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The Crystal Structure of 2*H*-Pyridaz-3-thione

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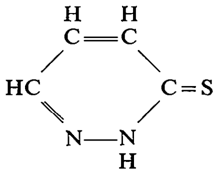
2*H*-Pyridaz-3-thione crystallizes in the monoclinic system with $a=5\cdot33\pm0\cdot02$, $b=12\cdot66\pm0\cdot04$, $c=7\cdot76\pm0\cdot03$ Å, $\beta=96°\pm0\cdot03°$, space group $P2_1/C$, $D_m=1\cdot416$ g.cm^{-3} and $Z=4$. The crystal structure was determined by the heavy-atom technique and was refined by least-squares and difference Fourier methods with the use of anisotropic temperature factors for each atom. The final discrepancy value (excluding the H atoms) was 0·118.

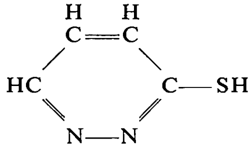
The planar molecules are arranged in layers almost parallel to (10$\bar{2}$). They form dimers through $-$S · · · H–N bonds around a centre of symmetry and lie in parallel planes with a perpendicular separation of 0·8 Å. The molecule itself is slightly distorted with the sulphur atom lying 0·03 Å from the mean plane of the ring system. A comparison is made between the bond lengths and angles of the ring system in this structure and those of the corresponding ring system in 6-amidopyridaz-3-one.

Introduction

The X-ray structure analysis of 2*H*-pyridaz-3-thione (hereafter called pyridaz-3-thione) was undertaken in the hope of obtaining information regarding the intramolecular bond distances in order to confirm if possible the existence, in the solid state, of the tautomeric form (I) which Hedgley (1956) identified in a solution of the compound prior to a description of certain pharmacological properties of the material by Hedgley, Heikel, Knight & Rimmington (1959). The present structure determination suffers from inaccuracies arising from visual estimation of the X-ray intensities, but it is sufficiently reliable to show that form (I) does in fact exist in the solid state. Support for this comes also from the observations that the dimensions of the pyridazine ring as found are not very different from those obtained in the X-ray analysis of 6-amidopyridaz-3-one, a derivative of the oxygen analogue of (I). (Cucka & Small, 1954; Cucka, 1963).



(I)



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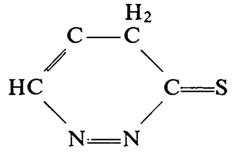

(III)

Experimental

The brilliant yellow crystals of pyridaz-3-thione, which were kindly supplied by Dr E. J. Hedgley, exhibit the following forms: {10$\bar{2}$}, {100}, with {010} dominating.* There is very easy cleavage parallel to (10$\bar{2}$). The crystals were found to be optically negative, with the optic axial plane lying parallel to (010) and with the α vibration direction lying perpendicular to (10$\bar{2}$).

The unit-cell dimensions are $a=5\cdot33\pm0\cdot02$, $b=12\cdot66\pm0\cdot04$, $c=7\cdot76\pm0\cdot03$ Å, $\beta=96°\pm0\cdot03°$. D_m obtained by flotation in a mixture of benzene and carbon tetrachloride is $1\cdot416$ g.cm^{-3}, giving $Z=4$. The space group was unambiguously determined to be $P2_1/c$.

Weissenberg photographs were taken about the three principal axes with Cu $K\alpha$ radiation, a different crystal being used for each axis, and each crystal was selected so as to be less than the optimum size needed to reduce absorption effects to a minimum. A multiple-film technique was employed to cover the necessary range of intensities and from these photographs it was possible to obtain 1126 independent reflexions out of a possible 1169. Of these reflexions, 237 were too weak to be recorded, leaving 889 reflexions with which to carry out the present investigation.

The intensities of the reflexions were estimated visually by comparison with a standard scale and the estimated intensity of each reflexion was taken as the arithmetic mean of three independent observations. The intensities of the recorded spectra were corrected for extension and contraction of the spots by Phillips's (1956) method. The reflexions from all layers taken about the three axes were corrected for Lorentz and polarization effects and finally placed on the same relative scale by a cross-correlation procedure.

An estimate of the standard deviation of $|F|^2$ was made by comparing $|F|^2$ values for reflexions about more than one axis. This revealed that the estimated standard deviation averaged about 8% for reflexions of moderate intensity, increasing to about 13% for the strong reflexions and to about 20% for the weak and very weak reflexions. The relative $|F|^2$ values were put on to an approximately absolute scale by Wilson's

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* The crystallization procedure can be obtained from Dr Hedgley of the Chemistry Department, Birkbeck College.

(1942) method and this gave an overall isotropic temperature factor of 3·17 Å^2.

Structure determination

The presence of the sharp cleavage plane ($10\bar{2}$) and the corresponding large observed intensity of the $10\bar{2}$ reflexion gave a reasonably clear indication that the molecules were lying approximately parallel to these planes. From a full three-dimensional sharpened Patterson vector distribution the sulphur atoms were unambiguously located in the unit cell. A straightforward application of the heavy-atom technique using the X-ray scattering contribution of the sulphur atom alone gave an indication of the signs of some 450 strong and moderately strong reflexions from which a partial three-dimensional electron density distribution was evaluated for one quarter of the unit cell $a \times \frac{1}{2}b \times \frac{1}{2}c$. As expected the distribution showed the sulphur peak (at 0·180, 0·045 and 0·301) with a maximum density of 20 e.Å^{-3} and in addition 8 other less well resolved peaks with heights ranging from 1·5 to 3·5 e.Å^{-3}. A careful scrutiny of these peaks led to the selection of positions which defined a ring system at about the right distance from the sulphur atom. Structure factors were calculated based on these atomic positions (treating them as carbon atoms) together with that of the sulphur atom and this yielded a reliability index $R = 0·383$.

This preliminary structure was refined by two complete rounds of structure factor calculations, followed in each case by three-dimensional electron density calculations. From the last electron density distribution, using about 600 terms, it was possible to identify the two nitrogen atoms of the pyridazine ring. Structure factor calculations at this stage gave an R value of 0·275.

The fall in R from 0·38 to 0·28 indicated this preliminary structure to be probably correct. This was in keeping with morphological and optical observations made on the crystals, firstly in that the molecules were shown to be lying very nearly in the ($10\bar{2}$) planes with van der Waals separations of about 3·5 Å, thus explaining the easy cleavage of the crystal parallel to these planes, and secondly in that the normal to the molecular planes coincided with the α vibration direction of the crystal.

Structure refinement

The three-dimensional refinement was carried out by least-squares and difference Fourier techniques, isotropic temperature factors being used for the initial calculations; these were later replaced by anisotropic parameters as they became known. The first stage of the refinement commenced with the positional parameters obtained from the Fourier syntheses using a single isotropic temperature factor $B = 3·17$ Å^2 for all atoms. The scattering curves for carbon and nitrogen used in these calculations are those given by Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal (1955) and the curve used for sulphur was taken from *International Tables for Crystallography* (1962). Only non-zero observed reflexions were included in these refinements.

In the first cycle the R value dropped from 0·275 to 0·220 and finally fell to 0·183. A three-dimensional difference Fourier synthesis at this stage indicated marked anisotropy of thermal vibrations for the atoms, particularly for the sulphur atom.

Table 1. *Final positional parameters and the calculated estimated standard deviations of the atoms*

Atom	x	y	z	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
S	0·1771	0·0436	0·2987	0·0003	0·0001	0·0002
N(1)	0·7038	0·2382	0·5150	0·0011	0·0004	0·0008
N(2)	0·5508	0·1554	0·4570	0·0011	0·0004	0·0007
C(1)	0·3292	0·1576	0·3597	0·0011	0·0005	0·0007
C(2)	0·2332	0·2580	0·3058	0·0013	0·0006	0·0009
C(3)	0·3749	0·3458	0·3665	0·0014	0·0005	0·0008
C(4)	0·6099	0·3310	0·4756	0·0014	0·0006	0·0009
H(1)	0·616	0·083	0·495			
H(2)	0·060	0·256	0·239			
H(3)	0·295	0·411	0·311			
H(4)	0·716	0·395	0·522			

Table 2. *The final anisotropic thermal parameters obtained for the* S, C, N *atoms*

$$T = \exp\{-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{23}kl + b_{31}lh + b_{12}hk)\}$$

The figures in brackets indicate $\sigma(b_{ij}) \times 10^{-4}$

Atom	b_{11}	b_{22}	b_{33}	b_{23}	b_{31}	b_{12}
S	0·0298 (10)	0·0030 (2)	0·0186 (5)	−0·0004 (4)	−0·0916 (11)	−0·0026 (5)
N(1)	0·0256 (30)	0·0037 (5)	0·0166 (15)	−0·0037 (15)	−0·0091 (33)	−0·0008 (20)
N(2)	0·0276 (28)	0·0039 (5)	0·0132 (12)	0·0020 (14)	−0·0039 (30)	−0·0024 (18)
C(1)	0·0217 (28)	0·0032 (5)	0·0108 (12)	−0·0054 (14)	−0·0045 (31)	−0·0016 (18)
C(2)	0·0263 (32)	0·0037 (6)	0·0133 (15)	0·0011 (15)	0·0057 (32)	0·0001 (20)
C(3)	0·0356 (40)	0·0033 (6)	0·0148 (16)	0·0011 (17)	−0·0007 (40)	0·0016 (22)
C(4)	0·0316 (37)	0·0036 (5)	0·0164 (17)	−0·0035 (18)	−0·0061 (39)	0·0005 (23)

In the second stage of the refinement, anisotropic temperature parameters were used and after the first cycle the R value dropped to 0·144. Thereafter in three cycles of refinement R was reduced to 0·118.*

A three-dimensional difference Fourier synthesis was calculated at this stage of the refinement. This map, besides showing four expected peaks at about the correct distances for H atoms from the atoms C(2), C(3), C(4) and N(2), revealed others of about the same height but none of the extra peaks lay anywhere near the sulphur atom.

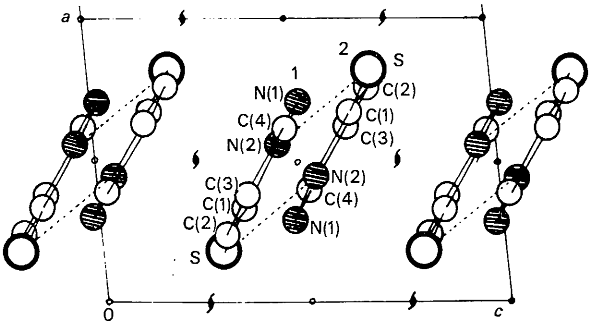

Fig. 1. A projection on (010) showing the alignment of the pyridaz-3-thione molecules.

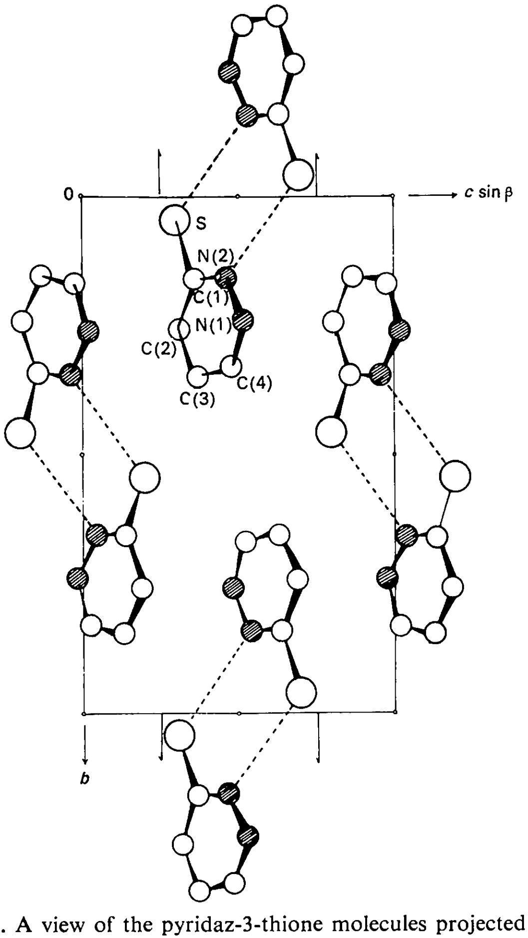

Fig. 2. A view of the pyridaz-3-thione molecules projected on (100).

Another set of structure factors were calculated, including this time the four hydrogen atoms at the positions indicated by the $(F_o - F_c)$ Fourier synthesis, but the R value merely decreased to 0·109 – an insignificant decrement which when taken together with results of difference Fourier synthesis clearly indicated that the limit of the refinement process had been reached in this analysis. Although the structure determination, accordingly, is not as accurate as is desirable in a problem of this sort, the results nevertheless permit the drawing of certain conclusions about the crystal and molecular structure.

The final positional and vibrational parameters are listed in Tables 1 and 2. The average standard deviation of the coordinates of the sulphur atom was 0·002 Å approximately, whereas that for the carbon and nitrogen atoms ranges from 0·005 to 0·007 Å. The thermal parameter function is such that it could include errors of various sorts; consequently the temperature parameters obtained at the end of the refinements should perhaps be treated with some reserve.

Description of the crystal structure

A view of the arrangement of the molecules as seen on (010) is shown in Fig. 1. The positional coordinates of molecule 1 are those given in Table 1, and molecule 1 is centrosymmetrically related to molecule 2, which lies on the negative side of the b axis.

There are two important features concerning the arrangements of the molecules in the crystal: firstly, molecules 1 and 2 may be said to form a dimer, held together by weak hydrogen bonding between the sulphur atom of molecule 1 and atom N(2) of molecule 2 with a separation of 3·366 Å. Similar sulphur–nitrogen bonds leading to the formation of dimers are also found in 2-thiopyridone (Penfold, 1953). Secondly, within each dimer the molecules lie on either side of a mean plane which is inclined at 4° to $(10\bar{2})$ and 2° to the b axis. The perpendicular separation between the molecules in a dimer is 0·8 Å.

The crystal may, therefore, be considered as a layered structure in which the mean planes of the adjacent dimers are tilted alternately 2° about the b axis so as to conform to the space group operations, and the layers themselves have a spacing of about 3·25 Å – the same as that of $10\bar{2}$ plane. Fig. 2 shows a view of the structure projected on (100).

Description of the molecule

The bond lengths and angles of pyridaz-3-thione are listed in Table 3, and Figs. 3 and 4 show respectively a composite electron density map of the molecule and a drawing of it (excluding the hydrogen atoms) indicating its bond lengths and bond angles.

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* The observed and calculated structure factors are available on request from this laboratory.

Table 3. *Bond lengths and bond angles*

Bond lengths	
C(1)–S	1·698 ± 0·006 Å
C(1)–C(2)	1·417 ± 0·009
C(2)–C(3)	1·398 ± 0·010
C(3)–C(4)	1·449 ± 0·010
C(4)–N(1)	1·301 ± 0·009
N(1)–N(2)	1·346 ± 0·007
N(2)–C(1)	1·379 ± 0·007
Angles	
S —C(1)–C(2)	122·2 ± 0·5°
S —C(1)–N(2)	120·6 ± 0·4
C(2)–C(1)–N(2)	117·1 ± 0·5
C(1)–C(2)–C(3)	116·6 ± 0·6
C(2)–C(3)–C(4)	119·9 ± 0·6
C(3)–C(4)–N(1)	122·8 ± 0·6
C(4)–N(1)–N(2)	115·7 ± 0·6
N(1)–N(2)–C(1)	127·7 ± 0·5

The best plane through the molecule is given by the equation $-0·562x'+0·032y+0·827z'=1·523$, where $x'=x+z\cos\beta$ and $z'=z\sin\beta$ expressed in orthogonal axes a, b and c^*. The perpendicular distances of the atoms from this plane are shown in Table 4, and it would appear that within limits of the experimental data the molecule is essentially planar, with perhaps some slight distortion as revealed by a subsequent calculation which shows that the sulphur atom lies about 0·033 Å away from the best plane through the ring atoms. Cucka (1963) finds in a recent recalculation of the atomic parameter of 6-amidopyridaz-3-one (1963) that the O(1) atom (which replaces the S atom in pyridaz-3-thione) also deviates slightly but significantly from the plane of this ring system. For purposes of comparison Table 5 shows the bond lengths and bond angles relating only to the ring systems of the two structures. Again within experimental errors there is a close similarity in the dimension of the ring structures for the different molecules.

Evidence to support the existence of the tautomer (I) favoured by Hedgley (1953) is shown to a certain extent by the C(1)–S bond length, which is observed

Table 4. *Analysis of the planarity in the pyridaz-3-thione molecule*

Equation of the plane referred to orthogonal axes:

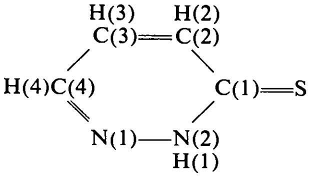
$$m_1x+m_2y+m_3z=d$$

Best plane through

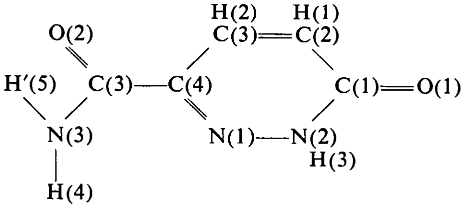
	(*a*) All atoms		(*b*) Pyridazine ring atoms only
m_1	−0·56164	m_1	−0·5650
m_2	0·03175	m_2	0·02374
m_3	0·82677	m_3	0·82302
d	1·523	d	1·480

Atom	Deviation Δ	Deviation Δ
S	+0·006 Å	(+0·033) Å
N(1)	−0·014	−0·020
N(2)	−0·016	−0·010
C(1)	+0·013	+0·025
C(2)	−0·027	−0·022
C(3)	−0·002	−0·009
C(4)	+0·035	+0·021

Table 5. *Comparison of bond lengths and angles in the ring systems of* 2*H-pyridaz*-3-*thione and* 6-*amidopyridaz*-3-*one respectively*



2*H*-Pyridaz-3-thione (*a*)



6-Amidopyridaz-3-one (*b*)

Bonds	(*a*) *d*	(*a*) σ(*d*)	(*b*) *d*	(*b*) σ(*d*)
C(1)–C(2)	1·417	0·009	1·4270	0·0095
C(1)–N(2)	1·379	0·007	1·3694	0·0084
C(2)–C(3)	1·398	0·010	1·3397	0·0097
C(3)–C(4)	1·449	0·010	1·4037	0·0091
C(4)–N(1)	1·301	0·009	1·4049	0·0078
N(1)–N(2)	1·346	0·007	1·3539	0·0068
			θ	σ(θ)
C(2)–C(1)–N(2)	117·1°	0·5°	114·0°	1·0°
C(1)–C(2)–C(3)	116·6°	0·6	120·4	1·2
C(2)–C(3)–C(4)	119·9°	0·6	119·6	1·2
C(3)–C(4)–N(1)	122·8	0·6	122·7	1·2
C(4)–N(1)–N(2)	115·7	0·6	116·2	1·0
N(1)–N(2)–C(1)	127·7	0·5	126·8	1·2

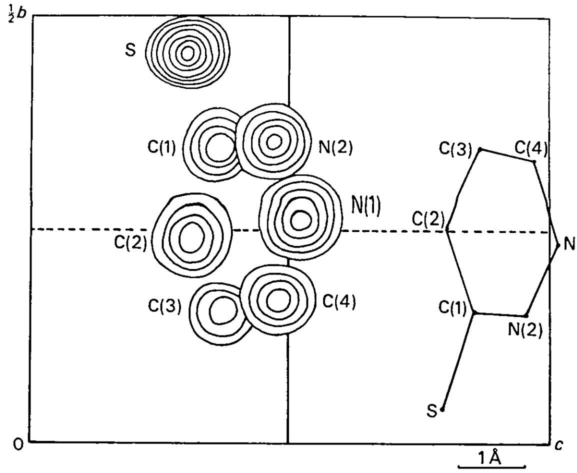


Fig. 3. A composite electron-density map of the pyridaz-3-thione molecule. Contour levels at 2 e.Å^{-3}, starting at 2 e.Å^{-3}.

to be 0·112 Å shorter than the sum of the Pauling covalent radii for carbon and sulphur. This bond must therefore possess considerable double-bond character.

Cucka (1963) also puts forward an argument for the existence of a similar ring system in that his calculations support the evidence for hydrogen atoms attached to C(2), C(3), C(4) and N(2). Thus it appears, from these two X-ray investigations and Hedgley's observations, that there is now sufficient evidence to confirm the existence of the tautomeric form (I) of pyridaz-3-thione not only in solution but in the solid state as well.

We should like to acknowledge the very helpful suggestions that came from Professor Dame Kathleen Lonsdale and Dr Judith Milledge concerning the attempts made to analyse the thermal vibrations of this structure. Although the analysis did yield qualitative indications of the molecular vibrations to be found in structures of this type, they were not sufficiently accurate to merit publication. The calculations were carried out with Dame Kathleen's kind permission on the Pegasus computer in her department, and in this connection we are grateful to Dr C. J. Brown for the use of his programs.

We also acknowledge the use of programs written by Drs J. S. Rollett, Jean Dollimore and J. W. Jeffery, and one of us (M.B.H.) is grateful to the Commonwealth Scholarships Commission, for the tenure of an award while in this country.

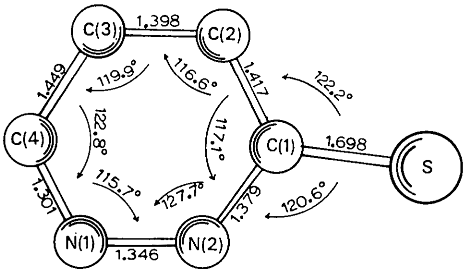


Fig. 4. A drawing of the pyridaz-3-thione molecule (minus H atoms) showing bond lengths and bond angles.

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A Mathematical Model-Building Procedure for Proteins

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The procedure is intended primarily as an intermediate step between the interpretation of an electron density map of medium resolution and the refinement of the structure. The procedure builds a representation of a polypeptide using images of amino acids as determined in small structures, rendered suitably flexible by rotations about single bonds (and other lines if required) and uses the method of least squares to fold the resulting chain and side chains to approach the guide points (derived from the electron density map or otherwise) as closely as possible. Thus an idealized structure can be derived from a selection of rough coordinates and a knowledge of the sequence. The procedure is also capable (with limitations) of bridging uncertain regions.

Some novel mathematical techniques of general interest are described and employed. These include reversion and a sliding filter as means of combating non-linearity. The sliding filter is a means of suppressing large shifts by excluding from the least-squares process those eigenvectors of the normal matrix which have small eigenvalues. This is done in a manner depending on the residual.

A means of achieving accurate rotations in three dimensions without setting up a matrix is also given.

1. Introduction

1.1. *General*

It is a difficult matter, even at the highest resolution, to determine atomic coordinates in a protein with an accuracy better than 0·25 Å. It follows that if a flexible chain with idealized links can be threaded through such coordinates (here called *guide coordinates*) with comparable accuracy then such a chain is reasonable in its stereochemistry and equally consistent with the