°
N(1)-C(2)-N(3)	128.2°	129.0°
C(2)-N(3)-C(4)	112.0°	111.8°
N(3)-C(4)-C(5)	125.5°	125.6°
N(3)-C(4)-N(9)	128.8°	128.3°
C(5)-C(4)-N(9)	105.7°	106.1°
C(4)-C(5)-C(6)	115.8°	117.0°
C(4)-C(5)-N(7)	110.8°	110.1°
C(6)-C(5)-N(7)	133.4°	132.9°
C(5)-C(6)-N(1)	120.9°	119.0°
C(5)-C(6)-S	118.2°	119.3°
N(1)-C(6)-S	120.9°	121.6°
C(5)-N(7)-C(8)	103.0°	103.7°
N(7)-C(8)-N(9)	114.9°	114.0°
C(4)-N(9)-C(8)	105.6°	106.1°
C(6)-S-C(10)	102.1°	102.9°
C(11)-C(10)-S	132.0°	—
C(11)-C(10)-N(14)	103.5°	—
N(14)-C(10)-S	124.2°	—
C(10)-C(11)-N(12)	113.0°	—
C(10)-C(11)-N(16)	126.6°	—
N(12)-C(11)-N(16)	120.3°	—
C(11)-N(12)-C(13)	103.4°	—
N(12)-C(13)-N(14)	112.8°	—
C(13)-N(14)-C(10)	107.2°	—
C(13)-N(14)-C(15)	125.1°	—
C(10)-N(14)-C(15)	127.7°	—
C(11)-N(16)-O(17)	119.2°	—
C(11)-N(16)-O(18)	117.0°	—
O(17)-N(16)-O(18)	123.8°	—

[a] Estimated standard deviations are about 0.3° for azathioprine and 0.2° for 6-methylmercaptopurine.

The purine rings are almost planar, and none of the atoms deviates from the least-squares purine planes by more than 0.015 Å in azathioprine and 0.008 Å in 6-methylmercaptopurine. In azathioprine, atoms S and C(10) are displaced from the purine plane by 0.021 and 0.307 Å, respectively; in 6-methylmercaptopurine, these two atoms are displaced by 0.036 and 0.023 Å, respectively. The large displacement of C(10) of azathioprine is probably due to steric hindrance between the bulky nitroimidazolyl moiety and the purine ring.

The crystal-packing scheme for azathioprine is depicted in Fig. 2. Hydrogen-bond distances and angles are listed in Table V. Azathioprine molecules are joined by pairs of N(9)-H···N(3) hydrogen bonds across crystallographic inversion centers. The purine moieties are stacked in the *a* direction, with adjacent bases along *a* being separated by an interplanar spacing of 3.29 Å; the stacking pattern, as viewed perpendicular to the plane of the purine moiety, is shown in Fig. 3*a*. The water molecules, which display extremely large apparent thermal motion, are hydrogen bonded together, resulting in channels that run parallel to the *a* axis.

Figure 4 depicts the crystal-packing scheme for 6-methylmercaptopurine. Hydrogen-bond dimensions are included in Table V. The water molecules are hydrogen bonded together and to the

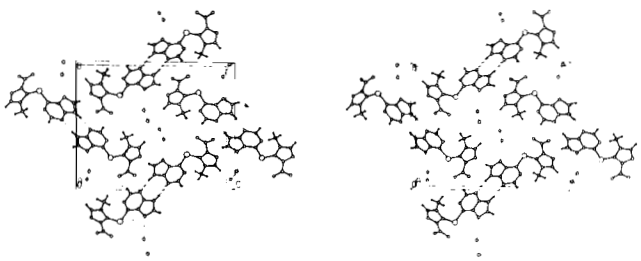


Figure 2—*Stereo drawing of the crystal packing of azathioprine dihydrate, as viewed down the* a *axis. The water molecules are represented by circles. Hydrogen bonds are depicted as fine lines.*

Table V—Hydrogen Bond Distances and Angles[a]

Donor Atom	Hydrogen Atom	Acceptor Atom	Distances, Å		Donor–Hydrogen–Acceptor Angle
			Donor–Acceptor	Hydrogen–Acceptor	
Azathioprine Dihydrate					
N(9)	H(N9)	N(3) e	2.929	2.02	169°
O(W1)[b]		N(7) b	2.810		
O(W1)[b]		O(W2) a	2.618		
O(W1)[b]		O(W2) b	2.635		
O(W2)[b]		O(W1) a	2.618		
O(W2)[b]		O(W1) c	2.635		
O(W2)[b]		O(W2) d	2.992		
6-Methylmercaptopurine Trihydrate					
N(9)	H(N9)	O(W2) a	2.689	1.81	173°
O(W1)	H(W1)	O(W3) f	2.804	1.98	171°
O(W1)	H′(W1)	N(3) a	2.893	2.15	166°
O(W2)	H(W2)	O(W3) g	2.817	2.05	169°
O(W2)	H′(W2)	O(W1) h	2.807	2.04	173°
O(W3)	H(W3)	N(7) a	2.884	2.07	179°
O(W3)	H′(W3)	O(W1) e	2.808	1.98	177°

[a] Symmetry codes—a: x, y, z; b: x − 1, y, z; c: x + 1, y, z; d: −x + 1, −y, −z; e: −x + 1, −y + 1, −z; f: x − 1, −y + ½, z − ½; g: −x + 1, y − ½, −z + ½; and h: −x, −y + 1, −z. [b] Possible hydrogen-bonded contacts. Positions of these hydrogen atoms could not be determined.

N(3), N(7), and N(9) sites. The channels of hydrogen-bonded water molecules run in the *b* direction. There are no hydrogen bonds between molecules of 6-methylmercaptopurine. The bases form planar ribbons running in the *c* direction and lying nearly parallel to the *ac* plane. The ribbons of bases are stacked in the *b* direction, with interpurine stacking distances of 3.33 and 3.24 Å. The stacking pattern is shown in Fig. 3*b*.

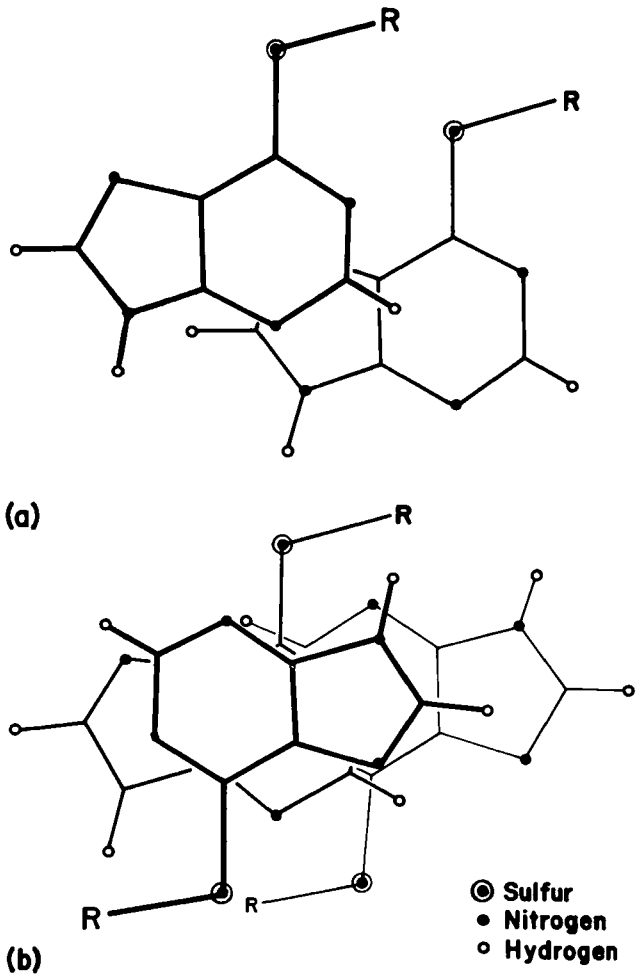


Figure 3—*Base stacking patterns, as viewed perpendicular to the planes of the purine rings. Key: (a), azathioprine; and (b), 6-methylmercaptopurine.*

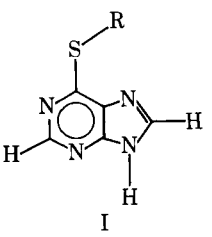
DISCUSSION

Mercaptopurine derivatives with a substituent bonded to the sulfur atom would be expected to assume one of two conformations that are related to each other by a rotation of 180° around the C(6)-S bond. To maintain partial double-bond character in the C(6)-S bond, the mercapto group must be approximately coplanar with the purine moiety; therefore, the substituent must point either toward (Structure I) or away from (Structure II) the imidazole ring of the base.

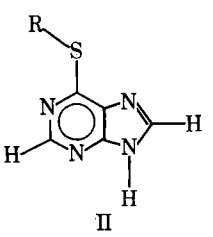
Examination of N^6-methyladenine (19) and other N^6-monosubstituted adenine derivatives (20–22) revealed that even relatively small aliphatic groups at the N(6) position tend to point away from the imidazole ring [*trans* to the C(5)-C(6) bond]. Molecular orbital calculations for N^6-monosubstituted adenine derivatives indicate that this *trans*-conformation is the more stable (23), and examination of space-filling molecular models suggests that the alternate conformation (in which the substituent is positioned *cis* to the imidazole moiety) is destabilized by interference between the substituent and atom N(7). Molecular models of azathioprine and 6-methylmercaptopurine show that similar interactions occur between atom N(7) and the substituents of these compounds when the substituents are *cis* to the imidazole moiety, so it is not surprising to find that both azathioprine and 6-methylmercaptopurine assume the *trans*-conformation depicted in Structure II.

Azathioprine and 6-methylmercaptopurine both crystallize in the N(9)-H tautomer form, the same tautomer found in crystals of N^6-(Δ^2-isopentenyl)-2-methylmercaptoadenine (24), another derivative that contains a substituent bonded to the sulfur atom. In contrast, 6-mercaptopurine (25, 26), 6-thioguanine (27), and 2-thio-6-methylpurine (28, 29), all of which possess unsubstituted thio groups, crystallize as N(7)-H tautomers.

It appears that the sulfur atoms of 6-methylmercaptopurine and azathioprine may be poor hydrogen bond acceptors, since neither of these atoms participates in hydrogen bonding in the crystal structures. Similarly, in the crystal structure of N^6-(Δ^2-isopentenyl)-2-methylmercaptoadenine (24), the sulfur atom is not in-



I



II

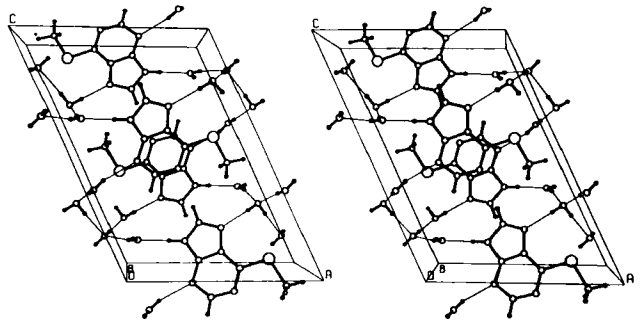


Figure 4—*Stereo drawing of the crystal packing of 6-methylmercaptopurine trihydrate, as viewed down the* b *axis. Hydrogen bonds are depicted as fine lines.*

volved in hydrogen bonding. In contrast, the unsubstituted thio groups are hydrogen bond acceptors in the crystal structures of 6-mercaptopurine (25, 26), 6-thiopurine riboside (30), 6-thioguanine (27), 6-thioguanosine (31), and 2-thio-6-methylpurine (28, 29). These crystallographic results suggest that the addition of substituents to the sulfur atom of 6-mercaptopurine may have an appreciable effect on the hydrogen-bonding properties of the base.

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[x] To whom inquiries should be directed.