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Effects of Sulfur Substituents on the Structural Properties of Purines: Crystal Structures of Guanine Picrate Monohydrate and 6-Thioguanine Picrate Monohydrate

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Crystals of guanine picrate monohydrate and 6-thioguanine picrate monohydrate are isostructural (isomorphous), and are monoclinic, space group $C2/c$, with $Z=8$. For the guanine salt, $a=30{\cdot}993$ (5), $b=4{\cdot}993$ (2), $c=19{\cdot}606$ (4) Å and $\beta=95{\cdot}33$ (2)°. For the thioguanine salt, $a=30{\cdot}933$ (2), $b=5{\cdot}137$ (1), $c=20{\cdot}193$ (2) Å and $\beta=98{\cdot}031$ (5)°. The structures were solved by the use of three-dimensional X-ray diffractometer data and were refined by least-squares calculations. Except for differences involving atom C(6), bond lengths and angles for thioguanine and guanine are in agreement. The base-stacking patterns are similar to those found in crystal structures of other acid salts of guanine. Hydrogen-bonding patterns are identical in the two crystal structures, although hydrogen-bond lengths are considerably different. The finding that the structural properties of guanine and thioguanine are sufficiently similar to permit the two bases to occupy the same crystalline environment is compatible with the observation that thioguanine can substitute for guanine in certain biological processes. The results support the hypothesis that the antimetabolite activity of thioguanine may be related to distortions in hydrogen-bonded contacts at those biological sites where thioguanine substitutes for guanine.

Introduction

A number of synthetic purine and pyrimidine analogs are effective metabolic inhibitors with useful chemotherapeutic activity (Roy-Burman, 1970; Balis, 1968; Hitchings & Elion, 1963). Little is known about the detailed mechanisms by which these analogs act, but it appears that they often mimic and competitively substitute for natural purines and pyrimidines in various biological processes (Roy-Burman, 1970; Balis, 1968; Hitchings & Elion, 1963). To act effectively in this manner, it is likely that the analogs must simultaneously satisfy two broad structural requirements. Presumably, they must be similar enough to the corresponding natural bases to compete for enyme binding sites, to substitute for the natural bases in nucleic acids, or to simulate normal metabolites that are involved in cellular control mechanisms. At the same time, they must be sufficiently different from the natural bases they supplant to disrupt normal biological processes.

Of those purine analogs with chemotherapeutic activity, several thio-derivatives are particularly effective, and their mechanisms of action have been studied in some detail (Roy-Burman, 1970; Balis, 1968; Hitchings & Elion, 1963). A notable example is 6-thioguanine, which, *in vivo*, acts as a metabolic inhibitor with antitumor activity, and is readily incorporated into nucleic acids (LePage & Junga, 1963; LePage & Jones, 1961; Adams, 1963), probably by substituting for guanine. Previous crystallographic studies in our laboratory (Bugg & Thewalt, 1970; Thewalt & Bugg, 1972; Bugg, Thewalt & Marsh, 1968; Thewalt, Bugg & Marsh, 1970, 1971) indicate that guanine and thioguanine have closely related structural properties, except for significant differences in the C(6)–O(6) and C(6)–S bond lengths, and in the dimensions of hydrogen bonds involving the C(6) substituents. Results of these studies led us to postulate that the antimetabolite and antitumor activity of thioguanine is probably related to the influence of the sulfur substituent on hydrogen-bonding interactions in biological systems (Bugg & Thewalt, 1970; Thewalt & Bugg, 1972).

In this paper we describe the crystal structures of guanine picrate monohydrate and 6-thioguanine picrate monohydrate (Fig. 1). Crystals of these two salts are of particular interest because they are isostructural, thus providing direct evidence that the structural properties of thioguanine and guanine are similar enough to permit the bases to occupy the same crystalline environments. Also, since the crystalline environments are identical, these salts serve as convenient model systems for comparing the structural properties of thioguanine and guanine when the bases are subjected to the same solid-state interactions.

Experimental

Guanine picrate monohydrate and thioguanine picrate monohydrate were crystallized as yellow needles by slowly cooling hot aqueous solutions of the salts.

Weissenberg and oscillation photographs showed the crystals to be monoclinic. Space groups $C2/c$ or Cc were indicated by the systematic absence of reflexions hkl with $h+k$ odd and $h0l$ with l odd. Since the observed densities were consistent with eight formula units per unit cell, we assumed the space group to be $C2/c$; this assumption was corroborated by the final structure analysis. The crystals of guanine picrate monohydrate displayed sharp diffraction patterns; however, thioguanine picrate monohydrate crystals produced Weissenberg photographs in which the spots were streaked, thus indicating poor mosaic order.

Data for the guanine salt were obtained from a needle fragment with approximate dimensions of 0·32, 0·12, and 0·07 mm. Data for the thioguanine salt were obtained from a needle fragment with approximate dimensions of 0·16, 0·10, and 0·04 mm. All angular and intensity data were collected with a Picker FACS-1 X-ray diffractometer, 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 the collection of intensity data were calculated by a least-squares analysis of the angular settings for several medium-angle reflections (Cu $K\bar{\alpha}$, $\lambda = 1{\cdot}5418$ 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 (Cu $K\alpha_1$, $\lambda = 1{\cdot}54051$ Å). The final cell parameters were based on 11 and 10 reflections for the guanine and thioguanine salts, respectively; these parameters were not significantly different from those obtained prior to data collection. Crystal data, including the final cell parameters, are given in Table 1.

Table 1. *Crystal data*

Unit-cell parameters were measured at 25±2°C. Densities were measured by flotation in a mixture of benzene and ethylene dibromide.

	$C_5H_6N_5S.$ $C_6H_2N_3O_7.H_2O$	$C_5H_6N_5O.$ $C_6H_2N_3O_7.H_2O$
Stoichiometry		
Z	8	8
Space group	$C2/c$	$C2/c$
a	30·933 (2) Å	30·993 (5) Å
b	5·137 (1)	4·993 (2)
c	20·193 (2)	19·606 (4)
β	98·031 (5)°	95·33 (2)°
ϱ(calculated)	1·732 g cm^{-3}	1·751 g cm^{-3}
ϱ(observed)	1·72 g cm^{-3}	1·75 g cm^{-3}
μ	24·1 cm^{-1}	13·7 cm^{-1}

Intensity data were measured by use of a 2θ scanning technique. The scanning speeds for the guanine and thioguanine salts were 0·5 and 1° min^{-1}, respectively. A 20 s background measurement was performed at each terminus of the scans and measurements were made for all unique reflections with $2\theta < 128°$. For the guanine salt 2508 independent reflections were measured, and for the thioguanine salt 2596 independent reflections were measured. Those reflections with net negative scan counts were assigned intensity values of 0·0 and were retained in all subsequent calculations.

The intensities were assigned variances, $\sigma^2(I)$, according to counting statistics plus a correctional term $(0{\cdot}03S)^2$, 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* (Wehe, Busing & Levy, 1962). The data sets were scaled by means of Wilson (1942) plots.

We solved the structure of thioguanine picrate monohydrate first. Trial coordinates for the nonhydrogen atoms were obtained by direct methods, using the computer program *MULTAN* (Main, Woolfson & Germain, 1971). The trial structure was refined by use of a modified version of the full-matrix least-squares program *ORFLS* (Busing, Martin & Levy, 1962; Busing, 1971). The quantity minimized was $\sum w(F_o^2 - F_c^2/k^2)^2$, where k is a scale factor and the weight w is equal to $1/\sigma^2(F_o^2)$. Scattering factors for the nonhydrogen atoms were from *International Tables for X-ray Crystallography* (1962); anomalous dispersion correction factors for these atoms were from Cromer & Liberman (1970). Hydrogen-atom scattering factors were from Stewart, Davidson & Simpson (1965). All hydrogen atoms were located in difference Fourier maps that were calculated during the latter stages of refinement. Final cycles of refinement included all positional parameters, as well as anisotropic temperature factors for the heavy atoms, isotropic temperature factors for the hydrogen atoms, and Zachariasen's (1963) isotropic extinction parameter g (as formulated by Coppens & Hamilton, 1970). Because of the limited core-storage capacity of the computer it was impracticable to refine all parameters simultaneously; consequently, the atomic parameters were divided into two blocks, those for the purine moiety in one block and those for the water molecule and the picrate anion in the other. Each of these blocks also contained the scale factor and extinction parameter. The blocks of parameters were alternated in successive cycles of refinement. The final R index ($\sum||F_o| - |F_c||/\sum|F_o|$) is 0·107 and the

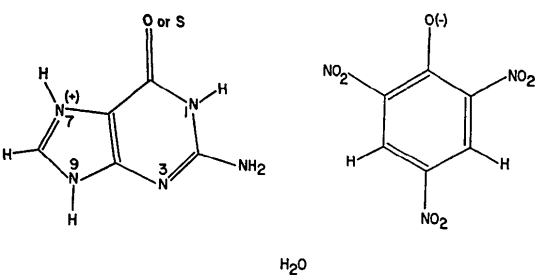

Fig. 1. Structural formulas for guanine picrate monohydrate and thioguanine picrate monohydrate. At the 6-position of the purine, guanine and thioguanine have oxygen and sulfur substituents, respectively.

final goodness-of-fit, $[\sum w(F_o^2-F_c^2/k^2)^2/(m-s)]^{1/2}$, where m is the number of reflections used and s is the number of parameters refined, is 2·0; the poor mosaic order of the crystal used for measuring intensity data may account, in large part, for the relatively high value of the R index. During the final cycle of refinement, no parameter shifted more than one-third of its estimated standard deviation, except the β_{12} parameter of atom C(15), which shifted by 0·50σ. A final three-dimensional difference Fourier map showed a single spurious peak of 0·7 e Å^{-3} and one spurious hole of −0·6 e Å^{-3}; no other fluctuations displayed magnitudes in excess of 0·4 e Å^{-3}.

Refinement of the guanine salt was initiated by using the parameters determined for thioguanine picrate monohydrate. The same procedure was followed as that described for refinement of the thioguanine salt. The final R index is 0·060 and the goodness-of-fit is 1·95. During the final cycle of refinement no parameter shifted more than one-third of its standard deviation. A final difference Fourier map showed no peaks or troughs with magnitudes that exceeded 0·3 e Å^{-3}.

Table 2. *Heavy-atom parameters and their standard deviations*

Values for x, z, β_{11}, β_{13}, and β_{33} have been multiplied by 10^5; all other values have been multiplied by 10^4. Temperature factors are in the form $T=\exp(-\beta_{11}h^2-\beta_{22}k^2-\beta_{33}l^2-2\beta_{12}hk-2\beta_{13}hl-2\beta_{23}kl)$. The values of the isotropic extinction parameter are $g=0{\cdot}079$ (6) for guanine picrate monohydrate and $g=0{\cdot}020$ (5) for thioguanine picrate monohydrate.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Guanine Picrate Monohydrate									
N(1)	22073(6)	7625(4)	11875(9)	46(2)	278(9)	206(6)	-3(1)	19(3)	10(2)
C(2)	23342(7)	9487(5)	7337(11)	59(2)	223(10)	155(6)	-2(1)	2(3)	-3(2)
N(2)	20278(7)	11074(5)	4367(11)	53(2)	334(10)	249(6)	0(1)	17(3)	24(2)
N(3)	27398(6)	9737(4)	5755(9)	52(2)	253(8)	184(5)	-1(1)	18(2)	9(2)
C(4)	30076(7)	7947(5)	9147(10)	52(2)	209(10)	159(6)	-5(1)	12(3)	-4(2)
C(5)	29081(7)	6075(4)	13799(10)	55(2)	225(10)	161(6)	-1(1)	8(3)	-2(2)
C(6)	24746(7)	5783(5)	15551(11)	64(2)	231(10)	170(6)	-5(1)	17(3)	-1(2)
O(6)	23352(5)	4182(4)	19534(8)	80(2)	312(8)	246(5)	-4(1)	42(2)	27(2)
N(7)	32864(6)	4715(4)	15946(10)	59(2)	238(9)	184(5)	3(1)	5(3)	5(2)
C(8)	35994(7)	5731(5)	12692(12)	53(2)	288(11)	205(6)	3(1)	11(3)	2(2)
N(9)	34443(6)	7685(4)	8527(10)	48(2)	308(10)	206(5)	-1(1)	28(3)	13(2)
C(11)	40461(7)	8408(5)	-8409(11)	56(2)	260(10)	158(6)	-2(1)	6(3)	3(2)
O(11)	36853(5)	8045(4)	-6337(9)	65(2)	473(10)	296(6)	-20(1)	5(3)	-34(2)
C(12)	42220(7)	6836(5)	-13783(11)	58(2)	224(10)	160(6)	-7(1)	-4(3)	3(2)
N(12)	39655(6)	4717(4)	-17197(10)	77(2)	244(9)	180(5)	-6(1)	4(3)	-0(2)
O(12)	36120(6)	4148(4)	-15381(11)	88(2)	497(11)	423(7)	-35(1)	74(3)	-58(2)
O(12)'	41158(6)	3488(4)	-21862(9)	120(2)	454(10)	256(5)	-24(1)	50(3)	-52(2)
C(13)	46313(7)	7168(5)	-15794(11)	70(2)	278(11)	136(6)	1(1)	17(3)	-2(2)
C(14)	48961(7)	9147(5)	-12793(11)	48(2)	322(11)	169(6)	-2(1)	9(3)	3(2)
N(14)	53314(6)	9457(5)	-14771(11)	61(2)	491(12)	213(6)	-8(1)	25(3)	-7(2)
O(14)	54681(6)	7832(5)	-18719(10)	83(2)	803(14)	308(6)	-4(2)	60(3)	-60(3)
O(14)'	55523(6)	11285(5)	-12147(12)	84(2)	656(14)	505(9)	-37(2)	70(4)	-56(3)
C(15)	47566(7)	10822(5)	-7840(11)	57(2)	249(11)	163(6)	-5(1)	-6(3)	6(2)
C(16)	43497(7)	10473(5)	-5736(11)	56(2)	226(10)	140(5)	0(1)	12(3)	3(2)
N(16)	42305(6)	12308(4)	-499(9)	73(2)	268(9)	175(5)	-2(1)	15(3)	-3(2)
O(16)	38742(6)	12094(4)	1789(10)	103(2)	463(10)	339(6)	-12(1)	90(3)	-62(2)
O(16)'	44855(6)	14073(4)	1501(10)	101(2)	375(9)	289(6)	-19(1)	21(3)	-41(2)
O(W)	34097(7)	6411(4)	24780(11)	96(2)	367(10)	323(6)	12(1)	35(3)	45(2)
Thioguanine Picrate Monohydrate									
N(1)	22429(13)	7527(8)	10999(19)	55(4)	276(19)	158(10)	-11(2)	25(6)	11(4)
C(2)	23465(14)	9411(9)	6738(22)	62(5)	192(19)	150(12)	-8(3)	31(6)	-11(4)
N(2)	20299(14)	10929(9)	3821(22)	60(5)	350(23)	187(12)	3(3)	34(6)	11(4)
N(3)	27511(11)	9740(8)	5193(18)	53(4)	227(17)	170(10)	1(2)	23(5)	6(4)
C(4)	30345(14)	8019(9)	8389(21)	57(5)	241(22)	152(12)	-10(3)	25(6)	-17(4)
C(5)	29534(13)	6132(9)	12804(21)	52(5)	218(20)	138(11)	-5(3)	14(6)	-7(4)
C(6)	25246(14)	5765(9)	14433(21)	69(5)	214(21)	139(12)	-8(3)	22(6)	-14(4)
S	23837(4)	3516(3)	19542(6)	90(1)	249(5)	177(3)	-8(1)	50(2)	9(1)
N(7)	33373(12)	4810(9)	14813(20)	60(4)	237(19)	192(11)	1(2)	9(6)	1(4)
C(8)	36402(16)	5844(10)	11794(25)	62(5)	234(23)	233(15)	-4(3)	20(7)	7(5)
N(9)	34726(12)	7799(9)	7897(21)	49(4)	302(21)	233(13)	-9(2)	47(6)	11(4)
C(11)	40335(16)	8465(11)	-8528(23)	57(5)	316(23)	184(13)	-7(3)	18(7)	10(5)
O(11)	36794(10)	8113(8)	-6661(18)	82(4)	547(21)	304(12)	-18(2)	68(5)	-8(4)
C(12)	41979(14)	6941(10)	-13739(23)	66(5)	243(22)	162(12)	-8(3)	14(6)	7(4)
N(12)	39372(13)	4841(9)	-17065(21)	83(5)	350(22)	204(12)	-11(3)	16(6)	8(5)
O(12)	35976(14)	4265(10)	-15162(24)	128(6)	767(31)	545(18)	-69(3)	141(8)	-95(6)
O(12)'	40751(12)	3688(9)	-21400(20)	121(5)	519(22)	296(12)	-23(3)	53(6)	-50(5)
C(13)	45982(15)	7316(11)	-15674(24)	74(6)	343(25)	150(13)	-7(3)	21(7)	-7(5)
C(14)	48675(14)	9247(11)	-12881(24)	49(5)	378(26)	199(14)	-10(3)	21(7)	-5(5)
N(14)	52975(14)	9566(12)	-14829(25)	65(5)	721(34)	327(17)	-24(4)	54(8)	-31(6)
O(14)	54269(13)	7998(12)	-18606(23)	94(5)	1077(37)	430(16)	-20(4)	116(8)	-91(7)
O(14)'	55219(14)	11343(11)	-12264(29)	107(6)	944(35)	768(25)	-65(4)	153(10)	-117(8)
C(15)	47479(16)	10860(11)	-7956(25)	65(6)	327(27)	191(14)	-8(3)	14(7)	-2(5)
C(16)	43640(14)	10678(10)	-5862(23)	62(5)	247(21)	170(12)	2(3)	17(7)	5(4)
N(16)	42463(14)	12259(9)	-717(21)	91(5)	296(21)	213(12)	-8(3)	31(7)	-1(4)
O(16)	38918(14)	12012(9)	1567(22)	152(6)	502(23)	446(16)	-25(3)	170(8)	-34(5)
O(16)'	44913(13)	14020(8)	1082(20)	123(5)	409(21)	351(14)	-22(3)	52(7)	-45(5)
O(W)	34683(15)	740(9)	23610(23)	94(5)	399(22)	365(15)	14(3)	30(7)	44(5)

Results

Table 2 lists the heavy-atom parameters and their estimated standard deviations. Table 3 gives the hydrogen-atom parameters and their standard deviations. In the guanine structure, the estimated standard deviations in positional coordinates are approximately 0·002 Å for the nonhydrogen atoms and 0·03 Å for the hydrogen atoms. In the thioguanine structure, corresponding estimates are about 0·001 Å for the sulfur atom, 0·005 Å for the carbon, oxygen, and nitrogen atoms, and 0·06 Å for the hydrogen atoms.*

Table 3. *Hydrogen-atom parameters and their standard deviations*

Positional parameters have been multiplied by 10^3.

	x	y	z	B(Å^2)
Guanine picrate monohydrate				
H(N1)	192 (1)	756 (5)	122 (1)	2·9 (0·5)
H(N2)	211 (1)	1239 (6)	15 (1)	3·9 (0·6)
H(N2)′	177 (1)	1093 (6)	54 (1)	4·5 (0·7)
H(N7)	334 (1)	334 (6)	191 (1)	3·8 (0·6)
H(C8)	389 (1)	508 (5)	134 (1)	2·2 (0·5)
H(N9)	360 (1)	849 (6)	57 (1)	3·9 (0·6)
H(C13)	472 (1)	601 (5)	−190 (1)	2·8 (0·5)
H(C15)	493 (1)	1216 (5)	−59 (1)	3·1 (0·3)
H(O*W*)	318 (1)	1 (8)	265 (2)	7·0 (1·0)
H(O*W*)′	362 (1)	−38 (7)	256 (2)	6·2 (0·9)
Thioguanine picrate monohydrate				
H(N1)	198 (2)	734 (10)	114 (2)	3·0 (1·2)
H(N2)	208 (2)	1221 (12)	8 (3)	5·9 (1·7)
H(N2)′	181 (2)	1095 (9)	56 (2)	2·3 (1·1)
H(N7)	336 (2)	338 (11)	176 (3)	4·9 (1·4)
H(C8)	396 (2)	544 (11)	127 (2)	4·9 (1·3)
H(N9)	360 (1)	871 (8)	55 (2)	1·1 (0·9)
H(C13)	469 (1)	612 (9)	−187 (2)	2·0 (1·0)
H(C15)	491 (2)	1230 (10)	−6 (2)	3·4 (1·3)
H(O*W*)	325 (2)	14 (15)	256 (3)	7·7 (2·1)
H(O*W*)′	368 (2)	−17 (12)	249 (3)	5·5 (1·7)

The conformations, heavy-atom thermal ellipsoids, and bond lengths are shown in Fig. 2. Bond angles are listed in Table 4. Except for a few isolated differences, corresponding bond lengths and angles within the guanine and thioguanine moieties are in agreement. There is a significant difference between the length of the C(6)–O(6) bond of guanine (1·224 Å) and the C(6)–S bond of thioguanine (1·674 Å), as well as between the lengths of the N(1)–C(6) bonds (1·375 Å for thioguanine and 1·393 Å for guanine). Significant differences also occur in the angles about C(6) in the two molecules. Deviations from least-squares planes through the purine moieties are listed in Table 5. For both guanine and thioguanine, the nine atoms of the purine

* Tables of structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30599 (13 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

ring are nearly coplanar, with atom N(1) displaying the largest deviation from the plane (0·014 Å for guanine and 0·017 Å for thioguanine). The substituents on the purine rings deviate significantly from the purine planes; the general directions of displacement are similar for guanine and thioguanine. Corresponding bond lengths and angles for the picrate anions are in agreement in the two crystal structures. The benzene rings are nearly planar (the maximum displacement is 0·02 Å), although substituents immediate to the rings deviate 0·02–0·06 Å from the best benzene planes. The N(2), N(4), and N(6) nitro groups in the guanine structure are rotated out of the benzene plane by 5·6, 5·2, and 1·7°, respectively, and in the thioguanine structure by 6·5, 5·9, and 2·1°, respectively.

Fig. 3 depicts the crystal-packing and hydrogen-bonding scheme and Table 6 lists hydrogen-bond lengths and angles. The hydrogen-bonding scheme appears to utilize all hydrogen atoms that are bonded to oxygen or nitrogen atoms, although several of the distances are relatively long. In addition, there are close C(8)–H···O(14)′ contacts that may be interpreted as weak hydrogen bonds. Purine moieties are joined by N(2)–H···N(3) hydrogen bonds across crystallographic inversion centers; there are no other direct hydrogen-bonded contacts between purines. In both

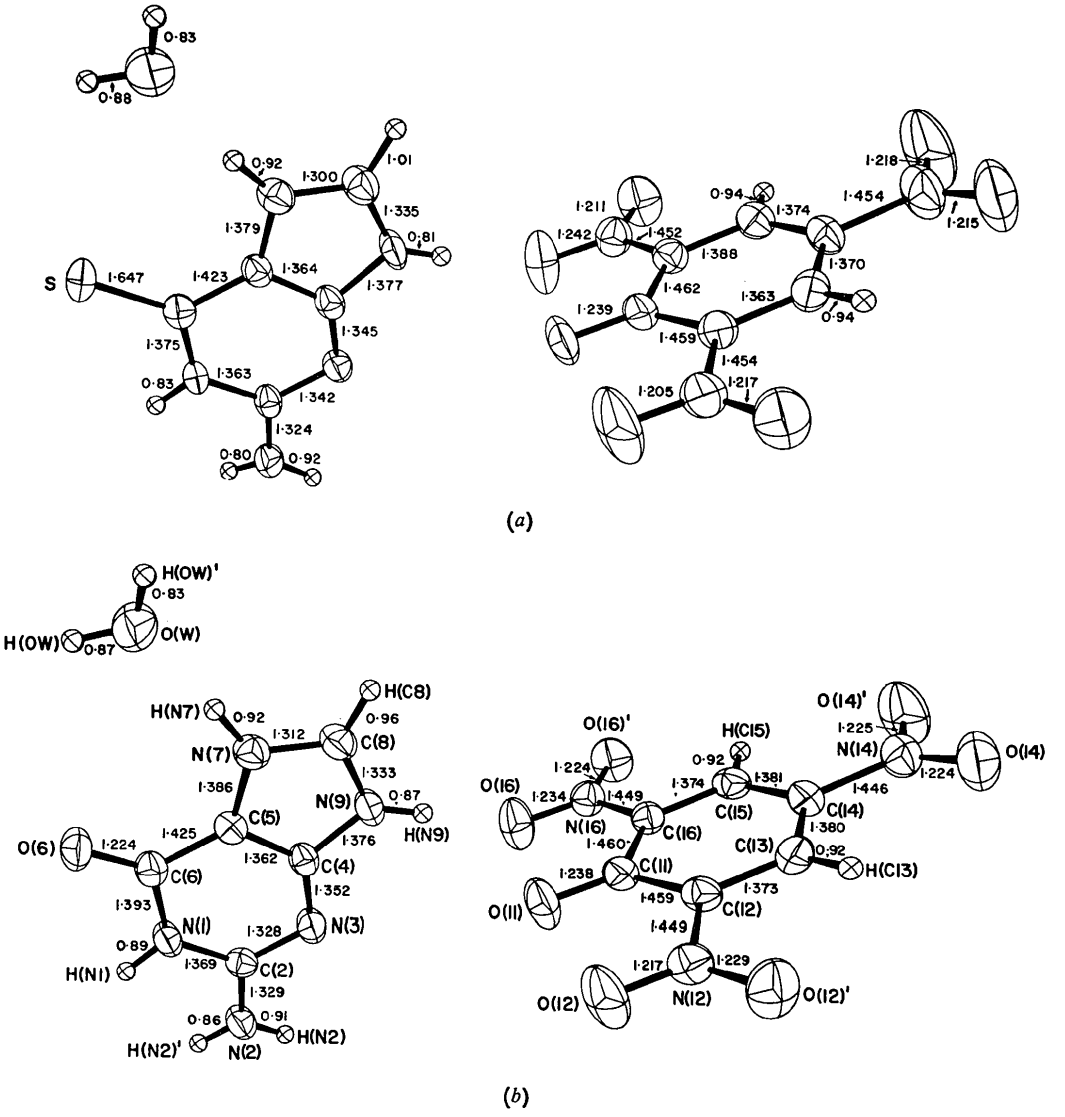

Fig. 2. A perspective view of the molecules, including bond lengths. (*a*) Thioguanine picrate monohydrate, and (*b*) guanine picrate monohydrate. E.s.d.'s in lengths of bonds between nonhydrogen atoms are about 0·007 and 0·004 Å for the thioguanine and guanine structures, respectively. E.s.d.'s in bond lengths involving hydrogen atoms are about 0·07 and 0·04 Å in the thioguanine and guanine 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 0·1 Å radius. (This drawing and that of Fig. 3 were prepared by using the computer program *ORTEP*: Johnson, 1965.)

Table 4. *Bond angles involving only nonhydrogen atoms*

Estimated standard deviations are about 0·2° for guanine picrate monohydrate and 0·4° for thioguanine picrate monohydrate.

	Guanine picrate monohydrate	Thioguanine picrate monohydrate		Guanine picrate monohydrate	Thioguanine picrate monohydrate
C(2)—N(1)—C(6)	126·3°	126·7°	C(11)–C(12)–N(12)	120·0°	120·3°
N(1)—C(2)—N(2)	116·9	118·3	C(11)–C(12)–C(13)	124·0	123·6
N(1)—C(2)—N(3)	123·4	123·1	N(12)–C(12)–C(13)	115·9	116·1
N(2)—C(2)—N(3)	119·7	118·6	C(12)–N(12)–O(12)	120·4	119·2
C(2)—N(3)—C(4)	112·0	111·8	C(12)–N(12)–O(12)′	118·6	118·6
N(3)—C(4)—C(5)	128·1	127·9	O(12)–N(12)–O(12)′	121·0	122·2
N(3)—C(4)—N(9)	125·7	127·0	C(12)–C(13)–C(14)	119·5	120·3
C(5)—C(4)—N(9)	106·2	105·2	C(13)–C(14)–N(14)	119·7	119·3
C(4)—C(5)—C(6)	120·6	120·5	C(13)–C(14)–C(15)	121·4	122·0
C(4)—C(5)—N(7)	107·6	108·3	N(14)–C(14)–C(15)	119·0	118·7
C(6)—C(5)—N(7)	131·8	131·2	C(14)–N(14)–O(14)	119·0	119·7
N(1)—N(6)—C(5)	109·7	110·0	C(14)–N(14)–O(14)′	117·8	117·1
N(1)—C(6)—S(O(6))	122·2	125·0	O(14)–N(14)–O(14)′	123·1	123·1
C(5)—C(6)—S(O(6))	128·1	125·1	C(14)–C(15)–C(16)	119·4	118·4
C(5)—N(7)—C(8)	107·8	107·9	C(11)–C(16)–C(15)	124·1	124·1
N(7)—C(8)—N(9)	109·9	109·8	C(11)–C(16)–N(16)	120·2	120·8
C(8)—N(9)—C(4)	108·5	108·9	C(15)–C(16)–N(16)	115·7	115·0
O(11)–C(11)–C(12)	124·6	125·4	C(16)–N(16)–O(16)	119·9	119·3
O(11)–C(11)–C(16)	123·9	123·0	C(16)–N(16)–O(16)′	118·9	119·5
C(12)–C(11)–C(16)	111·6	111·6	O(16)–N(16)–O(16)′	121·2	121·1

Table 5. *Deviations* (Å) *of atoms from least-squares planes through the nine atoms of the purine rings*

The equations of the least-squares planes, where the coefficients of X, Y, Z are equal to direction cosines with respect to the axes a, b and c^* and X, Y, Z are orthogonal Å coordinates are:

Guanine: $-0{\cdot}1200X-0{\cdot}6612Y-0{\cdot}7505Z=-5{\cdot}043$ Å,
Thioguanine: $-0{\cdot}1018X-0{\cdot}6411Y-0{\cdot}7607Z=4{\cdot}843$ Å.

	Guanine picrate monohydrate	Thioguanine picrate monohydrate
N(1)	0·014	0·017
C(2)	−0·002	0·000
N(2)	0·011	0·035
N(3)	−0·010	−0·006
C(4)	−0·002	−0·005
C(5)	−0·009	−0·017
C(6)	−0·001	−0·004
O(6),S	0·012	0·019
N(7)	−0·006	−0·002
C(8)	0·005	0·013
N(9)	0·011	0·003
H(N1)	0·09	0·10
H(N2)	0·01	0·05
H(N2)′	0·01	−0·16
H(N7)	−0·02	0·05
H(C8)	−0·05	−0·09
H(N9)	0·09	0·03

structures, the water molecule accepts a hydrogen bond from atom N(7) of the purine, and donates hydrogen bonds to the picrate anion and to the C(6) substituent [O(6) or S] of the purine. The remaining hydrogen bonds are involved in purine–picrate interactions.

The purine moieties are stacked in the **b** direction. As depicted in Fig. 4, the base-stacking pattern is such that adjacent purine rings do not overlap. The major contact between adjacent purines involves the interaction of the C(6) substituent with atom C(2) of the adjacent base. In the thioguanine structure, the S···C(2) contact of 3·326 Å is about 0·2 Å shorter than a normal van der Waals contact. The stacking patterns are similar to those found earlier for thioguanine (Bugg & Thewalt, 1970) and for numerous protonated purines (Bugg, Thomas, Sundaralingam & Rao, 1971), and strongly resemble the patterns in the crystal structures of 9-methylguanine hydrobromide (Bugg, 1972; Sobell & Tomita, 1964), guanine hydrochloride monohydrate (Bugg, 1972; Broomhead, 1951), and guanine hydrochloride dihydrate (Bugg, 1972; Iball & Wilson, 1965). In addition to the interactions depicted in Fig. 4, an unusually short contact of 3·396 Å occurs between

Table 6. *Hydrogen-bond distances* (Å) *and angles* (°)

Values in parentheses correspond to 6-thioguanine picrate monohydrate, and others correspond to guanine picrate monohydrate.

Symmetry code

a	$x, \quad y, \quad z$	*e*	$x, \quad -y, \quad z+\frac{1}{2}$
b	$-x+\frac{1}{2}, \; -y+\frac{3}{2}, \; -z$	*f*	$-x+1, \; -y+2, \; -z$
c	$-x+\frac{1}{2}, \; -y+\frac{5}{2}, \; -z$		
d	$-x+\frac{1}{2}, \; y-\frac{1}{2}, \; -z+\frac{1}{2}$		

D	H	*A*	*D*···*A*	H···*A*	∠*DHA*
N(1)	H(N1)	O(11) *b*	2·896	2·14	142
			(2·891)	(2·16)	(147)
N(2)	H(N2)	N(3) *c*	3·016	2·11	175
			(3·011)	(2·10)	(173)
N(2)	H(N2)′	O(12) *b*	3·067	2·37	139
			(3·204)	(2·46)	(154)
		O(11) *b*	3·070	2·44	130
			(3·121)	(2·60)	(123)
N(7)	H(N7)	O(W) *a*	2·676	1·75	177
			(2·735)	(1·82)	(172)
N(9)	H(N9)	O(16) *a*	2·949	2·16	151
			(2·909)	(2·13)	(161)
O(*W*)	H(O*W*)	O(6) *d*	2·754	1·89	171
		S	(3·345)	(2·46)	(175)
O(*W*)	H(O*W*)′	O(12)′ *e*	3·034	2·21	172
			(3·021)	(2·24)	(159)
C(8)	H(C8)	O(14)′ *f*	3·032	2·53	113
			(2·957)	(2·31)	(121)

the sulfur atoms of thioguanine moieties that are related by the screw axes; this contact is about 0·3 Å shorter than a normal van der Waals distance.

Discussion

In view of the large differences in the electronegativities and in the atomic radii of oxygen and sulfur (Pauling, 1960), it might be regarded as somewhat surprising that this crystal-packing scheme can accommodate either guanine or thioguanine. However, it has also been found that one of the crystalline forms of inosine (Subramanian, Madden & Bugg, 1973) is isostructural with crystals of 6-thiopurine riboside (Shefter, 1968) [a purine analog that can compete with inosine in certain biological reactions (Roy-Burman, 1970; Balis, 1968; Hitchings & Elion, 1963)], so it is not completely unexpected to find that crystals of these guanine and thioguanine salts are isostructural. Crystals of 8-azaguanine (MacIntyre, Singh & Werkema, 1965; Sletten, Sletten & Jensen, 1968) and of guanine monohydrate (Thewalt, Bugg & Marsh, 1971) are also isostructural, despite the differences in the hydrogen bonding capabilities of these two bases. Like thioguanine, 8-azaguanine can substitute for guanine in certain metabolic pathways (Roy-Burman, 1970; Balis, 1968; Hitchings & Elion, 1963). Thus it has now been demonstrated that thioguanine, 8-azaguanine, and 6-thiopurine riboside, which are all capable of simulating natural purine derivatives in biological processes, can form crystal structures that are isostructural with those of the corresponding natural bases.

Earlier crystallographic studies showed that the sulfur substituents of thiopurines and thiopyrimidines are suitable hydrogen-bond acceptors (Thewalt & Bugg, 1972). Crystallographic findings also suggested that replacement of a carbonyl oxygen atom by a sulfur substituent affects the lengths of hydrogen bonds, but exerts negligible influence on the hydrogen-bonding patterns of purines and pyrimidines (Bugg & Thewalt, 1970; Thewalt & Bugg, 1972). Our results support these earlier conclusions. The hydrogen-bonding schemes for guanine picrate and thioguanine picrate, though closely related, exhibit significant differences in hydrogen-bond lengths (Table 6). The major difference occurs in the lengths of the hydrogen bonds to the sulfur substituent of thioguanine and to the corresponding carbonyl oxygen atom of guanine. Both of these atoms accept a hydrogen bond from a water molecule, but the hydrogen bond to the sulfur substituent is about 0·6 Å longer than that to atom O(6) of guanine. This finding agrees with earlier results, which indicated that hydrogen bonds involving thio groups are 0·3–0·7 Å longer than those involving carbonyl groups (Thewalt & Bugg, 1972).

Our earlier crystallographic studies of guanine (Bugg, Thewalt & Marsh, 1968; Thewalt, Bugg & Marsh, 1971), 6-thioguanine (Bugg & Thewalt, 1970), guanosine (Bugg, Thewalt & Marsh, 1968; Thewalt, Bugg & Marsh, 1970) and 6-thioguanosine (Thewalt & Bugg, 1972) suggested the following relationships between the structural properties of guanine and thioguanine derivatives. (1) Bond lengths and angles within the bases are nearly the same, except for the large difference in C(6)–S and C(6)–O(6) bond lengths. (2) There is little difference in the crystallographic base stacking patterns. (3) Hydrogen-bonding patterns involving the bases are closely related, except for differences in hydrogen-bond lengths. Our investigation of guanine picrate and thioguanine picrate corroborates these conclusions and shows that the structural properties of guanine and thioguanine are, indeed, similar enough to permit these bases to occupy closely related crys-

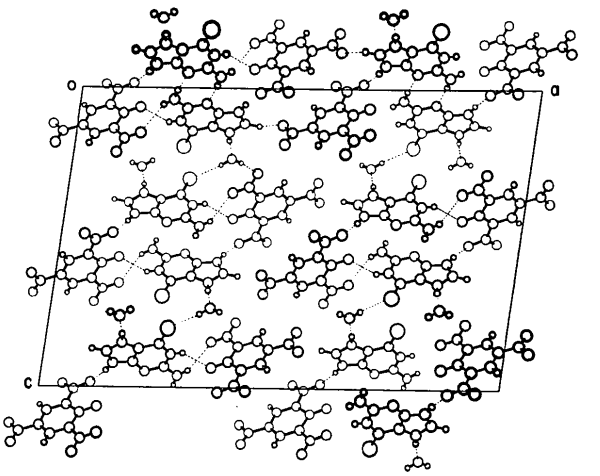

Fig. 3. Crystal packing in the thioguanine picrate monohydrate structure, as viewed down the *b* axis. Hydrogen bonds are represented by dashed lines. Essentially the same crystal-packing and hydrogen-bonding schemes are found in the crystal structure of guanine picrate monohydrate.

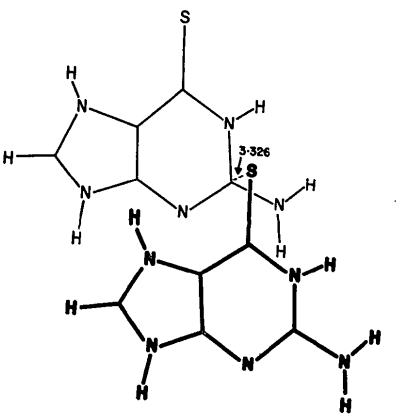

Fig. 4. Base-stacking pattern in the crystal structure of thioguanine picrate monohydrate, as viewed perpendicular to the plane of the purine ring. Essentially the same pattern is found in the crystal structure of guanine picrate monohydrate, where the O(6)···C(2) contact is 3·349 Å. Interplanar spacings are about 3·30 Å in both structures.

talline environments. In view of these similarities, it is not surprising that thioguanine can mimic guanine in biological processes and substitute for it in certain metabolic pathways. At the same time, differences in the lengths of hydrogen bonds involving these two bases might be expected to interfere with certain biological processes in which thioguanine substitutes for guanine, thus contributing to the antimetabolite activity of this base analog.

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The Crystal Structures at 20 and 1000°C of Bismuth Uranate, Bi_2UO_6

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The crystal structures of two modifications of the catalyst bismuth uranate, Bi_2UO_6, have been solved by powder methods. The phase stable at 1000°C has a trigonal fluorite-like structure, space group $P\bar{3}$, with one molecule per cell and with lattice constants $a=4{\cdot}045$ (5) and $c=9{\cdot}90$ (1) Å. The final R index was 0·05. The phase stable at 20°C has a closely related monoclinic structure, $a=6{\cdot}872$ (2), $b=4{\cdot}009$ (1) and $c=9{\cdot}690$ (3) Å, $\beta=90{\cdot}16$ (1)°; the space group is $C2$ and the cell contains two molecules. The final R index was 0·10. Both structures can be regarded as stackings of layers of interlocked UO_8 polyhedra and layers of a Bi–O network.

Introduction

The oxidative conversion of toluene to benzene has been shown by Steenhof de Jong, Guffens & Van der Baan (1972, 1973) to be catalysed by bismuth uranate, Bi_2UO_6. A selectivity of up to 70% is obtained if toluene vapour reacts with bismuth uranate without gaseous oxygen being present; the partially reduced