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## The Crystal and Molecular Structure of 6-Mercaptopurine Monohydrate. A Second, Independent X-ray Diffraction Determination\*

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The structure of 6-mercaptopurine monohydrate,  $C_5H_4N_4S.H_2O$  was determined by the heavy-atom method. The space group is  $C2/c$ ;  $a=15.3314(4)$ ,  $b=7.7255(1)$ ,  $c=12.3397(2)$  Å,  $\beta=101.526(2)^\circ$ ,  $Z=8$ . These cell parameters differ significantly from those of Sletten, Sletten and Jensen (*Acta Cryst.* (1969) **B25**, 1330) Counter data were recorded for 3792 independent reflections (Mo radiation,  $\sin\theta/\lambda \leq 0.86$ ) and corrected for absorption. The use of anisotropic thermal parameters for the hydrogen atoms results in no significant changes in other structure parameters. The most reliable parameters for the C, N and S atoms are taken to be those from refinement in which the low-angle data ( $\sin\theta/\lambda \leq 0.55$  Å<sup>-1</sup>) are excluded. The corresponding bond lengths (with standard errors from 0.0011 to 0.0016) show some small but significant differences from those of Sletten *et al.* On analysis by the Schomaker-Trueblood method the thermal parameters of the C, N and S atoms show an excellent fit to the rigid-body model. The apparent positions determined for the hydrogen atoms are remarkably close to those found by Sletten *et al.*

### Introduction

The determination at Oak Ridge (OR) of the crystal structure of 6-mercaptopurine monohydrate was undertaken for essentially the same reasons that prompted the parallel study at the University of Washington (UW)—see the accompanying paper of Sletten, Sletten & Jensen (1969). The discovery of the duplication of effort was made when a summary of the preliminary OR results was published in abstract form (Brown, 1967) at just the time that the manuscript of Sletten *et al.* on the UW results was refereed for publication in this journal.

On interchange of information it was found that the agreement between the two sets of cell parameters was rather poor, though each set had apparently been determined with moderately high precision. Furthermore, even when the same set of cell parameters was used in calculating bond lengths from the two sets of coordinates, there were maximum and mean absolute differences of 0.007 and 0.0034 Å for bonds not involving hydrogen atoms, showing a level of agreement somewhat disappointing in view of the apparent high precision of the two determinations. On the other hand, the agreement for the bonds C–H, N–H, and O–H (maximum and mean absolute differences of 0.030 and 0.015 Å) could hardly have been expected to be better.

The cell parameters have now been redetermined in both laboratories with nearly the same results as before,

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the discrepancies remaining much as they were. Further extensive refinement calculations have been performed at Oak Ridge, including some with the data of Sletten *et al.*, which show that the small differences in bond lengths are inherent in the two sets of data and are not consequences of the different weighting schemes and different choices of the observational variable ( $F_o$  versus  $F_o^2$ ) in the two original least-squares determinations. The work at Oak Ridge evolved, because of the stimulus of the slightly different results from the University of Washington, into a study of the sensitivity of the derived structure parameters to some parameters or conditions of the least-squares refinement, especially the sensitivity to the weighting of the data. The structure parameters considered to represent the actual structure most accurately are those from a least-squares calculation using only the reflections having  $\sin \theta/\lambda$  values greater than  $0.55 \text{ \AA}^{-1}$ .

**Experimental**

*Crystal specimen*

The 6-mercaptapurine monohydrate used was Mann's analyzed grade\* ('paper chromatography, homogeneous,' 10.4% H<sub>2</sub>O and 37.07% N found, 10.59% H<sub>2</sub>O and 36.82% N calculated). Larger, faintly yellow crystals were grown from the supplier's fine crystals by slow cooling in a Dewar flask of a boiling saturated aqueous solution, as described by Hoogsteen (1956). Most of the crystals grown were needles, but the specimen used in the cell determination and in the collection of intensity data was cut from one of a few

chunky crystals in the batch. It measured approximately 0.5, 0.5, and 0.3 mm in the *a*, *b*, and *c* directions and was mounted approximately along *b*.

*Unit cell and space group*

From the preliminary X-ray investigation of Hoogsteen (1956) approximate unit-cell dimensions and the possible space groups were known, and the number of formula units per cell was known to be 8. In preliminary work with film methods this information was readily verified; the systematic extinctions, *hkl* absent for  $h+k=2n+1$ , *h0l* absent for  $l=2n+1$ , confirmed the possible space groups as *Cc* and *C2/c*. The choice of the centrosymmetric group *C2/c* was later made by application of the zero-moment test (Howells, Phillips & Rogers, 1950), using the whole set of three-dimensional data; and this choice was confirmed by the success of the subsequent structure determination.

Brief descriptions and results are shown in Table 1 for four different least-squares determinations of cell parameters as follows: OR-1, the original determination on the OR crystal; OR-2, a redetermination on the same crystal; UW-2, a redetermination on the UW crystal by Sletten *et al.*; UW-3, a redetermination on the UW crystal at Oak Ridge. Determinations OR-2, UW-2, and UW-3 were made because of the rather poor agreement of parameters between OR-1 and UW-1, the original UW determination (see Sletten *et al.*, 1969). The differences between OR-1 and UW-1 of about 1 part in 600 for *a*, 1 part in 1100 for *b*, 1 part in 300 for *c*, and  $0.124^\circ$  for  $\beta$  are much larger than the estimated standard errors and were therefore considered to be unacceptable without further investigation.

\* Supplied by Mann Research Laboratories, 136 Liberty Street, New York, N.Y. 10006.

Table 1. *Least-squares determinations of unit-cell parameters for 6-mercaptapurine monohydrate*

OR-1 and OR-2 are determinations on the Oak Ridge crystal; UW-2 and UW-3 are redeterminations on the University of Washington crystal done at Seattle and Oak Ridge respectively. In each case the angle data were from measurements on a four-circle diffractometer. A standard error\* from the least-squares calculation appears in parenthesis adjacent to each parameter value. Unit weights were used in all determinations.

	OR-1	OR-2	UW-2	UW-3
No. of reflections	12	12	40	12†
2θ range	50-55°	119-132°	13-40°	80-94
Doublets resolved?	See text	Yes	No	No
Observations	2θ, χ, φ	2θ, χ, φ	2θ	2θ
Wavelength (Å)	0.70926 (Mo Kα <sub>1</sub> )	1.54051 (Cu Kα <sub>1</sub> )	0.71069 (Mo K α <sub>1</sub> - α <sub>2</sub> wtd. mean)	1.54178 (Cu K α <sub>1</sub> - α <sub>2</sub> wtd. mean)
<i>a</i> (Å)	15.3208 (29)	15.3314 (4)	15.3013 (13)	15.2975 (9)
<i>b</i>	7.7252 (16)	7.7255 (1)	7.7348 (11)	7.7313 (3)
<i>c</i>	12.3409 (19)	12.3397 (2)	12.3789 (13)	12.3719 (5)
β (°)	101.514 (14)	101.526 (2)	101.623 (8)	101.638 (5)
σ <sub>1</sub>	0.020	0.006	—	0.007

\* The effects of absorption were not considered in the least-squares determinations. For determinations OR-1 and UW-2 with Mo Kα radiation, for which the absorption coefficient μ is only 3.84 cm<sup>-1</sup>, no significant error results from absorption. However, for determinations OR-2 and UW-3 with Cu Kα radiation, for which μ is 34.6 cm<sup>-1</sup>, the error from neglect of absorption must be considered. The maximum error in the cell translations from this source is estimated to be only 1 part in 10,000 for either OR-2 or UW-3. Although this error is larger than the least-squares standard errors given in the Table for OR-2 and UW-3, it is still quite small and of no significance in bond length and angle calculations - nor would it be if it were actually larger than the estimate by a factor of 2 or 3.

† In this determination for nearly every reflection *hkl* used 2θ observations were made for both *hkl* and  $\bar{h}\bar{k}l$ , each on both sides of the 2θ zero. In the least-squares calculation 12 average values of 2θ were entered.

In the process of making a new set of very careful angle measurements for OR-2, it was discovered that the OR crystal gave very broad peaks in  $\theta$ - $2\theta$  scans for reflections having reciprocal-lattice vectors near  $\mathbf{a}^*$ . For such reflections, even those at the highest  $2\theta$  angles accessible with the diffractometer ( $\sim 160^\circ$ ), the  $\alpha$  doublet of Cu  $K$  radiation could not be resolved; consequently, it was clear that some of the reflections used in OR-1 could not possibly have been resolved as assumed. (Unfortunately and unwisely, the scan check for resolution had been made for only 2 or 3 of the reflections.) In the new determination each one of the reflections used was scanned and found to be resolved. Thus the small parameter differences appearing between OR-1 and OR-2, which approach chemical significance only in the case of  $a$ , have a reasonable explanation.

In redetermining the cell parameters of the UW crystal, Sletten *et al.* first used new measurements on the same 17 reflections used originally ( $2\theta$  range  $13$ – $30^\circ$ , Mo  $K\alpha$  radiation) and obtained essentially the same results as before, except that the standard errors derived were about  $\frac{2}{3}$  as large. When another 23 reflections in the  $2\theta$  range  $17$ – $40^\circ$  were included (see UW-2 in Table 1), the most significant change was an increase  $a$  of 1 part in 2200.

For the redetermination (UW-3) of the UW crystal at OR it was intended to use exactly the same apparatus and technique as used in OR-2. It proved impossible, however, to use exactly the same procedure, because the crystal shows more generally the broad peaks observed for a few reflections of the OR crystal. Every reflection which was scanned as a possible candidate for use in the least-squares determination turned out to be not resolvable into  $\alpha_1$  and  $\alpha_2$  components. It was decided to use data for reflections near  $90^\circ 2\theta$ , recorded with the tube take-off angle set to  $4^\circ$  to minimize the separation of  $\alpha_1$  and  $\alpha_2$ , and, correspondingly, to use the weighted mean wavelength  $1.54178 \text{ \AA}$  in the calculations. The parameters derived are very close to those of the original determination, UW-1, except in the case of  $c$ , for which the difference amounts to about  $6\sigma(c)$  of UW-1. This difference is, however, only about 1 part in 1500 – hardly enough to be concerned about in its effect on derived distances and angles.

Thus we find that for both the OR and UW crystal specimens the revised parameters are at most slightly different from the original ones and that the discrepancies between the parameters for the two crystals remain about as they were. One must conclude that the two crystal specimens are indeed to be described by slightly different sets of cell parameters. For this paper the parameters of determination OR-2 have been used in the calculation of bond lengths and angles. Sletten *et al.* (1969) have quite reasonably chosen to use their original cell parameters (UW-1), which, as already discussed, are not very much different from those of UW-2 and UW-3.

It now appears probable that the differences in cell parameters arise as effects of a difference of purity between the two samples of 6-mercaptopurine monohydrate used. An inquiry by Professor Jensen to the supplier of the 6-mercaptopurine used at UW has elicited the information that chromatographic analysis of the batch indicated the presence of about 2% of unknown impurity.

Another possibility is that the differences in cell parameters are related to the difference in extent through the reciprocal lattice of the peak-broadening effect, which was possibly caused by different conditions of growth for the two specimens. On the other hand, the different extent of broadening may itself be related to the difference of purity.

#### Intensity data

Molybdenum  $K\alpha$  radiation was chosen for recording the reflection intensities because of the low value of the absorption coefficient of the 6-mercaptopurine monohydrate (calculated  $\mu = 3.84 \text{ cm}^{-1}$ ) for this radiation. The X-ray tube was operated at 50 kV constant potential and 14 mA current. Intensity data were recorded for 3792 independent reflections with the Oak Ridge computer-controlled X-ray diffractometer (Busing, Ellison, Levy, King & Roseberry, 1968), with the  $\theta$ - $2\theta$  step-scan method to  $75^\circ$  in  $2\theta$  ( $\sin \theta/\lambda = 0.857 \text{ \AA}^{-1}$ ) and an  $\Omega$  step-scan method as well for the reflections in the range  $0^\circ$  to  $30^\circ 2\theta$ .

In the  $\theta$ - $2\theta$  technique the step width was  $0.05^\circ$  in  $2\theta$ , and the total width of scan for each reflection was  $2^\circ$  plus the width of the  $\alpha$  doublet separation. The counting time was set at 10 seconds for the background counts taken at the beginning and end and at 2 seconds for all other points in each scan. The take-off angle at the X-ray tube was  $3^\circ$ , giving an effective target  $0.13^\circ$  wide by  $0.32^\circ$  high; the receiving aperture at the counter was  $1.6$  by  $1.6^\circ$ . A  $0.004''$  niobium filter was used in recording data below  $60^\circ 2\theta$ ; no filter was used above  $60^\circ 2\theta$ .

In the  $\Omega$  step-scan technique (Levy, 1966) three scans were run for each reflection: (1) with the counter arm set at the computed  $2\theta$  value of the reflection; (2) and (3) with the arm offset first lower and then higher in  $2\theta$  just enough to determine background. The net count of the reflection was taken as the integrated count of scan (1) minus the average of the integrated counts of (2) and (3). This procedure, with proper choice of take-off angle, counter aperture, and  $2\theta$  offset, provides more reliable background determinations for the low-angle reflections than does the  $\theta$ - $2\theta$  technique, in which the effect of the absorption edge of the filter just below the peaks for  $\alpha$ -radiation makes proper background measurement impossible on the low-angle sides of the peaks.

The width of each  $\Omega$  scan was  $1^\circ$ , the step width was  $0.025^\circ$ , and the count time at each point was 2 seconds. The take-off angle at the X-ray tube was set at  $1^\circ$  (effective target  $0.04$  by  $0.32^\circ$ ), and the counter

slit and the counter offset  $\Delta(2\theta)$  were set so that the three scans for each reflection would not overlap and so that the slit width and  $\Delta(2\theta)$  (both the same) were always less than the angular separation between the  $\alpha$  peak and the  $2\theta$  position corresponding to the absorption edge but the slit width was always wide enough to admit the  $\alpha$  doublet. It was not possible to satisfy these conditions for the  $2\theta$  range  $0^\circ$  to  $30^\circ$  with a single value for counter aperture and  $\Delta(2\theta)$ ; accordingly, scans were run in the range  $0$  to  $15.2^\circ 2\theta$  with the aperture and  $\Delta(2\theta)$  at  $0.46^\circ$  and in the range  $15.2$  to  $30^\circ 2\theta$  with the aperture and  $\Delta(2\theta)$  at  $0.67^\circ$ .

In the  $2\theta$  scans the intensity of a reference reflection, 008, was recorded after each group of 20 reflections as a check on the stability of the instrument and that of the crystal specimen. Similarly, for the  $\Omega$  scans reflection 420 was used as a reference. There was no evidence from the reference intensities, or from visual inspection, of any deterioration of the crystal specimen. There were slow fluctuations (over many hours) of the standard intensities amounting to about 7.5%, probably resulting from imperfect stabilization of the line voltage to the X-ray generator and poor performance of the tube-current stabilizer. However, the short term

fluctuations between the recording of reference intensities were no more than 1%.

As the data were recorded, corrections for coincidence loss were made on the counts of the individual points in the step scans before integration. The computer subroutine for this purpose used for the apparent dead time the value  $1.8 \times 10^{-6}$  seconds obtained in a calibration study by H. A. Levy & R. D. Ellison.

The raw data from the diffractometer were converted by calculations with the CDC 1604A computer to a set of structure-factor squares  $F_o^2$  and statistical standard errors  $\sigma_c(F_o^2)$ . The variations of intensity of each reference reflection were assumed to represent slowly varying X-ray output; and the reference intensities were used to normalize the data to a single standard value of intensity for each reference reflection, a linear relation of X-ray intensity to time being assumed to hold between each pair of adjacent reference intensities. Absorption corrections calculated by the method of Busing & Levy (1957) were applied; the range of correction factors was only 1.12 to 1.16. The first three derivatives of the transmission factor with respect to  $\mu$  were also computed, for subsequent use in correcting

Table 2. Summary of various least-squares refinement calculations on 6-mercaptapurine monohydrate

Cal. no.	Data set	Obs.	Weight scheme	sin $\theta/\lambda$ range	Hydrogen thermal parameters	No. of observations	Measures of agreement <sup>a</sup>			
							$R(F)$	$R(F^2)$	$R_w$	$\sigma_1$
1	UW	$F$	UW	$\leq 0.71$	ISO.	1838 <sup>b</sup> 2186 <sup>c</sup>	0.038 —	— —	0.037 —	2.01 —
2	UW	$F$	UW	$\leq 0.71$	ISO.	1860 <sup>d</sup> 1835 <sup>b</sup> 2186 <sup>c</sup>	0.038 0.038 0.054	0.041 0.041 0.043	0.037 — 0.042	2.18 2.19 2.25
3	UW	$F^2$	OR	$\leq 0.71$	ISO.	1859 <sup>d</sup> 2186 <sup>c</sup>	0.038 0.054	0.044 0.046	0.087 0.093	1.64 1.62
4	OR	$F$	UW	$\leq 0.71$	ISO.	1877 <sup>d</sup> 1842 <sup>b</sup> 2182 <sup>c</sup>	0.033 0.032 0.048	0.038 0.038 0.040	0.031 — 0.034	2.01 2.03 2.04
5	OR	$F^2$	OR	$\leq 0.71$	ISO.	2182 <sup>c, d</sup> 1967 <sup>e</sup>	0.040 0.034	0.039 0.039	0.076 0.076	1.57 1.64
6	OR	$F^2$	OR	$\leq 0.86$	ISO.	3792 <sup>c, d</sup> 3139 <sup>e</sup>	0.063 0.048	0.045 0.044	0.086 0.085	1.40 1.52
7	OR	$F^2$	OR	$\leq 0.86$	ANISO.	3792 <sup>c, d</sup> 3139 <sup>e</sup>	0.062 0.048	0.044 0.048	0.084 0.083	1.38 1.50
8	OR	$F^2$	OR	$> 0.55$	ISO.	2792 <sup>c, d</sup> 2182 <sup>e</sup>	0.101 0.071	0.078 0.072	0.093 0.090	1.06 1.16
9	OR	$F^2$	OR	$\leq 0.55$	ISO.	1000 <sup>c, d</sup> 957 <sup>e</sup>	0.024 0.023	0.035 0.035	0.064 0.064	1.72 1.76

<sup>a</sup> Definitions:

$$\begin{aligned}
 R(F^m) &\equiv \Sigma ||F_o|^m - |F_c|^m| / \Sigma |F_o|^m, \\
 R_w &\equiv [\Sigma w(|F_o|^m - |F_c|^m)^2 / \Sigma w|F_o|^{2m}]^{1/2} \\
 \sigma_1 &\equiv [\Sigma w(|F_o|^m - |F_c|^m)^2 / (n-p)]^{1/2}.
 \end{aligned}$$

In these equations  $w$  is the weight of the observation  $F_o$  or  $F_o^2$ , and  $p$  is the number of parameters fitted to the  $n$  observations; the weights and the structure factors are on the correct absolute scale established by the refinement. For each refinement calculation both  $R(F)$  and  $R(F^2)$  are given; however, the values  $R_w$  and  $\sigma_1$  are calculated either for  $m=1$  or  $m=2$  according as the observational variable in column 3 is  $F$  or  $F^2$ .

<sup>b</sup> Omits any observation included in refinement for which  $F_c < 2\sigma(F_o)$ .

<sup>c</sup> Total number of observations in specified range of sin  $\theta/\lambda$ .

<sup>d</sup> Number of observations actually included in least-squares refinement.

<sup>e</sup> Number of observations for which  $F^2 > \sigma(F_o^2)$ .

for extinction. The data for the  $\Omega$  scans in the range  $0^\circ$  to  $15^\circ 2\theta$  were scaled to the other data by use of the intensities of reflections 420 and 008, after correction for absorption. Different scale-factor identifiers were assigned to groups of data as follows: (1)  $\Omega$  scans,  $0$  to  $15^\circ 2\theta$ ; (2)  $\Omega$  scans,  $15.2$  to  $30^\circ 2\theta$ ; (3)  $2\theta$  scans,  $0$  to  $60^\circ$ ;  $2\theta$  scans,  $60$  to  $75^\circ$  (unfiltered radiation).

The value  $2.0 \text{ \AA}^2$  for the overall isotropic temperature factor and an approximate scale factor on the observations were obtained by the method of Wilson (1942).

### Solution and refinement

The procedures by which the structure was found through application of the classic heavy-atom method and subsequently refined to the stage reported earlier (Brown, 1967) were nearly identical with those used by Sletten, Sletten & Jensen (1969). At this stage the usual reliability index calculated on  $F$  was  $0.035$  and the estimated errors of the lengths of bonds not involving hydrogen atoms were about  $0.002 \text{ \AA}$ . No absorption corrections had been made, and only 1634 reflections ( $\sin \theta/\lambda \leq 0.65 \text{ \AA}^{-1}$ , equivalent to the Cu  $K\alpha$  sphere) were included in the refinement. Data from  $\Omega$  scans and  $\theta-2\theta$  scans had simply been averaged.

Further refinement of the 6-mercaptopyrine structure based on the OR data was made after the data had been corrected for absorption effects. The data from  $\theta-2\theta$  scans below  $30^\circ 2\theta$  were omitted in favor of the data from the  $\Omega$  scans which had been run in the same range. The data set showed very slight effects of extinction, the maximum effect for the most intense reflection being a reduction of intensity of only about

15% below the calculated intensity. The least-squares program used includes a correction for extinction according to the second-order approximation of Zachariasen (1965). Correction factors for the values  $F_c^2$  are calculated with Zachariasen's equation (14) to the third power in  $X_H$ , the quantity  $g_2$  being optimized with the other parameters. Only 20 reflections were affected by as much as 1%.

Least-squares refinement calculations based on the OR data were carried to convergence under a number of different conditions as regards weighting scheme, range in  $\sin \theta/\lambda$  of the data included, kind of thermal parameters used for hydrogen atoms, and so forth. Some additional refinement calculations were also performed with the UW data, which were kindly supplied by Sletten *et al.* for this purpose. In all of the calculations the scattering factors used were the same as those used by Sletten *et al.* The conditions of the various refinement calculations and the fits obtained are set forth in Table 2. In all of the calculations, except as noted below, the extinction parameter, the four scale factors for different groups of data, and the parameters of the hydrogen atoms were optimized, along with the usual nine parameters for each of the other atoms. Each calculation is assigned an arbitrary identifying number for purposes of discussion. It is not possible, of course, to show in detail how the structure parameters vary from one calculation to another; however, the results of the various calculations are placed in structural-chemical perspective by appropriate comparisons of the bond lengths derived from the coordinates (see Table 3).

The entries in Table 2 under calculation (1) describe the refinement of Sletten, Sletten & Jensen (1969) with

Table 3. Comparison of bond lengths in the 6-mercaptopyrine molecule as calculated from the parameters from the various refinement calculations of Table 2

Column 1-3, for example, contains the differences in bond lengths ( $\text{\AA} \times 10^3$ ) between calculations 1 and 3 (1 minus 3). The atoms are numbered as in Figs. 4 and 5. The last column gives the standard errors of the bond lengths from the parameters of calculation 8.

Bond	Comparison														$\sigma$
	1-3	1-4	1-5	1-7	1-8	3-5	4-5	5-6	5-7	5-9	6-7	6-8	7-8	8-9	
C(2)-N(3)	-1	4	2	1	-2	3	-2	0	-1	0	-1	-4	-3	4	1.6
N(1)-C(2)	0	-2	-2	-3	-8	-2	0	0	-1	6	-1	-6	-5	12	1.3
N(9)-C(4)	0	-1	-2	-2	-5	-2	-1	0	0	-1	0	-3	-3	2	1.4
N(3)-C(4)	1	-4	-1	-1	3	-2	3	0	0	-3	0	4	4	-7	1.3
C(4)-C(5)	-1	7	4	4	3	5	-3	1	0	7	-1	-2	-1	8	1.1
C(5)-N(7)	0	-4	-2	-2	-3	-2	2	0	0	0	0	-1	-1	1	1.4
C(5)-C(6)	-2	-2	-6	-6	-8	-4	-4	0	0	2	0	-2	-2	4	1.4
C(6)-N(1)	0	4	6	9	12	6	2	2	3	-2	1	4	3	-8	1.3
C(6)-S	1	4	3	1	-3	2	-1	-1	-2	1	-1	-5	-4	7	0.9
C(8)-N(9)	-2	1	-2	-2	-7	0	-3	-1	0	4	1	-4	-5	9	1.4
N(7)-C(8)	0	-2	-2	-2	-6	-2	0	1	0	4	-1	-5	-4	8	1.5
Avg. $ \Delta $	0.7	3.2	2.9	3.0	5.5	2.7	1.9	0.5	0.6	2.7	0.6	3.6	3.2	6.4	1.4
R.m.s. $\Delta$	1.0	3.6	3.3	3.8	6.2	3.2	2.3	0.8	1.2	3.4	0.8	3.8	3.3	7.1	
C(2)-H(2)	0	-24	-15	-11	-11	-15	9	1	4	20	3	3	0	-16	12
C(8)-H(8)	7	-22	-7	-9	5	-14	15	6	-2	-2	-8	6	14	-14	13
N(1)-H(1)	9	-40	-25	-15	-26	-34	15	-6	10	7	16	5	-11	8	15
N(7)-H(7)	-13	-36	-16	-7	-12	-3	20	-1	9	31	10	5	-5	27	15
O-H(10)	-19	-32	-28	-37	-25	-9	4	2	-9	0	-11	1	12	-3	16
O-H(11)	12	-16	-8	-15	-12	-20	8	2	-7	-13	-9	-3	6	-12	18
Avg. $ \Delta $	10	28	17	16	15	16	12	3	7	12	10	4	8	13	15
R.m.s. $\Delta$	12	30	18	19	17	19	13	4	7	16	10	4	9	15	

the UW data. Calculation (2) in Table 2 was in effect a replicate of (1) performed at OR, partly to check results from the OR least-squares computer program against those from the UW program and partly to check a subroutine used in calculation (4) for computing weights according to the UW scheme. The parameters from (2) are nearly identical with those from (1). There is an inconsistency in the fact that the standard errors of parameters from (2) are generally 5 to 10% higher than those from (1) and the  $\sigma_1$  values for (2) are also higher by about 10%, but the weighted discrepancy indices  $R_w$  are equal for (1) and (2).

In calculation (3) with the UW data, the quantities  $F_o^2$  were used as observations, and the weighting scheme was the one usually found appropriate in this laboratory:\*

$$\begin{aligned}\sigma^2(F_o^2) &= \sigma_o^2(F_o^2) + (0.03F_o^2)^2, \\ w(F_o^2) &= 1/\sigma^2(F_o^2).\end{aligned}$$

The variance  $\sigma_o^2(F_o^2)$  is, as defined earlier, the purely statistical variance. The quantity  $F_o^2$  in the correction term is systematically somewhat smaller than the term  $\sigma_o^2(F_o^2)$  used (in effect) by the UW group, but the important difference between the OR and UW weighting schemes is the use of the coefficient 0.03 in the former rather than the factor 0.01 in the latter. This term in the OR scheme has the effect of diminishing to a greater degree the importance of the larger  $F_o^2$  values relative to that of the smaller ones.† It was intended to allow, at least in part, for deficiencies in the model, as well as for imperfect stability of the circuitry. It turns out that the parameters and standard errors from (3) are only trivially different from those of (2).

Calculation (4) on the OR data corresponds to (1) and (2) on the UW data. The fit is slightly better than for (2) and the parameter errors are generally about 10% smaller than in (1).

Calculation (5) on the OR data corresponds to (3) on the UW data; that is, the observational data were the quantities  $F_o^2$  and the OR weighting scheme was used. The fit in (5) is distinctly better than in (4), just as it was better for (3) than for (2). The standard errors of coordinates from (5) are about 10% smaller than those from (4).

Comparison 1–3 in Table 3 shows how little the derived bond lengths change when one changes from the UW to the OR refinement scheme. Comparisons 1–4 and 3–5 show that appreciable differences in bond lengths remain between the structures based on the UW and OR data sets for the same  $\sin \theta/\lambda$  range, no matter which scheme is used in refinement. The difference of purity between the OR and UW specimens

may be, in part, the source of these differences as well as those between the two sets of cell parameters. See, however, the discussion at the end of this section regarding the comparison of the two sets of  $F_o^2$  data.

From comparison 4–5 it appears that the bond lengths derived from the OR data are slightly more sensitive to the choice of refinement scheme than those from the UW data (comparison 1–3). Comparisons 5–6, 5–7, and 6–7 in Table 3 show that the effects on the molecular geometry of increasing the  $\sin \theta/\lambda$  cutoff value from 0.714 to 0.877 Å<sup>-1</sup> and of using anisotropic instead of isotropic thermal parameters for the hydrogen atoms are trivial.

The conditions of calculation (6) were the same as those of (5) except that the full set of OR data was used in (6). Number (7) differed from (6) only in that anisotropic thermal parameters were used for the hydrogen atoms. A calculation (7a), not represented in Table 2, differed from (7) in that the ~200 negative values of  $F_o^2$  (resulting from statistical fluctuations and instrumental errors) were retained in the least-squares calculations, rather than replaced by zero values as in all the other refinements with the OR data. The standard errors from (6), (7), and (7a) are all about the same and generally somewhat smaller than those from (5). The values of  $\sigma_1$  from (6), (7), and (7a) are about 10% lower than  $\sigma_1$  for (5), indicating a better fit, on the average, to the high-angle data than to the low-angle data. The parameters (other than the thermal parameters of the hydrogen atoms) from (6) and (7) are only trivially different; the parameters from (7) and (7a) are nearly identical.

It is of some interest that the quadratic forms of the temperature-factor exponents of the hydrogen atoms all remained positive-definite in calculation (7), since attempts at refinement from X-ray data of anisotropic thermal parameters have rarely been successful. The  $R$  factor ratio test (Hamilton, 1965) indicates that the slight improvement in fit from (6) to (7) is significant (probability >99.5%). It is clear, however, that the thermal parameters of H(1) and H(7), on N(1) and N(7) respectively, cannot be interpreted in terms of thermal motion only, for the probability ellipsoids of H(1) and H(7) have odd shapes and orientations (see Fig. 1), which may be related to deficiencies in the model as it describes the electron density in the molecule.

Following calculation (7) a partial-difference Fourier synthesis (not shown) in the average plane of the nearly planar 6-mercaptapurine molecule was computed by use of magnitudes  $|F_o| - |F_c|$  calculated without including the hydrogen contributions, and signs calculated including these contributions. There is some elongation in the peaks representing H(1) and H(7), though not so much as might be expected from Fig. 1. A striking feature of the map, which is quite similar to the composite difference map shown by Sletten *et al.* and also similar to the final map (see Fig. 2) subsequently prepared in this analysis, is that there is a low peak (0.15 to 0.40 e.Å<sup>-3</sup>, to be compared with peaks of 0.82

\* It was not possible to calculate exactly from the values  $F_o$  and  $\sigma(F_o)$  supplied by Sletten *et al.* the weights according to the OR scheme; however, a satisfactory approximation was made by correcting each variance  $\sigma^2(F_o^2)$  by the addition of the term 0.0008  $F_o^4$ .

† For the largest values  $F_o^2$  the OR weights are  $\sim \frac{1}{3}$  those of the UW weights; for the weakest reflections,  $\sim \frac{1}{3}$ .

to  $0.87 \text{ e.}\text{\AA}^{-3}$  for the hydrogen atoms) centered near the middle of each ring bond.

The appearance in the difference map of the 'bonding' peaks suggests the desirability of modifying the model for structure-factor calculation so as to take account of bonding effects on electron distribution, as has been done in a few X-ray structure studies (see, for example, Cady & Larson, 1965, and Fritchie, 1966). As a practical matter, however, it is not possible for me to undertake the necessary computer programming at this time. Instead I have chosen to make further refinement calculations excluding the low-angle reflections, for which the calculated structure factors are most aberrant because of the use of scattering factors for spherical atoms. Such a procedure was originally suggested by Jeffrey & Cruickshank (1953) as a means of obtaining more reliable thermal parameters; but, as pointed out by Cruickshank (1956), it should in principle result in more reliable coordinates as well. The OR data set for 6-mercaptopyrine is particularly suitable for this purpose, since it extends unusually far in  $\sin \theta/\lambda$ , at least for an organic crystal.

In least-squares calculation (8) the reflections included were limited to those having  $\sin \theta/\lambda$  greater than  $0.55 \text{ \AA}^{-1}$ . The starting parameters were from calculation (6), and the scale factors, extinction parameter, and hydrogen-atom parameters were held fixed. It appears that the parameter changes from (6) to (8) are significant, though small, for the  $R$  factor ratio test shows that the parameters from (8) fit the limited data set much better than those from (6) (probability  $> 99.5\%$ ). The standard error of fit is markedly smaller than for calculation (6),  $1.06$  instead of  $1.38$ , showing that the model fits the high-angle data better than the low-angle data, if one assumes that the relative weights for high and low angle data have been assigned correctly. This point is emphasized by calculation (9), including only the reflections having  $\sin \theta/\lambda \leq 0.55 \text{ \AA}^{-1}$ , for which the value of the standard error of fit is  $1.72$ . Although the fit is better for (8) than for (6), the standard errors derived for (8) are higher by about 20%. Additional least-squares calculations (not represented in Table 2) with lower limits in  $\sin \theta/\lambda$  of  $0.50$  and  $0.59 \text{ \AA}^{-1}$  established that the structure parameters are insensitive to the precise choice of limit in this range.

A partial-difference Fourier synthesis in the average molecular plane was computed following refinement calculation (8), including the terms with  $\sin \theta/\lambda \leq 0.71$ . The resulting map (see Fig. 2) shows peaks for the hydrogen atoms from  $0.87$  to  $0.90 \text{ e.}\text{\AA}^{-3}$  in height and bonding peaks of  $0.21$  to  $0.46 \text{ e.}\text{\AA}^{-3}$ . Curiously, the peaks H(1) and H(7) do not have shapes that are consistent with the corresponding ellipsoids of Fig. 1. Another map computed only with terms having  $\sin \theta/\lambda \leq 0.55$  shows the same general features and has bonding peaks  $0.82$  as high, on the average, as those in Fig. 2. It thus appears that most of the perturbing effects of the deficiencies of the structure model have been avoided by the omission of the low-angle data in cal-

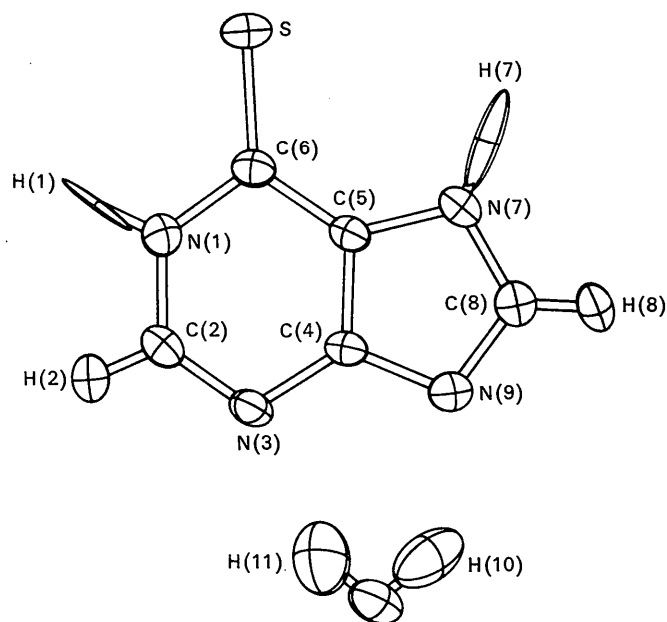


Fig. 1. The 50% probability thermal ellipsoids from the thermal parameters of least-squares calculation (7). View is in the direction of the normal to the molecular plane for each molecule.

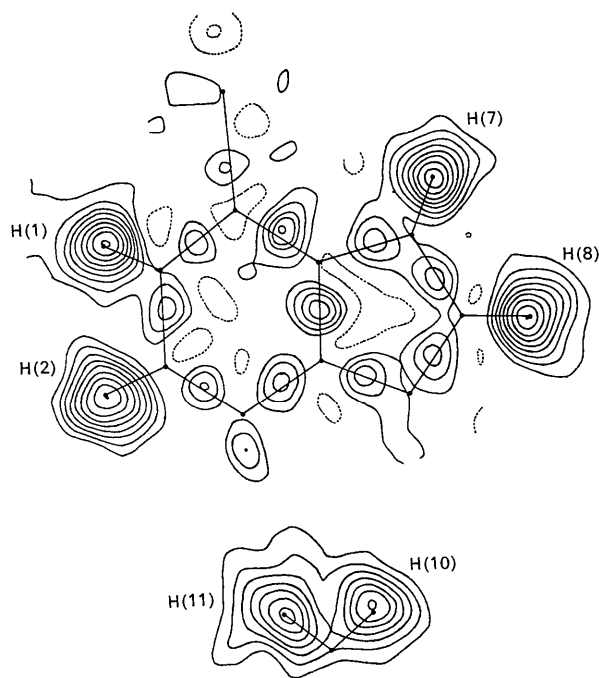


Fig. 2. Partial difference maps in planes of 6-mercaptopyrine and the water molecule, after least-squares calculation (8). Terms were included for those reflections having  $\sin \theta/\lambda \leq 0.71$ . The lowest positive contour is at the  $0.1 \text{ e.}\text{\AA}^{-3}$  level; the highest negative contour is at the  $-0.1 \text{ e.}\text{\AA}^{-3}$  level.

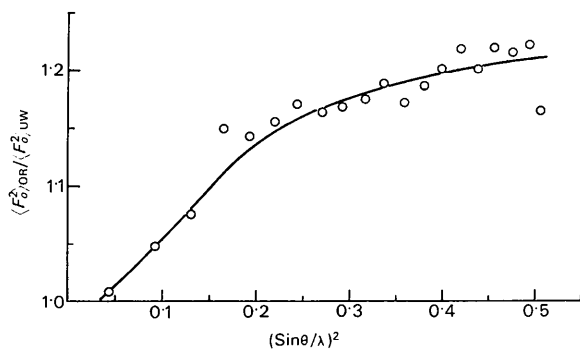


Fig. 3. Plot showing the agreement between the OR  $F_o^2$  data and the UW  $F_o^2$  data as a function of  $(\sin \theta / \lambda)^2$ .  $\langle F_o^2 \rangle_{OR}$  and  $\langle F_o^2 \rangle_{UW}$  denote averages over small ranges of  $(\sin \theta / \lambda)^2$ .

ulation (8). It therefore seems reasonable to regard the parameters from (8), shown in Table 4, as representing most accurately the actual structure of 6-mercaptopurine monohydrate. Similarly, Furberg & Jensen (1968) have concluded that the best parameters for the crystal structure of thiocytosine result when only the higher-order data are used. In Table 4 the extra entries for the hydrogen coordinates are empirically corrected values (see text below under the heading *Molecular structure*).

Table 5 compares the values  $F_o$  with the values  $F_c$  computed from the parameters of calculation (8). The values of  $F_o$  are on the scale established in the refine-

ment and include the computed extinction corrections. The standard error  $\sigma(F_o)$ , computed as  $\sigma(F_o^2)/2F_o$ , is given for each reflection for which  $F_o^2 > \sigma(F_o^2)$ ; the error  $\sigma(F_o^2)$  is given for each reflection (marked *W*) for which  $F_o^2 \leq \sigma(F_o^2)$ .

At the end of the refinement process, the sets of  $F_c^2$  data from the OR and UW determinations were systematically examined over their common range of  $\sin \theta / \lambda$  for their agreement as a function of diffraction angle. Reflections which were weak in either set ( $F_o^2 \leq \sigma(F_o^2)$  for OR data;  $F_o^2 < 2\sigma(F_o^2)$  for UW data) were excluded in the comparison. The OR data were scaled as in Table 5, and the UW data as in Table 6 of Sletten *et al.* (1969). Fig. 3 shows a plot against  $(\sin \theta / \lambda)^2$  of  $\langle F_o^2 \rangle_{OR} / \langle F_o^2 \rangle_{UW}$ , where the brackets  $\langle \rangle$  denote an average over a small range of  $(\sin \theta / \lambda)^2$ . Each point in the plot represents roughly the same number of reflections. It is clear from the Figure that systematic errors of measurement were made in the determination of one of the other, or both, of the sets of data. The value of the discrepancy index  $R = \Sigma |F_o^2_{OR} - F_o^2_{UW}| / (\frac{1}{2} \Sigma (F_o^2_{OR} + F_o^2_{UW}))$  is 0.092; the corresponding index computed on  $F_o$  instead of on  $F_o^2$  is 0.070. These indices in comparison with the corresponding discrepancy indices given in Table 2, which are smaller by a factor of  $\sim 2$ , demonstrate that the  $R$  values can give a misleading impression as to the quality of a crystal-structure determination. In one or the other of the two determinations, or perhaps in both, the parameters have been adjusted in such a way as

Table 4. *Final parameters of the structure of 6-mercaptopurine monohydrate*

The elements  $B_{ij}$  form the symmetric matrix  $\mathbf{B}$  in the temperature factor  $\exp \{-\frac{1}{4}[h_i b_i]^T \mathbf{B} [h_i b_i]\}$ , where each of the three elements of the one-column matrix  $[h_i b_i]$  is the product of a reflection index and the corresponding reciprocal translation ( $\text{\AA}^{-1}$ ). The additional entries in italics for the coordinates of the hydrogen atoms are empirically adjusted values (see text under heading *Molecular structure*).

	1st digit = tenths digit			1st digit = units digit					
	<i>x</i>	<i>y</i>	<i>z</i>	$B_{11}$	$B_{22}$	$B_{33}$	$B_{12}$	$B_{13}$	$B_{23}$
S	44648 (2)	66250 (5)	35602 (3)	269 (1)	330 (1)	230 (1)	-034 (1)	127 (1)	013 (1)
C(2)	36701 (8)	66858 (18)	64218 (8)	244 (4)	261 (4)	151 (2)	-009 (3)	031 (2)	-010 (3)
C(4)	26259 (7)	51572 (14)	53004 (7)	186 (3)	205 (3)	145 (2)	004 (2)	055 (2)	010 (2)
C(5)	30600 (7)	53754 (14)	44193 (7)	194 (3)	205 (3)	137 (2)	-005 (2)	052 (2)	000 (2)
C(6)	38605 (7)	63068 (14)	45370 (8)	194 (3)	202 (3)	165 (2)	004 (2)	057 (2)	022 (2)
C(8)	18392 (8)	38889 (18)	39083 (10)	233 (4)	259 (4)	211 (3)	-034 (3)	037 (3)	-027 (3)
N(1)	41145 (7)	69536 (14)	55884 (8)	206 (3)	239 (3)	179 (2)	-022 (2)	030 (2)	-002 (2)
N(3)	29289 (7)	58078 (16)	63318 (7)	240 (3)	271 (4)	139 (2)	-005 (3)	055 (2)	003 (2)
N(7)	25409 (7)	45494 (15)	35347 (7)	240 (3)	259 (3)	150 (2)	-018 (3)	044 (2)	-028 (2)
N(9)	18610 (7)	42230 (16)	49729 (8)	212 (3)	266 (4)	206 (2)	-030 (2)	068 (2)	-012 (3)
O	44130 (9)	09908 (19)	36929 (10)	282 (4)	343 (4)	282 (4)	-082 (3)	101 (3)	008 (3)
H(1)	4587 (10)	7623 (18)	5755 (12)	40 (3)					
	<i>4684</i>	<i>7759</i>	<i>5789</i>						
H(2)	3939 (8)	7255 (15)	7093 (10)	29 (3)					
	<i>3974</i>	<i>7328</i>	<i>7180</i>						
H(7)	2637 (10)	4510 (19)	2861 (12)	46 (3)					
	<i>2655</i>	<i>4503</i>	<i>2733</i>						
H(8)	1380 (9)	3231 (15)	3456 (10)	28 (3)					
	<i>1319</i>	<i>3144</i>	<i>3396</i>						
H(10)	4067 (11)	1023 (21)	4122 (12)	45 (4)					
	<i>3988</i>	<i>1030</i>	<i>4220</i>						
H(11)	4525 (11)	-0068 (23)	3678 (13)	52 (4)					
	<i>4543</i>	<i>-0236</i>	<i>3676</i>						

$g_2 = 1.02 \times 10^{-6}$   
 $\sigma(g_2) = 0.27 \times 10^{-6}$



Table 5. Observed and calculated structure factors for 6-mercaptopurine monohydrate

For each reflection, identified by the indices  $K$  and  $L$  of a subheading and the running index  $H$ , the values of  $F_o \times 10$  and  $F_c \times 10$  are given. The standard error  $\times 10$  of  $F_o$  (see text) is given under the heading SG, except that for each reflection marked  $W$ , for which  $F_o^2 < \sigma(F_o^2)$ , the standard error  $\times 1$  of  $F_o^2$  is given instead.

K	L	H	$F_o \times 10$	$\sigma(F_o)$	SG	$F_c \times 10$	$\sigma(F_c)$
005	005	1	173	10		173	10
005	005	2	173	10		173	10
005	005	3	173	10		173	10
005	005	4	173	10		173	10
005	005	5	173	10		173	10
005	005	6	173	10		173	10
005	005	7	173	10		173	10
005	005	8	173	10		173	10
005	005	9	173	10		173	10
005	005	10	173	10		173	10
005	005	11	173	10		173	10
005	005	12	173	10		173	10
005	005	13	173	10		173	10
005	005	14	173	10		173	10
005	005	15	173	10		173	10
005	005	16	173	10		173	10
005	005	17	173	10		173	10
005	005	18	173	10		173	10
005	005	19	173	10		173	10
005	005	20	173	10		173	10
005	005	21	173	10		173	10
005	005	22	173	10		173	10
005	005	23	173	10		173	10
005	005	24	173	10		173	10
005	005	25	173	10		173	10
005	005	26	173	10		173	10
005	005	27	173	10		173	10
005	005	28	173	10		173	10
005	005	29	173	10		173	10
005	005	30	173	10		173	10
005	005	31	173	10		173	10
005	005	32	173	10		173	10
005	005	33	173	10		173	10
005	005	34	173	10		173	10
005	005	35	173	10		173	10
005	005	36	173	10		173	10
005	005	37	173	10		173	10
005	005	38	173	10		173	10
005	005	39	173	10		173	10
005	005	40	173	10		173	10
005	005	41	173	10		173	10
005	005	42	173	10		173	10
005	005	43	173	10		173	10
005	005	44	173	10		173	10
005	005	45	173	10		173	10
005	005	46	173	10		173	10
005	005	47	173	10		173	10
005	005	48	173	10		173	10
005	005	49	173	10		173	10
005	005	50	173	10		173	10
005	005	51	173	10		173	10
005	005	52	173	10		173	10
005	005	53	173	10		173	10
005	005	54	173	10		173	10
005	005	55	173	10		173	10
005	005	56	173	10		173	10
005	005	57	173	10		173	10
005	005	58	173	10		173	10
005	005	59	173	10		173	10
005	005	60	173	10		173	10
005	005	61	173	10		173	10
005	005	62	173	10		173	10
005	005	63	173	10		173	10
005	005	64	173	10		173	10
005	005	65	173	10		173	10
005	005	66	173	10		173	10
005	005	67	173	10		173	10
005	005	68	173	10		173	10
005	005	69	173	10		173	10
005	005	70	173	10		173	10
005	005	71	173	10		173	10
005	005	72	173	10		173	10
005	005	73	173	10		173	10
005	005	74	173	10		173	10
005	005	75	173	10		173	10
005	005	76	173	10		173	10
005	005	77	173	10		173	10
005	005	78	173	10		173	10
005	005	79	173	10		173	10
005	005	80	173	10		173	10
005	005	81	173	10		173	10
005	005	82	173	10		173	10
005	005	83	173	10		173	10
005	005	84	173	10		173	10
005	005	85	173	10		173	10
005	005	86	173	10		173	10
005	005	87	173	10		173	10
005	005	88	173	10		173	10
005	005	89	173	10		173	10
005	005	90	173	10		173	10
005	005	91	173	10		173	10
005	005	92	173	10		173	10
005	005	93	173	10		173	10
005	005	94	173	10		173	10
005	005	95	173	10		173	10
005	005	96	173	10		173	10
005	005	97	173	10		173	10
005	005	98	173	10		173	10
005	005	99	173	10		173	10
005	005	100	173	10		173	10

Table 5 (cont.)

Table with multiple columns containing numerical data and labels (e.g., H, C, N, S, O) for various atoms. The table is extremely dense and contains many rows of data, likely representing vibrational displacement components or related parameters for different atoms in a molecule.

to compensate for the systematic errors indicated by Fig. 3. Crystallographers are accustomed to regarding the set of thermal parameters as a sink for absorbing errors; however, in the present case the compensation for errors must involve the coordinates as well, since differences in thermal parameters could not possibly compensate for the form of the curve in Fig. 3. It is in fact surprising, in view of Fig. 3, that the two sets of molecular parameters agree as well as they do.

**Rigid-body analysis**

By the method of Schomaker & Trueblood (1968) as embodied in a program by Johnson (1965) a least-squares rigid-body analysis of the thermal parameters\*  $U_{ij}$  of the S, C, and N atoms of the 6-mercaptapurine

\* The  $U_{ij}$ 's, derived from the  $B_{ij}$ 's of Table 4, are the components of the tensors of mean-square vibrational displacement referred to a Cartesian coordinate system.

molecule was performed, with unit weight for each  $U_{ij}$ . The unusually low value, 0.0009 Å<sup>2</sup> for the standard deviation of an observation of unit weight, which is in this case the root-mean-square  $\Delta U_{ij}$  corrected according to the number of degrees of freedom, shows that the fit to the rigid-body model is excellent.

In the rigid-body analysis the origin was chosen† so as to make **S** symmetric and minimize the trace of **T**, and the constraint that the trace of **S** be zero was applied. The detailed description of the rigid-body motion resulting from the analysis is given in Table 6, including the description of the motion preferred by Schomaker & Trueblood, in terms of 3 independent screw librations (helical motions) about non-intersecting axes and 3 reduced translations.

The root-mean-square amplitudes about the principal axes of librational motion are 3.13°, 2.54°, and 2.46° for axes  $K=1, 2,$  and  $3$  respectively. Axis 1 lies only 4° from the molecular plane; axis 2, 13°; axis 3, 76°.

† The choice was actually made by letting the program find this origin in a preliminary calculation starting with an arbitrary origin.

Fig. 4 shows graphically how well the calculated and observed ellipsoids agree. The left side of the Figure shows, at the top, the observed 50% probability ellipsoids (see Johnson, 1965) viewed in the direction perpendicular to the best plane through the nonhydrogen atoms and, at the bottom, the same ellipsoids viewed at 60° from the perpendicular. For each nonhydrogen atom the three principal r.m.s. vibrational amplitudes (Å) are given, and for each hydrogen atom the single r.m.s. amplitude corresponding to the isotropic thermal parameter  $B$  is given. The right side of the Figure shows corresponding views of the calculated ellipsoids from the rigid-body analysis, with the calculated r.m.s. amplitudes. Calculated anisotropic ellipsoids are included for the hydrogen atoms. The plus sign (+) in each molecular drawing marks the center of gravity of the molecule, and the cross (×) marks the origin used in the rigid-body calculation. The center of gravity and the origin are respectively -0.001 Å and +0.090 Å from the best plane, the latter deviation being toward the molecule related to the reference molecule by inversion through the center at  $\frac{1}{4}, \frac{3}{4}, \frac{1}{2}$  (see Fig. 3 of Sletten *et al.* and Fig. 6 below).

Table 6. Description of the motion of the 6-mercaptopurine molecule from the Schomaker-Trueblood rigid-body analysis

The Cartesian coordinate system to which the tensor components below are referred is oriented as follows: base vector **i** is along the unit normal **n** to the least-squares best plane through the 10 nonhydrogen atoms of the molecule; base vector **k** is along **n** × **m**, where **m** is the vector from C(5) to C(4); base vector **j** is along **k** × **i**.

	Crystal coordinates			Cartesian coordinates (Å)			
	<i>x</i>	<i>y</i>	<i>z</i>	<i>X</i>	<i>Y</i>	<i>Z</i>	
Components of <b>n</b>	-0.03408	0.10912	-0.02185	1.0000	0.0	0.0	
Centroid	0.32651	0.56911	0.46983	-0.0911	-0.3470	0.0118	
Origin for calculation (see text)	0.31195	0.57309	0.48915	0.0	0.0	0.0	
	Tensor elements × 10 <sup>5</sup> (standard errors × 10 <sup>5</sup> )						
Tensor	11	22	33	12	13	23	
L (rad. <sup>2</sup> )	186 (9)	219 (17)	276 (16)	-2 (13)	9 (12)	-43 (12)	
T (Å <sup>2</sup> )	2308 (56)	1735 (33)	2374 (31)	76 (38)	116 (34)	-259 (28)	
S (rad. × Å)	-6 (10)	39 (16)	-33 (18)	-21 (11)	-9 (12)	27 (22)	
	Helical axis <i>K</i> or principal axis <i>K</i>						
				1	2	3	
Helical motions about non-intersecting axes							
R.m.s. amplitude (radians)				0.0547	0.0444	0.0429	
(degrees)				3.13°	2.54°	2.46°	
Pitch (Å rad. <sup>-1</sup> )				-0.130	0.172	0.028	
Orientation angles of helical axes to Cartesian base vectors				<b>i</b>	85.6°	102.8°	13.6°
				<b>j</b>	118.0°	150.2°	99.3°
				<b>k</b>	28.4°	116.4°	99.8°
Displacement (Å) of each helical axis <i>K</i> from the other two helical axes <i>J</i>				<i>J</i> =1	0.156	-0.167	
				2	-0.028	0.045	
				3	0.052	-0.079	
Reduced translation							
R.m.s. amplitude (Å)				0.158	0.151	0.127	
Orientation angles of principal axes to Cartesian base vectors				<b>i</b>	65.3°	153.3°	80.3°
				<b>j</b>	104.4°	106.9°	157.5°
				<b>k</b>	29.1°	69.9°	110.1°

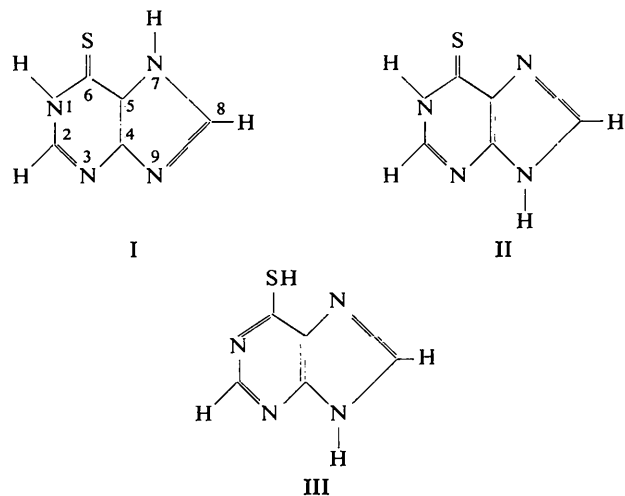
Of course, only for the nonhydrogen atoms are the calculated and observed ellipsoids directly comparable; and for these the agreement seems remarkably good, consistent with the low value of the standard deviation of an observation of unit weight quoted above. The differences between the calculated and the observed ellipsoids for atoms C(4), C(5), and C(6) which appear in the drawings are misleading, because for each of these atoms both the calculated and observed ellipsoids are nearly ellipsoids of revolution, with only one principal-axis direction well determined.

Rigid-body analyses were also performed on the sets of thermal parameters  $U_{ij}$  from least-squares refinement calculations (6) and (7) (see Table 2). The descriptions of thermal motion resulting are quite close to the one already given from the  $U_{ij}$  of calculation (8). The standard errors of the components of **L**, **T**, and **S** are somewhat larger, however, than those in Table 6; and the standard errors of fit are higher, both about  $0.0011 \text{ \AA}^2$ . This suggests that the parameters of calculation (8) really are more reliable than those of (6) and (7).

**Molecular structure**

Perhaps the most interesting result so far as molecular structure is concerned is the finding that the tautomeric

form of the 6-mercaptapurine molecule in the crystal is that of the thione of formula I, with hydrogen atoms on N(1) and N(7). So far as the five-membered ring is concerned, this structure corresponds to that of purine (Watson, Sweet & Marsh, 1965).



The finding of the thione form is in agreement with results from spectroscopic studies. Apparently the only

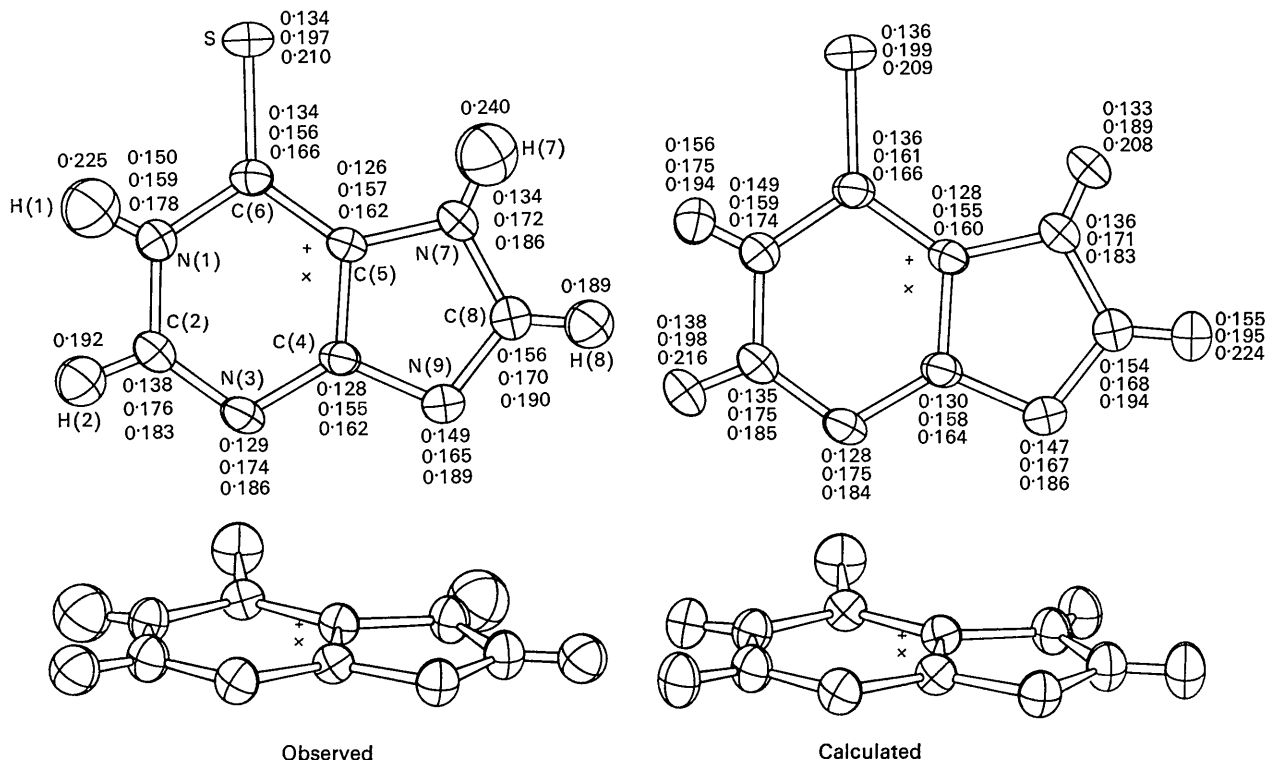


Fig. 4. Comparison of observed thermal ellipsoids (left side of Figure) for the nonhydrogen atoms of the 6-mercaptapurine molecule with ellipsoids calculated (right) from the rigid-body analysis according to the Schomaker-Trueblood method. Top views are in the direction of the normal to the best plane through the nonhydrogen atoms; bottom views are in the direction  $60^\circ$  from the normal. The principal r.m.s. vibrational amplitudes are shown. The symbol + marks the centroid of the molecule and the symbol x marks the origin used in the rigid-body analysis.

physical evidence for a thiol tautomeric form for 6-mercaptopyrine is in the report (Mason, 1957) that 2-, 6-, and 8-mercaptopyrines in the solid state show weak infrared bands in the region of the S-H stretching frequency, but this report included the cautionary remark that these bands are not unequivocal evidence for the thiol forms. The weight of the evidence from ultraviolet spectroscopy (Elion, 1957; Mason, 1957) of neutral and acid solutions of 6-mercaptopyrine and various monomethyl derivatives is that a thione form predominates. Similarly, an infrared study of a chloroform solution of 7-methyl-6-mercaptopyrine (Mason, 1957) suggests that 6-mercaptopyrine, which is itself not soluble in chloroform, exists partly in thione form. Katritsky & Ambler (1963) make the generalization that, 'most six-membered heteroaromatics with mercapto groups  $\alpha$  or  $\gamma$  to a ring nitrogen exist predominantly in the thione form.' For 6-mercaptopyrine the thione form has usually been formulated as in II, with a hydrogen atom on N(9) instead of on N(7), because of the similarity of the ultraviolet spectra of the parent compound and its 1-methyl and 9-methyl derivatives (Elion, 1957). In spite of the generally contrary evidence from spectroscopy, the thiol formula, III, has continued to appear frequently in the chemical and medical literature, consistent with the established use of the misnomer 6-mercaptopyrine.

Bond lengths and valence angles as calculated directly from the parameters of least-squares calculation (8) are listed in Table 7; those in the 6-mercaptopyrine molecule are also shown in Fig. 5. The librational ten-

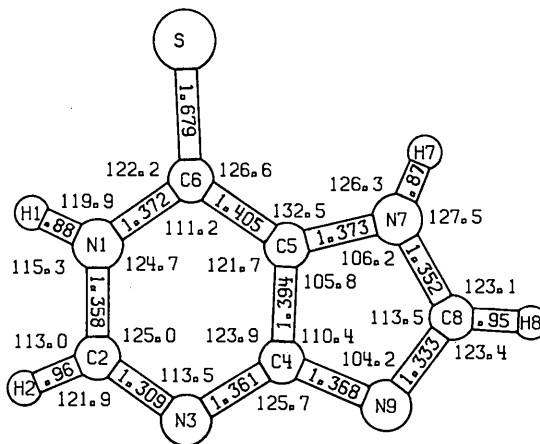


Fig. 5. Bond lengths (Å) and valence angles (°) in the 6-mercaptopyrine molecule.

sor from the rigid-body analysis was used to correct each bond length between heavy atoms for the effects of librational motion in the way indicated by Busing & Levy (1964), equivalent to the prescription of equation (22) of Schomaker & Trueblood (1968). The corrected bond lengths are included in Table 7. Although the corrections are small, from 0.0025 to 0.0039 Å, the average value of 0.0031 Å is 2.2 times the average standard error of the uncorrected lengths. Since the fit to the rigid-body model is exceptionally good, the corrections should be quite reliable.

Table 7. Bond lengths and angles in the crystal structure of 6-mercaptopyrine monohydrate, with standard errors

For the bonds in the 6-mercaptopyrine molecule not involving hydrogen atoms corrected values computed from the results of a rigid-body analysis are included (italic numerals).

Bond lengths (Å)		Angles (°)	
N(1)-C(2)	1.3583 (13) <i>1.3614</i>	C(6)-N(1)-C(2)	124.74 (10)
C(2)-N(3)	1.3088 (16) <i>1.3133</i>	N(1)-C(2)-N(3)	124.97 (10)
N(3)-C(4)	1.3609 (13) <i>1.3641</i>	C(2)-N(3)-C(4)	113.52 (08)
C(4)-C(5)	1.3939 (11) <i>1.3971</i>	N(3)-C(4)-C(5)	123.91 (09)
C(5)-C(6)	1.4050 (14) <i>1.4077</i>	C(4)-C(5)-C(6)	121.65 (09)
C(6)-N(1)	1.3720 (13) <i>1.3753</i>	C(5)-C(6)-N(1)	111.18 (08)
C(6)-S	1.6786 (09) <i>1.6825</i>	C(5)-C(6)-S	126.64 (08)
C(5)-N(7)	1.3729 (14) <i>1.3759</i>	N(1)-C(6)-S	122.18 (08)
N(7)-C(8)	1.3523 (15) <i>1.3550</i>	C(6)-C(5)-N(7)	132.52 (08)
C(8)-N(9)	1.3326 (14) <i>1.3359</i>	C(4)-C(5)-N(7)	105.83 (09)
N(9)-C(4)	1.3675 (14) <i>1.3702</i>	C(5)-N(7)-C(8)	106.17 (08)
N(1)-H(1)	0.880 (15)	N(7)-C(8)-N(9)	113.46 (10)
C(2)-H(2)	0.956 (12)	C(8)-N(9)-C(4)	104.16 (09)
N(7)-H(7)	0.874 (15)	N(9)-C(4)-C(5)	110.38 (09)
C(8)-H(8)	0.954 (13)	N(9)-C(4)-N(3)	125.71 (08)
O-H(10)	0.822 (16)	C(6)-N(1)-H(1)	119.9 (9)
O-H(11)	0.837 (18)	H(8)-C(8)-N(9)	123.4 (8)
		H(1)-N(1)-C(2)	115.3 (9)
		N(1)-C(2)-H(2)	113.0 (8)
		H(2)-C(2)-N(3)	121.9 (7)
		C(5)-N(7)-H(7)	126.3 (10)
		H(7)-N(7)-C(8)	127.5 (10)
		N(7)-C(8)-H(8)	123.1 (8)
		H(10)-O-H(11)	101.9 (14)

Such small corrections, though applicable in principle to bonds C(2)–H(2), C(8)–H(8), N(1)–H(1), and N(7)–H(7), have no practical meaning for these bonds because of the larger standard errors of the apparent bond lengths and, more important, because of the usual large systematic error of shortening which is observed for these bonds and for bonds in the water molecule. The orientations of the thermal ellipsoids for H(2) and H(8) obtained in least-squares calculation (7) (see Fig. 1) suggest that as a gross approximation one might be justified in using the ‘riding’ model (Busing & Levy, 1964) for correcting the lengths of C(2)–H(2) and C(8)–H(8). However, the corrections calculated from the parameters of least-squares calculation (7) turn out to be only 0.019 and 0.016 Å; the bond lengths are still far from the known C–H internuclear distance of about 1.08 Å.

It is worth emphasizing that for 6-mercaptapurine monohydrate the use of anisotropic thermal parameters, successful in a formal mathematical sense, has not led to the pleasing kind of result reported by Delaplane & Ibers (1967) from a study of oxalic acid dihydrate, namely, that ‘normal O–H bond lengths were obtained after appropriate corrections for thermal motion’. Delaplane & Ibers suggest that a possible cause for the short bond lengths O–H, C–H, and so forth,

usually obtained from X-ray analyses is the use of the isotropic model for hydrogen vibration. The experience with 6-mercaptapurine offers no support for this view; thus, the relevant comparison, 6–7, in Table 3 shows an average absolute difference in lengths of bonds involving hydrogen which is less than the average standard error of the bond lengths. The very close agreement between the C–H, N–H, and O–H bond lengths derived from this analysis and those derived from the parallel analysis of Sletten, Sletten & Jensen (1969) is a strong argument for the view (see Stewart, Davidson & Simpson, 1965) that the centroids of the hydrogen electron distributions are shifted from coincidence with the proton positions as a result of chemical bonding.

The agreement in the values of the angles involving hydrogen atoms between this study and that of Sletten *et al.* is remarkably good (see Table 7 in this paper and Table 2 of Sletten *et al.*). Not one of the differences is as much as the corresponding standard error. Moreover, the standard errors of the angles are not large, being only about 1° except for the H–O–H angle, which involves two hydrogen atoms. It appears, therefore, that the directions, as distinct from the lengths, of the C–H, N–H, and O–H bonds have been determined to a degree of precision as good as that often

Table 8. Distances of atoms from best least-squares planes in the 6-mercaptapurine molecule

Distances in boldface type indicate the atoms included in each least-squares plane calculation. The Table includes the distances to the molecular centroid and the origin used in the rigid-body analysis and the distances to atoms involved in hydrogen bonding with atoms in the 6-mercaptapurine molecule; e.g. O [H(1)] means the oxygen atom to which H(1) is hydrogen bonded. The last column gives the standard deviations of position of each atom in the direction of the plane normals (essentially the same for planes *a*, *b* and *c*). The equations of the three planes are:

$$\begin{aligned} (a) \quad & 7.18355x - 6.51266y + 2.03908z = -0.40435 \text{ \AA} \\ (b) \quad & 7.37213x - 6.45951y + 2.00582z = -0.32746 \\ (c) \quad & 7.16989x - 6.54277y + 1.90682z = -0.48057 \end{aligned}$$

	Displacement from plane (Å)			$\sigma$
	(a)	(b)	(c)	
S	<b>-0.0230</b>	-0.0537		0.0004
N(1)	<b>0.0291</b>	<b>0.0100</b>		0.0011
C(2)	<b>0.0040</b>	<b>-0.0025</b>		0.0014
N(3)	<b>-0.0170</b>	<b>-0.0052</b>	0.0120	0.0012
C(4)	<b>-0.0128</b>	<b>0.0048</b>	<b>0.0002</b>	0.0011
C(5)	<b>-0.0028</b>	<b>0.0025</b>	<b>-0.0002</b>	0.0011
C(6)	<b>0.0047</b>	<b>-0.0097</b>	0.0127	0.0010
N(7)	<b>0.0125</b>	0.0290	<b>0.0002</b>	0.0012
C(8)	<b>0.0103</b>		<b>0.0000</b>	0.0012
N(9)	<b>-0.0049</b>	0.0310	<b>-0.0001</b>	0.0013
H(1)	0.092	0.061		0.014
H(2)	0.044	0.032		0.012
H(7)	0.055		0.034	0.014
H(8)	0.004		<b>-0.015</b>	0.012
O [H(1)]	0.016	0.11		
O [H(2)]	0.52	0.50		
O [S]	2.83	2.78		
O [N(9)]	0.50		0.52	
N(3) [H(7)]	-0.05		-0.09	
H(7) [N(3)]	-0.31	-0.29		
H(10) [N(9)]	0.28		0.29	
H(11) [S]	1.94	1.89		
$\frac{1}{2}, \frac{2}{3}, \frac{1}{2}$	1.665			
$\frac{1}{2}, \frac{2}{3}, \frac{1}{2}$	-1.592			
Centroid	-0.001			
Rigid-body origin	0.090			

reported for bonds C–C, C–N, *etc.* in less precise work. To complete the specification of atomic coordinates in the crystal, it seems appropriate to compute corrected coordinates for the hydrogen atoms. This may be done for a C–H bond, for example, by ‘moving’ the hydrogen atom along the bond direction away from the carbon atom the appropriate distance to correct for the systematic error in bond length. The adjusted hydrogen coordinates given in Table 4 were obtained by this procedure. The lengths assumed for the internuclear separations were: N(1)–H(1), 1.06; N(7)–H(7), 1.04; O–H(11), 1.01; O–H(10), 0.97; C(2)–H(2), 1.08 Å. (The first three values are the expected lengths in Table 4 of Sletten *et al.*) These corrected coordinates are surely to be preferred to the uncorrected ones for calculation of van der Waals contacts and the description of hydrogen bonds.

The equations of the least-squares best planes were calculated by the method of Schomaker, Waser, Marsh & Bergman (1959) for (a) the 10 atoms of the 6-mercaptopyrine molecule excluding hydrogen atoms, (b) the atoms of the six-membered ring only, and (c) the atoms of the five-membered ring only. The three equations and the distances (with standard errors) of various atoms from each plane are given in Table 8. Equation (a) is very close to the equation given by Sletten *et al.* for the same 10 atoms. Moreover, comparison of the distances of the atoms from plane (a) with those in Table 3 of Sletten *et al.* shows that the details of

the distortion from exact coplanarity of the atoms are nearly the same in the two structures.

The separate calculations (b) and (c) for the two different rings provide a better basis for understanding the distortions from planarity. Thus, the atoms of the six-membered ring are much closer to being coplanar than their distances from the overall plane (a) might suggest without careful scrutiny; and the five atoms of the other ring are nearly perfectly coplanar. The major departures from coplanarity result from bending about the bond C(4)–C(5) and from bending of the external bonds C–S, N–H, and C–H. The angle between the normals to planes (b) and (c) is  $1.16^\circ$ . The sulfur atom is out of plane (b) by 0.054 Å, and the bond C(6)–S makes an angle of  $1.50^\circ$  with plane (b).

When the equations of planes (b) and (c) above were recomputed with the coordinates from least-squares refinement calculation (6), the fit in each case was slightly poorer than for the coordinates from calculation (8) used above. Thus, the sums of the squares of the deviations from the planes for the atoms included in the best-plane calculations were  $6.38 \times 10^{-6}$  and  $2.90 \times 10^{-4}$  instead of  $1.41 \times 10^{-7}$  and  $2.56 \times 10^{-4}$  Å<sup>2</sup> for (a) and (b) respectively. Similarly, the sums are  $3.70 \times 10^{-6}$  and  $2.81 \times 10^{-4}$  Å<sup>2</sup> for planes calculated from the coordinates of least-squares refinement (7). Since it seems improbable that a closer approach to coplanarity of the atoms in each ring would occur accidentally, this is another indication that the coor-

Table 9. *Parameters of the hydrogen bonds in the crystal structure of 6-mercaptopyrine monohydrate*

The interaction C(2)–H(2)···O is included. The distances and angles in italics correspond to the adjusted coordinates for the hydrogen atoms (see text).

X–H···Y	Distances (Å)			Angle (°)
	X···Y	X–H	H···Y	
N(1)–H(1)···O	2.758	0.88 <i>1.06</i>	1.88 <i>1.70</i>	172.4 <i>171.6</i>
N(7)–H(7)···O	2.910	0.87 <i>1.04</i>	2.04 <i>1.87</i>	174.2 <i>173.7</i>
O—H(11)···S	3.379	0.84 <i>0.97</i>	2.56 <i>2.43</i>	166.3 <i>165.6</i>
O—H(10)···N(9)	2.800	0.82 <i>1.01</i>	1.99 <i>1.80</i>	170.9 <i>170.0</i>
C(2)–H(2)···O	3.331	0.96 <i>1.08</i>	2.39 <i>2.26</i>	170.4 <i>169.9</i>

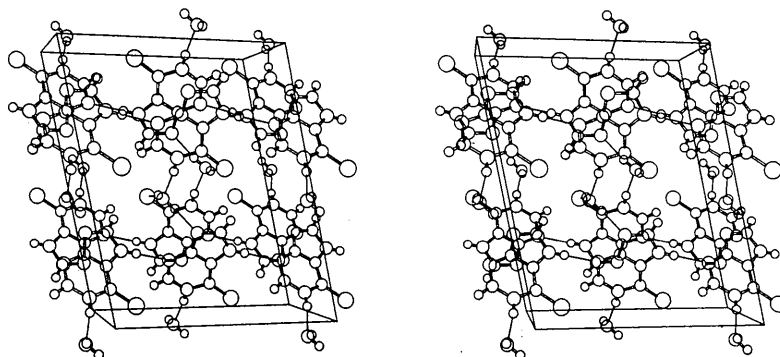


Fig. 6. Stereoscopic view of the crystal structure of 6-mercaptopyrine monohydrate. The direction is of view close to  $-b$ ;  $c$  is nearly horizontal;  $a$  is nearly vertical. The parallelepiped outlined has dimensions  $a$ ,  $b$ ,  $c$  and is centered on the point  $\frac{1}{2}, 0, \frac{1}{2}$ .

dinates from refinement calculation (8) are indeed more reliable than those from (6) or (7).

#### *Molecular packing and hydrogen bonding*

A stereoscopic drawing of the crystal structure is shown in Fig. 6 to complement the projection drawings of Sletten, Sletten & Jensen (1969).

In the stacking of the molecules along the *b* axis, the concave side of the reference molecule (see Fig. 3 of Sletten *et al.*) is in contact with the molecule related by the symmetry center at  $\frac{1}{4}, \frac{3}{4}, \frac{1}{2}$  (Fig. 4 of Sletten *et al.*), the spacing between the two overall average planes being 3.33 Å.

The description of the hydrogen bonds is given in Table 9. The C-H...O interaction is included, although according to Donohue (1968) it would not be considered a hydrogen bond in the usual sense. The corrected distances and angles in Table 9 were calculated using the corrected hydrogen parameters given in Table 4 (see explanation above under heading *Molecular structure*). The corrected angles are not significantly different from the uncorrected. The uncorrected hydrogen bond parameters are, of course, very close to those of Sletten *et al.*

Table 8 includes the distances from planes (*a*), (*b*), and (*c*) to the various atoms linked to the 6-mercaptopyrimidine reference molecule by hydrogen bonds. As Sletten *et al.* point out, the departures from planarity of the molecule are not solely determined by the disposition of the hydrogen bonds; for example, the sulfur atom is 0.054 Å out of least-squares plane (*b*) in the direction opposite to that in which it is hydrogen bonded to the water molecule.

The computer programs used in the various calculations are as follows:

Least-squares determination of cell parameters: part of the program package for the computer-controlled diffractometer (Busing *et al.*, 1968).

Absorption corrections: program modified by R. D. Ellison & H. A. Levy from *ORABS* (Wehe, Busing & Levy, 1962).

Fourier syntheses: a version of the program *FØR-DAPER* of A. Zalkin modified by G. Brunton; program *COMFO* by G. M. Brown.

Least-squares refinement of structure parameters: program *XFLS*, modified by R. D. Ellison, H. A. Levy & H. Yakel from *ORFLS* (Busing, Martin & Levy, 1962).

Bond lengths and angles: program *ORFFE II* by C. K. Johnson and modified version by R. D. Ellison & H. A. Levy.

Rigid-body analysis: program *ORSBA* of C. K. Johnson.

Least-squares best plane: program *BSPLAN*, modified by G. M. Brown from a program of W. C. Hamilton.

Table of  $F_o$ 's and  $F_c$ 's: program *EDIT* of G. M. Brown. Drawings: program *ORTEP* (Johnson, 1965).

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