

Crystal and molecular structure of an isostere of purine ring system: 7-benzylamino-2-methylmercaptothiazolo [5,4-d] pyrimidine

Amitabha De and P. Roychowdhury*

Department of Physics, University College of Science,
92 Acharya Parafula Chandra Road, Calcutta-700009, India

Received: July 17, 1988

Crystal structure | Thiazolo [5,4-d] pyrimidine

Abstract. The crystal and molecular structure of the title compound has been established by means of the X-ray diffraction method on a single crystal using MoK_α radiation. The crystals are monoclinic, space group $P2_1/a$ with $a = 8.745(2)$, $b = 13.230(8)$, $c = 11.729(2)$ Å, $\beta = 94.06(2)^\circ$. The structure was solved by the heavy-atom method, and refined by full-matrix least squares to a final R value of 0.035 with 1787 'observed' reflections. The five- and six-membered ring are planar and inclined to one another at 0.9° . In the five-membered ring the average C–S bond distance is 1.75 Å and the C–S–C angle is 87.9° .

Introduction

The observation that antimicrobial action (against *Lactobacillus casei*) is a general property of certain functional derivatives of condensed pyrimidine systems promoted the desire to study such derivatives. The thiazolo [5,4-d] pyrimidine system is an isostere of purine where '9–N' of purine is replaced by 'S'. Its value as an antipurine has earlier been recognised (Elion, Lange and Hitchings, 1956). The minor chemical modifications of replacing a purine carbon atom by a nitrogen atom has the effect of bringing about great changes in the biological activity of the base and nucleic acid components. The potential value of the compound as an anticancer agent added impetus to our studies.

* To whom all correspondence should be sent.

Table 1. Crystal data

Molecular formula	$C_{13}H_{12}N_4S_2$	Radiation (λ)	0.7107 Å
M_r	288.38	$\mu(\text{MoK}\alpha)$ (cm^{-1})	3.7
Space group	$P2_1/a$	Temperature (K)	297
a (Å)	8.745(2)	Scan type	$\omega/2\theta$
b (Å)	13.230(8)	Collection range (deg)	$2 \leq \theta \leq 25$
c (Å)	11.729(2)	Number of unique reflections	2359
β (deg)	94.06(2) $^\circ$	Number of data with $I \geq 3\sigma(I)$	1787
V_c (Å 3)	1353.61(9)	R	0.035
Z	4	$F(000)$	600
Density (calculated) (g cm $^{-3}$)	1.415		
Density (measured) (g cm $^{-3}$)	1.420		

Experimental

Transparent needle-shaped yellow crystals were grown from ethanol by slow evaporation at room temperature. Preliminary oscillation and Weissenberg photographs indicated a monoclinic crystal with systematic absences $OkO:k = \text{odd}$; $hOl:h = \text{odd}$, consistent with the space group $P2_1/a$. A crystal of dimensions about $0.40 \times 0.275 \times 0.125$ mm was selected for the intensity data collection on a CAD-4 diffractometer, using graphite-monochromatized $\text{MoK}\alpha$ radiation. The accurate cell parameters were determined by a least-squares refinement of the setting angles of 25 reflections lying on the range $14^\circ \leq \theta \leq 18^\circ$. An $\omega/2\theta$ -scan technique was used to record intensities of all reflections for which $2^\circ \leq \theta \leq 25^\circ$ with a scan width of $(0.60 + 0.35 \tan\theta)$. A total of 2359 unique reflections was measured in the range $h = -10$ to 10, $k = 0$ to 15, $l = 0$ to 13 of which 1787 had $I \geq 3\sigma(I)$ and were used for the structure determination and refinement. The intensities were corrected for the Lorentz and polarization factors, but not for absorption. During the data collection three standard reflections were used to monitor the centering and the stability of the crystal. No significant change in intensity (maximum variation $< 3\%$) was observed. Table 1 shows the crystal data.

Structure determination and refinement

The structure was solved by the heavy-atom method. The positional parameters for the two sulphur atom were determined from a three-dimensional Patterson map and all the remaining non-hydrogen atoms were obtained from a successive sulphur-phased Fourier synthesis. Full-matrix least-squares refinement (Busing, Martin and Levy, 1962), first using isotropic and then anisotropic thermal parameters, gave an R value of

Table 2. Fractional atomic coordinates and thermal parameters with estimated standard deviations in parentheses [the equivalent isotropic temperature factors B_{eq} (\AA^2) (Hamilton, 1959)] for non-hydrogen atoms.

Atoms	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}
S(1)	0.52202(8)	0.47834(5)	0.28041(6)	4.37
S(2)	0.38901(8)	0.67766(5)	0.21040(6)	4.92
N(1)	0.5987(2)	0.6447(1)	0.3906(2)	3.46
N(2)	0.7199(2)	0.3836(2)	0.4367(2)	4.12
N(3)	0.8520(2)	0.4855(2)	0.5831(2)	4.12
N(4)	0.8240(3)	0.6584(2)	0.5921(2)	4.37
C(1)	0.5130(3)	0.6098(2)	0.3055(2)	3.62
C(2)	0.6802(3)	0.5652(2)	0.4438(2)	3.23
C(3)	0.6541(3)	0.4702(2)	0.3975(2)	3.50
C(4)	0.8151(3)	0.3994(2)	0.5287(2)	4.41
C(5)	0.7855(3)	0.5706(2)	0.5409(2)	3.55
C(6)	0.9272(3)	0.6658(2)	0.6954(3)	4.55
C(7)	0.8476(3)	0.6473(2)	0.8028(2)	4.12
C(8)	0.8602(4)	0.5548(2)	0.8592(3)	5.23
C(9)	0.7807(5)	0.5356(3)	0.9545(3)	6.59
C(10)	0.6877(4)	0.6100(4)	0.9948(3)	7.03
C(11)	0.6742(4)	0.7024(3)	0.9414(3)	6.44
C(12)	0.7552(4)	0.7211(2)	0.8466(3)	5.10
C(13)	0.4339(4)	0.8043(2)	0.2533(4)	5.72

0.077. All the hydrogen atoms were located from the difference Fourier synthesis and were refined isotropically. The refinement was stopped at $R = 0.035$ when all the least-squares shifts were less than the corresponding standard deviations ($\text{shift}/\sigma < 0.05$). The function minimized was $\sum \omega(|F_o| - |F_c|)^2$ with $\omega = 1/\sigma^2|F_o|$. A final difference Fourier map showed peaks lying between -0.27 to $+0.31 e\text{\AA}^{-3}$. The scattering factors for the non-hydrogen atoms and that for the H-atoms were taken from Cromer and Waber (1965) and Stewart et al. (1965), respectively.

Results and discussions

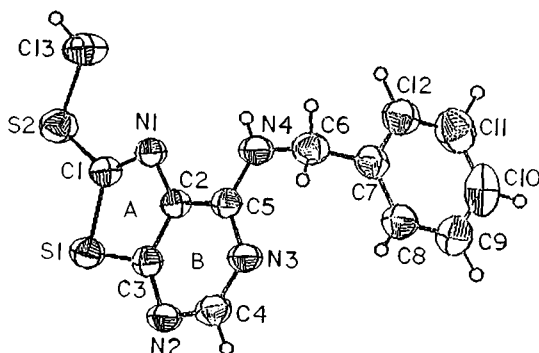
The final atomic position are listed in Tables 2 and 3. Figure 1 represents a perspective view of the molecule with the atomic numbering scheme.¹

The molecule consists of a benzylamino and methylmercapto substituted thiazolo [5,4-d] pyrimidine base and bears a strong resemblance to purine. The thiazolo [5,4-d] pyrimidine system is an isostere of purine.

¹ Additional material to this paper can be ordered from the Fachinformationszentrum Energie-Physik-Mathematik, D-7514 Eggenstein-Leopoldshafen 2, FRG. Please quote reference no. CSD 53505, the names of the authors and the title of the paper.

Table 3. Fractional atomic co-ordinates and thermal parameters [the isotropic temperature factors B (\AA^2)] for hydrogen atoms.

Atoms	x	y	z	B
H(4)	0.864(2)	0.340(2)	0.559(2)	3.33
H(8)	0.931(3)	0.509(2)	0.833(2)	6.00
H(9)	0.796(3)	0.475(2)	0.998(3)	9.11
H(10)	0.626(3)	0.594(2)	1.059(2)	8.81
H(11)	0.609(3)	0.765(2)	0.974(3)	12.32
H(12)	0.750(3)	0.789(2)	0.806(2)	6.26
H(N)4	0.783(3)	0.708(2)	0.569(2)	3.31
H(6)1	0.970(2)	0.735(2)	0.695(2)	4.74
H(6)2	1.017(3)	0.616(2)	0.689(2)	5.07
H(13)1	0.412(3)	0.814(2)	0.326(3)	9.20
H(13)2	0.386(5)	0.852(4)	0.106(4)	3.85
H(13)3	0.552(4)	0.815(3)	0.245(3)	9.82

**Fig. 1.** Molecular conformation and numbering of atoms in 7-benzylamino-2-methylmercaptopyrimidino [5,4-d] pyrimidine.

There are actually no significant differences in the six-membered rings of the two compounds but in the five-membered ring the '9-N' of purine is replaced by 'S'. The bond distance and angles of the base portion are presented in Figure 2a. For comparison, the bond distances, bond angles and formal bonding diagram of unsubstituted purine (Watson, Sweet and Marsh, 1965) are presented in Figure 2b.

In both the cases in the five-membered rings there are shortened bonds which indicate some degree of localisation of double bond character between atoms which are formally double bonded in the structural diagrams (Figs. 2a and 2b). However, none of the ring bonds is as short as an isolated double bond or as long as an isolated single bond.

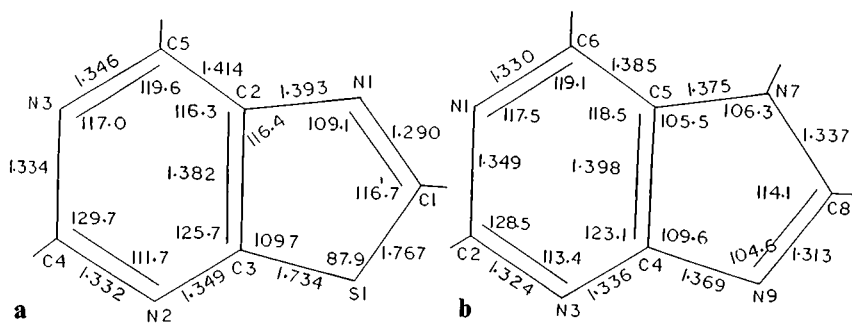


Fig. 2a. Bond distances and angles of the base portion of 7-benzylamino-2-methylmercaptothiazolo [5,4-d] pyrimidine.

Fig. 2b. Bond distances and angles of unsubstituted purine (Watson, Sweet and Marsh, 1965).

The magnitude of the valence angle of nitrogen atoms in the six-membered hetero-cyclic rings is dependent upon the extra-annular attachment to the nitrogen atom (Singh, 1965). Due to an extra-annular hydrogen attachment, the bond angles at nitrogen are markedly extended beyond that of nitrogen without any such attachment. It was noticed by Singh that in the pyrimidine ring when there is no extra-annular attachment to the nitrogen atom, the bond angles at the nitrogen atoms varies from 115° to 116° . However, in the present structure the same angle was found to be 111.7° . This was also observed by Sobell and Tomita (1964).

The nine atoms of the rings A and B are nearly coplanar with no atom deviating from the best least-squares plane by more than $0.011(2)$ Å. The thiazolo portion of the ring (A) lies approximately in the best least-squares planes of the pyrimidine moiety (B). The angle between the pyrimidine plane and the thiazolo plane is only 0.9° . The benzene ring is also nearly planar.

Although lacking unshared electron pairs, certain substituents like methyl or tert-butyl groups are able to cause a perturbation of the π -electron system of the phenyl ring very much like that caused by π -donors. The effect of π -electron releasing substituents on the geometry of the benzene ring has so far been attributed mainly due to hyperconjugation. But various Molecular Orbital (MO) calculations carried out on toluene (Libit and Hoffmann, 1974) support the idea that the π -electron system of the ring is polarised by the methyl group with little net electron transfer. The present structure seemed to be in agreement with this.

The packing of the molecules is shown in Figures 3 and 4. Two distinct types of ring stacking are observed; heterocyclic systems stack with the heterocyclic systems while the phenyl rings stack with the phenyl rings. The planar molecules are stacked in parallel sheets with an interplanar distance

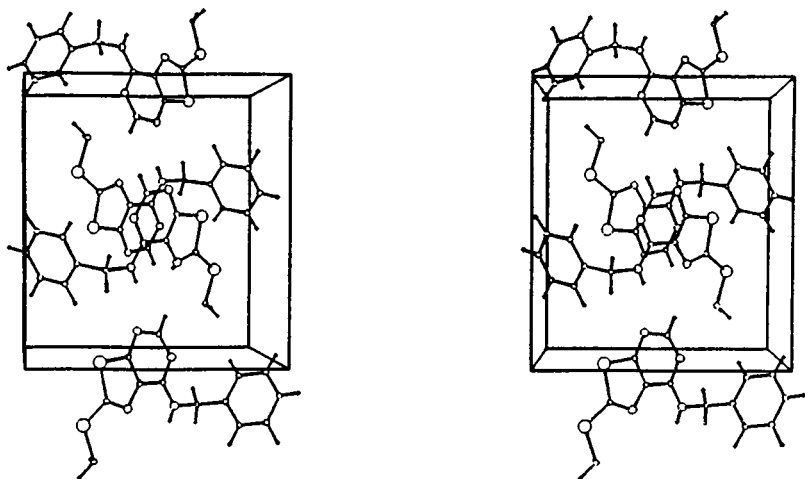


Fig. 3. A stereoscopic view of the molecule down the *a*-axis.

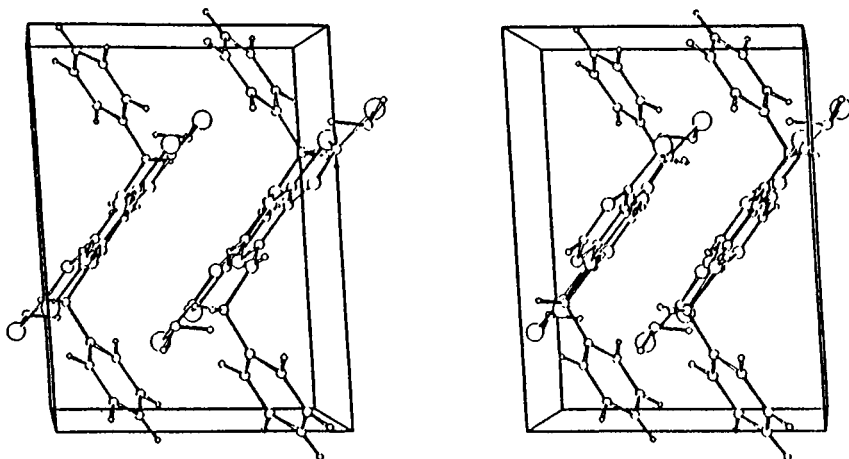


Fig. 4. A stereoscopic view of the molecule down the *b*-axis.

of 3.36 Å. This stacking distance is similar to values observed in a wide variety of purines e.g., in purine itself, the distance is 3.39 Å (Watson et al., 1965). The amino nitrogen N(4) forms a weak hydrogen bond with the N(2) atom of the symmetry related molecule. The hydrogen bonds are $N(4)-HN(4) = 0.790$ Å, $N(4)\dots N(2) = 3.020(2)$ Å, $HN(4)\dots N(2) = 2.318$ Å.

References

- Busing, W. R., Martin, K. O., Levy, H. A.: ORFLS. Report ORNL-JM-306. Oak Ridge National Laboratory, Tennessee (1962).
- Cromer, D. T., Waber, J. T.: Scattering factors computed from relativistic Dirac-Slater wave-functions. *Acta Crystallogr.* **18** (1965) 104–109.
- Elion, G. B., Lange, W. H., Hitchings, G. H.: Studies on condensed pyrimidine system. XVI. Purines and Thiazolo[5,4-d] pyrimidines from 4-Amino-5-formamido-6-mercaptopyrimidines. *J. Am. Chem. Soc.* **78** (1956) 2858–2863.
- Hamilton, W. C.: On the isotropic temperature factor equivalent to a given anisotropic temperature factor. *Acta Crystallogr.* **12** (1959) 609–610.
- Libit, L., Hoffmann, R.: Toward a detail orbital theory of substituent effects: Charge transfer, polarisation and the methyl group. *J. Am. Chem. Soc.* **96** (1974) 1370–1383.
- Singh, C.: Location of hydrogen atoms in certain heterocyclic compounds. *Acta Crystallogr.* **19** (1965) 861–864.
- Sobell, H. M., Tomita, K.: The crystal structures of salts of methylated purines and pyrimidines. IV. 9-methylguanine hydrobromide. *Acta Crystallogr.* **17** (1964) 126–131.
- Stewart, R. F., Davidson, E. R., Simpson, W. T.: Coherent X-ray scattering for the hydrogen atom in the hydrogen molecule. *J. Chem. Phys.* **42** (1965) 3175–3187.
- Watson, D. G., Sweet, R. M., Marsh, R. E.: The Crystal and molecular structure of purine. *Acta Crystallogr.* **19** (1965) 573–580.