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Crystal structure of 6-[(1-methyl-4-nitroimidazol-5-yl)thio] purine*

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Abstract. 6-[(1-methyl-4-nitroimidazol-5-yl)thio] purine, is an immunosuppressant derivative of the antitumour drug, 6-mercaptopurine. Crystals are monoclinic with $a = 4{\cdot}488(2)$, $b = 31{\cdot}886(4)$, $c = 8{\cdot}067(2)$Å and $\beta = 105{\cdot}99(2)°$ in the space group $P2_1/c$. The crystal structure was solved by direct methods using diffractometer data and refined by least squares to an R-index of 0·065 for 502 observed reflections. The molecule crystallizes in the N(9)-H tautomer form, in contrast to the N(7)-H tautomer form found in crystals of 6-mercaptopurine and assume a conformation in which the substituents on the sulphur atom are directed away from imidazole moiety of the purine.

Keywords. Mercaptopurine; crystal structure; direct methods; immunosuppressor.

1. Introduction

6-[(1-methyl-4-nitroimidazol-5-yl)thio] purine, azathioprine (AZTP) which is also known as imuran, is a purine analogue (figure 1). After its administration, it is converted to 6-mercaptopurine (6-MP) (which is effective in cancer chemotherapy). It is an immunosuppressant agent and has been employed for the treatment of '*rheumatoid arthritis*' (Wang 1979) and it has a significant anti-inflammatory action. AZTP can be converted *in vivo* to 6-MP by non-enzymic thiolysis and thereafter its mechanism of action is the same as that of 6-MP (Gale *et al* 1972). With the improved understanding of the drug action in view, the crystal structure of AZTP was analysed.

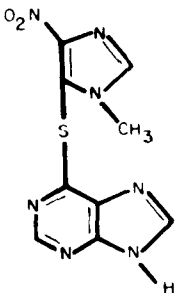

Figure 1. AZTP molecule.

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2. Experimental

Azathioprine (AZTP) (Sigma Chemical Company, Missouri, USA); $C_9H_7N_7O_2S$; M_r 277·3; small yellow flakes (from acetone solution); crystal dimension: 0·7 × 0·1 × 0·7 mm.; Enraf-Nonius CAD4-11M diffractometer; lattice parameters from 20 reflections ($12° < 2\theta < 26°$); monoclinic; $a = 4·488(2)$, $b = 31·886(4)$, $c = 8·067(2)$ Å, $\beta = 105·99(2)°$, $V = 1149·5$Å^3; $Z = 4$; D_m: benzene-carbontetrachloride mixture: 1·59; D_c: 1·60 Mgm^{-3}; m.p. = 413 K. Data collection: h, k, ± 1 with $2\theta \leqslant 48°$, MoK_α radiation ($\lambda = 0·7107$Å); graphite monochromator; $\omega - 2\theta$ scan mode, three standard reflections every 2000 seconds of x-ray exposure; 1912 independent, 502 with $F > 3\sigma(F)$, Lp correction, absorption and decay not applied; $P2_1/c$, general positions: $\pm(x, y, z; x, 1/2 - y, 1/2 + z)$ from systematic absences OkO, $k \neq 2n$ and hOl, $l \neq 2n$; direct methods (MULTAN-78; Main *et al* 1978; $176E > 1.62$), anisotropic full matrix for non-hydrogen atoms (LALS; Gantzel *et al* 1961); H from stereochemical considerations

Table 1. Positional coordinates with standard deviations for non-hydrogen atoms.

Atom	x	y	z	Beq (A)^2
S	0·540 (1)	0·3863 (1)	0·4318 (6)	3·3 (5)
N (1)	0·353 (3)	0·3885 (4)	0·723 (2)	2·1 (5)
C (2)	0·315 (4)	0·4101 (4)	0·856 (2)	2·1 (5)
N(3)	0·422 (3)	0·4466 (4)	0·915 (1)	2·0 (6)
C(4)	0·575 (3)	0·4655 (5)	0·810 (2)	2·4 (5)
C(5)	0·636 (3)	0·4462 (5)	0·667 (1)	2·4 (5)
C(6)	0·510 (3)	0·4086 (5)	0·628 (2)	2·5 (4)
N(7)	0·796 (3)	0·4711 (3)	0·587 (2)	2·2 (3)
C(8)	0·837 (3)	0·5039 (5)	0·684 (2)	2·6 (3)
N(9)	0·711 (3)	0·5005 (3)	0·822 (1)	3·0 (3)
C(10)	0·382 (4)	0·3377 (5)	0·442 (2)	3·3 (5)
C(11)	0·144 (5)	0·3168 (6)	0·334 (2)	2·5 (4)
N(12)	0·118 (5)	0·2780 (5)	0·373 (3)	2·7 (5)
C(13)	0·351 (7)	0·2754 (7)	0·512 (3)	3·6 (5)
N(14)	0·530 (4)	0·3086 (4)	0·559 (2)	2·9 (6)
C(15)	0·797 (5)	0·3125 (5)	0·710 (2)	3·4 (5)
N(16)	−0·082 (4)	0·3350 (5)	0·185 (2)	3·2 (6)
O(17)	−0.036 (3)	0·3696 (4)	0·136 (2)	3·7 (3)
O(18)	−0·316 (4)	0·3156 (5)	0·119 (2)	3·5 (3)

Table 2. Positional coordinates with standard deviations for hydrogen atoms

	x	y	z	Biso
H (C2)	0·25 (3)	0·385 (4)	0·96 (2)	2·8
H (C8)	0·97 (3)	0·537 (4)	0·66 (2)	3·2
H (N9)	0·64 (3)	0·515 (4)	0·87 (2)	3·7
H (C13)	0·44 (3)	0·246 (4)	0·59 (2)	4·6
H (C15a)	0·73 (3)	0·336 (4)	0·82 (2)	4·2
H (C15b)	0·82 (3)	0·281 (4)	0·73 (2)	4·2
H (C15c)	0·94 (3)	0·345 (5)	0·68 (2)	4·2

and verified from ΔF synthesis, only positions refined. $R = \Sigma[||F_o| - |F_c||]/\Sigma[|F_o|] = 0{\cdot}065$. $\Sigma w[|F_o| - |F_c|]^2$ minimised, where $w = [3{\cdot}5 + 1{\cdot}0|F_o| + 0{\cdot}02|F_o|^2]^{-1}$; final ΔF map featureless, $F(000) = 428{\cdot}0$. The atomic scattering factors were taken from the International Tables for X-ray Crystallography (1974). The final fractional coordinates for the non-H atoms and H atoms are listed in tables 1 and 2 respectively. Final anisotropic thermal parameters for all the non-H atoms and the values of observed and calculated structure factors can be supplied by the author on request.

3. Discussion

A perspective view of the molecule is shown in figure 2 (Johnson 1965). Mercaptopurine derivatives with a substituent bonded to the sulphur atom would be expected to have 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 coplanar with the purine moiety; therefore, the substituent must point either toward or away from the imidazole ring of the base. Careful examination of N^6-monosubstituted adenine derivatives (Sternglanz and Bugg 1973; Bugg and Thewalt 1972; Thewalt and Bugg 1972a) indicates 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]. However, molecular orbital calculations indicate that this *trans*-conformation is the stable one (Berthod and Pullman 1973). Further, an examination of the space-filling molecular model suggests that the alternative conformation where the substituent is *cis* to the imidazole moiety is unstable on account of the steric interactions between the substituent and the atom N(7). The same is true about the structure of AZTP reported here. The S–C(10) bond is *trans* to the C(5)–C(6) bond [C(5)–C(6)–S–C(10) = 175°] as the substituent bonded to the sulphur atom is directed away from the imidazole moiety of the base. Bond distances and angles of AZTP are listed in table 3. The two purine rings are almost planar. The significant difference between S–C(6) (1·77Å) and S–C(10) (1·72Å) bond lengths may be due to the effect of substituents.

The crystal structure of AZTP viewed down the *a* axis is shown in figure 3. The molecules are joined by pairs of N(9)–H . . . . N(3) hydrogen bonds [N(9)–H(N9)

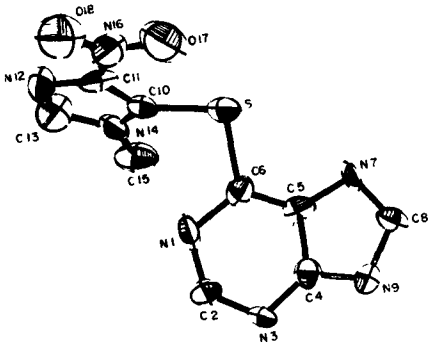

Figure 2. Perspective view of AZTP molecule with thermal ellipsoids scaled to 50% probability.

Table 3. Molecular dimensions with esd's in parentheses.

Bond distances (Å):			
S–C(6)	1·77(2)	S–C(10)	1·72(2)
C(5)–C(6)	1·32(2)	C(5)–C(4)	1·39(2)
C(5)–C(7)	1·35(2)	N(7)–C(8)	1·29(2)
C(8)–N(9)	1·38(2)	N(9)–C(4)	1·26(2)
C(4)–N(3)	1·37(2)	N(3)–C(2)	1·29(2)
C(2)–N(1)	1·33(2)	N(1)–C(6)	1·34(2)
C(10)–C(11)	1·35(2)	C(11)–N(16)	1·46(3)
N(16)–O(17)	1·21(3)	N(16)–O(18)	1·21(2)
C(11)–N(12)	1·29(2)	N(12)–C(13)	1·30(3)
C(13)–N(14)	1·32(3)	N(14)–C(15)	1·46(2)
N(14)–C(10)	1·35(2)		
Bond angles (deg):			
C(6)–S–C(10)	100·5(8)	C(6)–N(1)–C(2)	115(1)
C(5)–N(7)–C(8)	101(1)	N(7)–C(5)–C(4)	113(1)
N(7)–C(5)–C(6)	132(1)	C(4)–C(5)–C(6)	115(1)
N(7)–C(8)–N(9)	114(1)	C(5)–C(4)–N(3)	124(1)
N(9)–C(4)–N(3)	131(1)	C(4)–N(3)–C(2)	112(1)
S–C(6)–N(1)	120(1)	S–C(6)–C(5)	116(1)
N(1)–C(6)–C(5)	123(1)	N(1)–C(2)–N(3)	130(1)
C(10)–C(11)–N(12)	115(2)	C(10)–C(11)–N(16)	126(2)
N(12)–C(11)–N(16)	119(2)	S–C(10)–C(11)	132(1)
S–C(10)–N(14)	121(1)	C(11)–C(10)–N(14)	105(1)
N(14)–C(13)–N(12)	118(2)	C(13)–N(12)–C(11)	100(2)
C(10)–N(14)–C(13)	102(2)	C(10)–N(14)–C(15)	131(1)
C(13)–N(14)–C(15)	127(2)	O(17)–N(16)–C(11)	119(2)
O(17)–N(16)–O(18)	122(2)	C(11)–N(16)–O(18)	119(2)
C(5)–C(4)–N(9)	105(1)	C(8)–N(9)–C(4)	108(1)

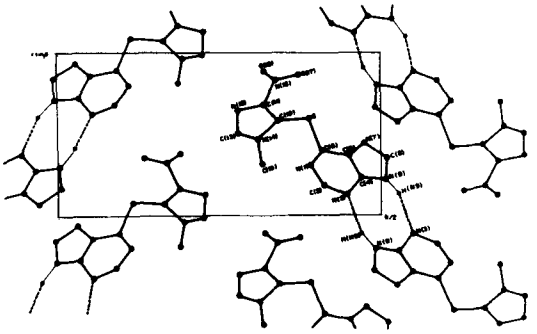

Figure 3. Molecular packing of AZTP along *a*.

= 0·85, N(9) . . . N(3) = 2·90, N(3) . . . H(N9) = 2·18Å and N(9)–H(N9) . . . N(3) = 162·2°] across a crystallographic inversion centre to yield hydrogen bonded dimers. AZTP exists in the N(9)–H tautomer form, similar to that found in crystals of N^6-(Δ^2-isopentenyl)-2-methyl-mercaptoadenine (Mc Mullan and Sundaralingam 1971), a derivative which contains a substituent bonded to sulphur atom. On the other hand, 6-

mercaptopurine (Sletten *et al* 1969; Brown 1969) which possess unsubstituted thio groups, crystallize as N(7)–H tautomers. However, no general straightforward correlation is known between the intrinsic stabilities of the isolated tautomeric forms and their presence in the crystals of the substances (Pullman and Pullman 1971). The sulphur atom in AZTP is a poor hydrogen bond acceptor. A similar observation was made in the crystal structure of N^6-(Δ^2-isopentenyl)-2-methyl-mercaptoadenine (Mc Mullan and Sundaralingam 1971). In contrast, the unsubstituted thio groups are hydrogen bond acceptors in the crystal structures of 6-thioguanosine (Thewalt and Bugg 1972b), 6-thioguanine (Bugg and Thewalt 1970) and 2-thio-6-methyl purine (Srinivasan and Chandrasekharan 1968; Donohue 1969) thus suggesting that the addition of substituents to the sulphur atom of 6-mercaptopurine may have an important effect on the hydrogen bonding properties of the base.

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