lowest R value was obtained when the two positions for C14 had half ocupancy.

Ring A is in chair form with C1 and C4 deviating from best plane through C2, C3, C5 and C6 by 0·70 and 0·62 Å, respectively. Ring B is in a twisted conformation with C10, C11 and C12 approximately in a plane, and C13 and C15 above and C14 below this plane. The hydroxyl and the methyl groups are attached to ring A in an axial orientation while ring B is attached in an equitorial position. The packing is stabilized by an O1—H···O2 hydrogen bond. The O1—H···O2 and H—O1···O2 angles are 163·4 (5) and 11·2 (5)°, respectively, and the O···H distance is 1·96 (2) Å. The two rings are almost perpendicular to each other as found in the case of 5-(3-oxocyclohexenyl)-5-ethylbarbituric acid (Chentli-Benchikha *et al.*, 1977). The best plane through the atoms in rings A and B makes an angle of 51·2 (1)° with C14 and 121·7 (1)° with C14P in the ring.

We thank Professor S. Swaminathan of the Organic Chemistry Department, University of Madras, India, for providing the sample.

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Structure of 7-Methyl-6,8-dithioxo-7,8-dihydroguanosine Monohydrate

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(*Received* 18 *December* 1989; *accepted* 5 *June* 1990)

Abstract. 2-Amino-7-methyl-9-β-D-ribofuranosyl-1*H*,9*H*-purine-6,8-dithione monohydrate (1), $C_{11}H_{15}N_5O_4S_2.H_2O$, $M_r = 363{\cdot}41$, monoclinic, $P2_1$, $a = 5{\cdot}9889\ (12)$, $b = 20{\cdot}772\ (4)$, $c = 6{\cdot}7374\ (15)$ Å, $\beta = 113{\cdot}843\ (16)°$, $V = 766{\cdot}6\ (3)$ Å^3, $Z = 2$, $D_x = 1{\cdot}574$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å, $\mu = 34{\cdot}141$ cm^{-1}, $F(000) = 380$, $T = 295$ K, $R = 0{\cdot}0253$ for 3105 reflections ($F \geq 4\sigma_F$). The sugar conformation and puckering parameters are $^2T_1$ ($C_{2'}$-*endo*/$C_{1'}$-*exo*), $P = 149{\cdot}1°$ and $\tau_m = 34{\cdot}8°$. The C5′–O5′ side chain is *gauche–gauche*. The glycosidic torsion angle is 61·0 (2)° corresponding to the *syn* conformation which is stabilized by the O5′—H···N3 intramolecular hydrogen bond [d(O5′···N3) = 2·900 (3) Å]. The purine ring is nearly planar [r.m.s. deviation: 0·020 (2) Å]; the dihedral angle between the pyrimidine and imidazole rings is 0·31 (8)°. Purine rings are parallel to the (101) planes but do not overlap. The only interbase interaction is a weak head-to-tail (N10···S13) hydrogen bond [3·329 (2) Å].

Introduction. The title compound (1) is a 6-thioxo derivative of 7-methyl-8-oxo- (2) and 7-methyl-8-thioxoguanosine (3) both of which have exhibited immunostimulatory activity. For example, (2) has been studied as an intracellular mitogen of murine splenic B lymphocytes (Goodman & Weigle, 1984) and as a promoter of proliferation and differentiation of murine T cells in the presence of other stimulating signals (Ahmad & Mond, 1986; Feldbush & Ballas, 1985). 7-Methyl-8-thioxoguanosine (3) has immunomodulating properties similar to (2) (Henry, Kini, Larson, Robins, Alaghamandan & Smee, 1990). On the other hand, (1) is also a derivative of 6-thioguanosine (4) which is currently utilized in the clinic as an anticancer agent (Fox, Wempen, Hampton & Doerr, 1958). The potential of (1) as both an immunomodulator and an antitumor drug was envisioned. However, 7-methyl-6,8-thioxoguano-

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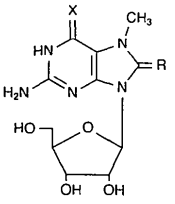
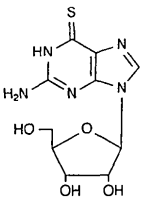
sine (1) exhibits neither biological activity. We present the structure of (1) in light of the structures of (2), (3) and (4).



(1) X = R = S
(2) X = R = O
(3) X = O; R = S



(4)

Experimental. 2-Chloro-7-methyl-8(7*H*)-thioxo-9-(2,3,5-tri-*O*-benzoylribofuranosyl)-9*H*-purine-6(1*H*)-one (Henry *et al.*, 1990) was thiated with P_2S_5 in dioxane. The product was isolated by chromatography, deblocked with $NaOCH_3$ in methanol, and aminated with liquid ammonia at 423 K in a steel bomb. Amber square-cross-sectioned needles of (1) crystallized from the CH_2Cl_2/methanol (95:5, *v*/*v*) eluent following chromatography. Table 1 summarizes data collection and refinement. Cell parameters were determined by least-squares refinement using the setting angles of 25 reflections having 2θ in the range 52·6–58·4°. An Enraf–Nonius CAD-4 diffractometer with graphite monochromator was used for all measurements. Data were reduced with *SDP-Plus* (Frenz, 1985) which included Lorentz and polarization corrections, crystal and instrument stability corrections (based on three check reflections measured every hour), and absorption correction (based on crystal-face measurements).

Initial crystallographic coordinates for all non-H atoms were obtained with *SHELXS*86 (Sheldrick, 1986). Initial positional parameters for all H atoms were determined from four difference maps as peaks of density 0·22–0·75 e Å^{-3} beginning at $R = 0{\cdot}039$. All positional parameters, anisotropic thermal parameters for non-H atoms and isotropic thermal parameters for H atoms were refined with *SHELX*76 (Sheldrick, 1976) subject to the following constraints: the N7-methyl group was found in ΔF maps to be rotationally disordered over two sites; H12*A*, H12*B*, and H12*C* are H atoms of one rotamer and H12*D*, H12*E* and H12*F* are H atoms of the other. The rotamers were constrained such that: d(C12—H) = 1·00 Å; all d(N7···H) were equal [refined to 2·030 (6) Å]; H—C12—H = 109·5° for each group, where H represents any H atom attached to C12; all U(H12) were set equal. Constraints for the water of hydration were: d(O*W*—H*WA*) = d(O*W*—H*WB*) = 0·95 Å, H*WA*—O*W*—H*WB* = 104°, and U(H*WA*) = U(H*WB*). The refined occupancies of the rotamers of the methyl group, which were constrained to sum to 1·0, were 0·570 (16) for H12*A*–H12*C* and 0·430 (16) for H12*D*–H12*F*. The function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w^{-1} = (\sigma_F^2 + 0{\cdot}0004F^2)$, $\sigma_F = F\sigma_I/2I$, and $\sigma_I = (N_{pk} + N_{bg1} + N_{bg2})^{1/2}$. Conventional definitions of R, wR and S were used. Scattering factors and anomalous-dispersion corrections were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV) except those of H which were taken from Stewart, Davidson & Simpson (1965). Least-squares-planes program from Cordes (1983); figures were drawn with *ORTEP*II (Johnson, 1976); parameter and geometry tables were produced with *FUER* (Larson, 1980) and structure-factor-amplitude tables were produced with *LISTFC* (Larson, 1980).

Table 1. *Crystallography summary for* (1)

Data collection (295 K)	
Mode	ω–2θ scan
Scan range (°)	0·80 + 0·15 tanθ
Background	Scan 0·25 times scan range before and after scan
Scan rate (° min^{-1})	1·4 – 16·49
Exposure time (h)	74·6
Stability correction range on I	1·000–1·003
Check reflections	2,10,$\bar{2}$; 2,$\bar{10}$,2; 291
2θ range (°)	3·0–152·0
Range in hkl, min.	0, – 26, – 8
max.	7,26,8
Total reflections, measured, unique	3468, 3193
R_{int}	0·0209
Crystal dimensions (mm)	0·31 × 0·145 × 0·145
Crystal volume (mm^3)	0·00637
Crystal faces	{100}; {010}; (0$\bar{1}\bar{1}$); ($\bar{1}\bar{2}$5)
Transmission-factor range	0·464–0·677
Structure refinement	
Reflections used, m ($F \geq 4\sigma_F$)	3105
No. of variables, n	284
Extinction parameter	2·3 (2) × 10^{-6}
Goodness of fit, S	1·429
R, wR	0·0253, 0·0381
R for all data	0·0269
Max., av. Δ/σ	0·0072, 0·0005
Max., min. $\Delta\rho$ in ΔF map (e Å^{-3})	0·37, – 0·28

Discussion. The atomic coordinates are listed in Table 2;* bond lengths and bond angles are listed in Table 3.

Glycosidic linkage. The molecular conformation and atom labelling are illustrated in Fig. 1. The aglycon is *syn* to the ribose ring with $\chi_{CN} = 61{\cdot}1\ (2)°$ (O4′— C1′—N9—C4) and is stabilized by the O5′—HO5′···N3 intramolecular hydrogen bond. Nucleosides (2) (Larson, Cottam & Robins, 1989) and (3)

* Tables of anisotropic thermal parameters, bond lengths and angles involving H atoms, torsion angles, least-squares planes and structure-factor amplitudes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53264 (17 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Positional and isotropic thermal parameters* (Å^2) *for all atoms in* (1)

	x	y	z	U/U_{eq}*
N1	0·5457 (3)	0·575	0·5196 (2)	0·0329 (5)
C2	0·5725 (3)	0·63987 (10)	0·5084 (3)	0·0325 (5)
N3	0·4785 (3)	0·68204 (9)	0·6026 (2)	0·0317 (5)
C4	0·3685 (3)	0·65428 (10)	0·7172 (2)	0·0288 (5)
C5	0·3344 (3)	0·58838 (10)	0·7364 (3)	0·0308 (5)
C6	0·4175 (3)	0·54493 (11)	0·6246 (3)	0·0318 (5)
N7	0·2046 (3)	0·58216 (10)	0·8676 (2)	0·0340 (5)
C8	0·1582 (3)	0·64131 (11)	0·9285 (3)	0·0327 (5)
N9	0·2631 (3)	0·68602 (9)	0·8360 (2)	0·0296 (4)
N10	0·7010 (3)	0·66051 (11)	0·3975 (3)	0·0455 (7)
S11	0·37938 (9)	0·46435 (7)	0·59752 (8)	0·0443 (2)
C12	0·1307 (4)	0·52238 (12)	0·9390 (4)	0·0458 (7)
S13	0·00853 (9)	0·65849 (7)	1·08192 (7)	0·0441 (2)
C1′	0·2298 (3)	0·75501 (10)	0·8431 (3)	0·0298 (5)
C2′	0·4644 (3)	0·79498 (11)	0·9087 (3)	0·0319 (5)
C3′	0·3634 (4)	0·85956 (10)	0·7963 (3)	0·0371 (6)
C4′	0·1370 (3)	0·84077 (11)	0·5964 (3)	0·0356 (6)
C5′	0·1697 (4)	0·84240 (13)	0·3862 (3)	0·0448 (7)
O2′	0·6017 (3)	0·79862 (10)	1·1340 (2)	0·0428 (5)
O3′	0·2852 (4)	0·90010 (10)	0·9293 (3)	0·0545 (6)
O4′	0·0787 (2)	0·77486 (9)	0·6298 (2)	0·0344 (4)
O5′	0·3860 (3)	0·80890 (10)	0·4065 (2)	0·0465 (5)
OW	0·7986 (3)	0·51767 (12)	0·2967 (4)	0·0667 (8)
H1	0·619 (5)	0·5499 (14)	0·457 (4)	0·048 (7)
H10*A*	0·758 (5)	0·6332 (15)	0·322 (5)	0·055 (8)
H10*B*	0·716 (7)	0·704 (2)	0·390 (6)	0·083 (11)
H12*A*	−0·0506 (12)	0·5175 (12)	0·866 (6)	0·059 (7)
H12*B*	0·210 (6)	0·4849 (4)	0·901 (6)	0·059 (7)
H12*C*	0·182 (7)	0·5238 (10)	1·1000 (13)	0·059 (7)
H1′	0·157 (4)	0·7642 (12)	0·933 (4)	0·038 (6)
H2′	0·571 (4)	0·7745 (10)	0·852 (3)	0·028 (5)
H3′	0·485 (5)	0·8816 (12)	0·747 (4)	0·048 (7)
H4′	0·003 (5)	0·8715 (14)	0·592 (4)	0·050 (7)
H5′*A*	0·031 (6)	0·821 (2)	0·273 (5)	0·059 (8)
H5′*B*	0·208 (6)	0·8898 (14)	0·354 (5)	0·060 (8)
HO2′	0·520 (6)	0·805 (2)	1·198 (5)	0·054 (8)
HO3′	0·388 (13)	0·912 (5)	1·071 (11)	0·207 (15)
HO5′	0·384 (6)	0·768 (2)	0·440 (5)	0·063 (8)
H*WA*	0·715 (10)	0·483 (2)	0·206 (8)	0·17 (2)
H*WB*	0·888 (10)	0·537 (3)	0·223 (8)	0·17 (2)
H12*D*	0·010 (8)	0·5323 (6)	1·003 (9)	0·059 (7)
H12*E*	0·277 (2)	0·5011 (15)	1·052 (7)	0·059 (7)
H12*F*	0·055 (10)	0·4927 (12)	0·813 (2)	0·059 (7)

* For non-H atoms, U is $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{A}_{ij}$, where $\mathbf{A}_{ij}$ is the dot product of the ith and jth direct-space unit-cell vectors.

Table 3. *Bond lengths* (Å) *and bond angles* (°) *in* (1)

1	2	3	1—2	1—2—3
C2	N1	C6	1·363 (2)	125·2 (2)
N3	C2	N10	1·333 (3)	120·2 (2)
N3	C2	N1		122·8 (2)
N10	C2	N1		117·0 (2)
C4	N3	C2	1·342 (3)	113·2 (2)
C5	C4	N9	1·332 (3)	107·3 (2)
C5	C4	N3	1·398 (3)	127·1 (2)
N9	C4	N3		125·6 (2)
C6	C5	N7	1·372 (3)	134·0 (2)
C6	C5	C4	1·390 (3)	119·2 (2)
N7	C5	C4		106·7 (2)
S11	C6	N1	1·399 (3)	118·04 (15)
S11	C6	C5	1·689 (3)	129·8 (2)
N1	C6	C5		112·2 (2)
C8	N7	C12	1·386 (3)	122·8 (2)
C8	N7	C5	1·359 (3)	109·9 (2)
C12	N7	C5		127·2 (2)
N9	C8	S13	1·463 (3)	126·0 (2)
N9	C8	N7	1·401 (3)	106·4 (2)
S13	C8	N7		127·7 (2)
C1′	N9	C4	1·658 (2)	126·6 (2)
C1′	N9	C8	1·450 (3)	123·2 (2)
C4	N9	C8		109·6 (2)
C2′	C1′	O4′	1·535 (3)	105·7 (2)
C2′	C1′	N9		115·0 (2)
O4′	C1′	N9	1·415 (2)	107·12 (14)
C3′	C2′	O2′	1·539 (3)	115·2 (2)
C3′	C2′	C1′		101·42 (14)
O2′	C2′	C1′	1·406 (2)	114·1 (2)
C4′	C3′	O3′	1·526 (2)	107·6 (2)
C4′	C3′	C2′		104·1 (2)
O3′	C3′	C2′	1·439 (3)	111·5 (2)
C5′	C4′	O4′	1·507 (3)	107·3 (2)
C5′	C4′	C3′		114·6 (2)
O4′	C4′	C3′	1·453 (3)	106·75 (14)
O5′	C5′	C4′	1·427 (3)	110·9 (2)
C1′	O4′	C4′		109·67 (13)

(Larson, Henry, Kini & Robins, 1990), which are isomorphous, also possess these features as well as other 8-substituted guanosines such as 8-chloro- (Birnbaum, Lassota & Shugar, 1984), 8-bromo- (Tavale & Sobell, 1970) and 8-methylguanosine (Hamada, Honda, Fujii, Fujiwara & Tomita, 1985). It has been suggested that the B-cell activity of 8-bromoguanosine is a result of its confinement to the *syn* conformation (Katze, 1985). The glycosyl bond length [1·450 (3) Å] is equivalent within experimental error to the corresponding bond lengths observed in (2) and (3).

The aglycon moiety. The imidazole ring is planar [r.m.s. deviation: 0·004 (1) Å]; the pyrimidine ring possesses a slight boat conformation [r.m.s. deviation: 0·023 (1) Å; N3 and C6 are up]. The dihedral angle between these planes is 0·31 (8)°; the overall r.m.s. deviation of the purine ring is 0·020 (1) Å. Atom C1′ is 0·1481 (14) Å above the imidazole plane, whereas C12 is in the plane [−0·041 (2) Å deviation].

The sugar moiety. The sugar is in the C_2-*endo*/C_1′-*exo* ($^2T_1$) conformation having phase angle of pseudorotation $P = 149·1°$ and amplitude of pucker $\tau_m = 34·8°$ (Altona & Sundaralingam, 1972), which are characteristic of *syn* nucleosides including those cited above (Hamada, Honda, Fujii, Fujiwara & Tomita, 1985). The C5′—O5′ side chain is in the requisite *gauche–gauche*$^+$ orientation to form the O5′···N3 intramolecular hydrogen bond. The bond lengths in the ribose moiety are normal as are the bond angles.

Packing. The hydrogen bonding is detailed in Table 4 and illustrated in the packing diagrams of Fig. 2. The O5′···N3 intramolecular hydrogen-bond strength, as measured by the O5′···N3 distance [2·900 (3) Å], falls in the middle of the range (2·79–3·01 Å) for the 8-substituted guanosines mentioned above (Larson, Cottam & Robins, 1989; Larson, Henry, Kini & Robins, 1990; Tavale & Sobell, 1970; Birnbaum, Lassota & Shugar, 1984; Hamada, Honda, Fujii, Fujiwara & Tomita, 1985). The base moieties are parallel to the (101) plane (Fig. 2*b*), but the purine rings are not overlapped (Fig. 2*a*). Purine rings translated by $1 + x, y, z - 1$ are bound by very weak head-to-tail amino (N10) to 8-thioxo (S13) interactions which constitute the only interbase hydrogen bonding in the structure. This interaction is similar to that observed in (2) (Larson, Cottam & Robins, 1989) and (3) (Larson, Henry, Kini & Robins, 1990). Strips of head-to-tail bases are separated by 3·40 Å. There are three C—H···X contacts

with $d(H\cdots X)$ distances that are 0·1–0·3 Å less than the sum of the van der Waals radii (Bondi, 1964).

The nearly identical conformations of 7-methyl-6,8-thioxo-7,8-dihydroguanosine and the congeners (2) and (3) suggest that the 6-oxo function is essential for immunomodulatory activity, perhaps because of the stronger hydrogen-bonding capabilities of that function as compared to the 6-thioxo function. The lack of antitumor activity compared to (4) suggests that the 7- and 8-substituents of (1) interfere with the binding at the active site at which (4) produces its antitumor effect. The differences in conformations [*syn* for (1) *versus anti* for (4) (Thewalt & Bugg, 1972)] probably has little to do with the antitumor inactivity of (1) since (4) could certainly assume a *syn* conformation as observed in the antitumor compounds sulfinosine and sulfonosine (Revankar, Hanna, Imamura, Lewis, Larson, Finch, Avery & Robins, 1990; Larson, Hanna, Revankar & Robins, 1990), the former of which exhibits both *syn* and *anti* conformations in the same crystal lattice.

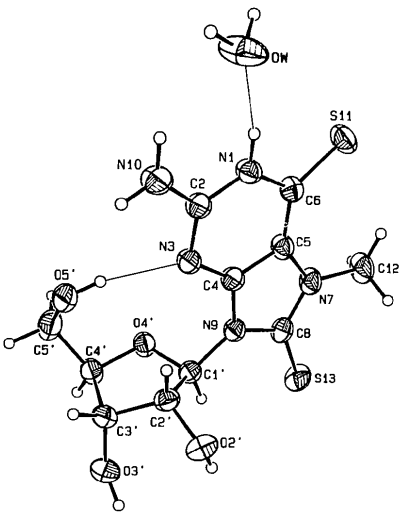


Fig. 1. Thermal-ellipsoid plot of (1) illustrating atom labeling, molecular conformation and intramolecular hydrogen bonding. The ellipsoids of non-H atoms are drawn at the 50% probability level.

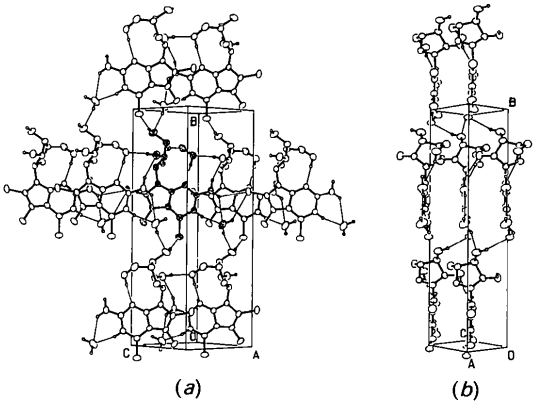


Fig. 2. Crystal packing diagrams of (1) with C—H hydrogens omitted and hydrogen bonds drawn as thin lines: (*a*) view along the **a**–**c** diagonal illustrating the lack of base stacking between the strips of purine bases that are created *via* weak head-to-tail hydrogen bonding; (*b*) view rotated ~90° from the view in (*a*).

Table 4. *Hydrogen bonding and close contacts in* (1)

D—H···A			Symmetry of A relative to D	d(D···A) (Å)	d(H···A) (Å)	(D—H···A) (°)
N1	H1	OW	x,y,z	2·794 (2)	1·93 (3)	164 (3)
N10	H10A	S13	1·0 + x,y,z − 1·0	3·329 (2)	2·67 (3)	130 (2)
N10	H10A	OW	x,y,z	3·151 (3)	2·43 (3)	136 (3)
N10	H10B	O2′	x,y,z − 1·0	3·299 (3)	2·53 (4)	144 (3)
C4′	H4′	S11	−x,0·5 + y,1·0 − z	3·820 (2)	2·87 (3)	156 (2)
C5′	H5′A	O2′	x − 1·0,y,z − 1·0	3·258 (3)	2·40 (3)	146 (3)
C5′	H5′B	S11	1·0 − x,0·5 + y,1·0 − z	3·672 (3)	2·82 (3)	138 (2)
O2′	HO2′	O5′	x,y,1·0 + z	2·647 (2)	1·88 (3)	166 (3)
O3′	HO3′	S11	1·0 − x,0·5 + y,2·0 − z	3·287 (2)	2·37 (8)	167 (8)
O5′	HO5′	N3	x,y,z	2·900 (3)	2·06 (3)	162 (3)
OW	HWA	O3′	1·0 − x,y − 0·5,1·0 − z	2·814 (3)	1·95 (4)	151 (5)
OW	HWB	S13	1·0 + x,y,z − 1·0	3·702 (2)	2·90 (6)	143 (4)

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