The Crystal and Molecular Structure of 1,2-Dithiolane-4-carboxylic Acid

OLAV FOSS and OLAV TJOMSLAND

Chemical Institute, University of Bergen, Bergen, Norway

The crystals of 1,2-dithiolane-4-carboxylic acid are triclinic, with $a = 5.34$ Å, $b = 5.85$ Å, $c = 10.75$ Å, $\alpha = 93\frac{1}{4}°$, $\beta = 89\frac{1}{4}°$, $\gamma = 109\frac{1}{4}°$, and two molecules per unit cell. The space group is $C_i^1 - P\overline{1}$. A structure analysis based on 268 observed $0kl$ and $h0l$ reflections has shown that the 1,2-dithiolane ring is not planar, the dihedral angle CSS/SSC being $26.6 \pm 1°$.

The bond lengths in the ring were found to be, $S_1 - S_2 = 2.096 \pm 0.009$ Å, $S_2 - C_3 = 1.85$ Å, $C_3 - C_4 = 1.48$ Å, $C_4 - C_5 = 1.55$ Å, $C_5 - S_1 = 1.83$ Å, and the angles, $C_5 - S_1 - S_2 = 92.6 \pm 0.7°$, $S_1 - S_2 - C_3 = 96.6 \pm 0.6°$, $S_2 - C_3 - C_4 = 111°$, $C_3 - C_4 - C_5 = 114°$, $C_4 - C_5 - S_1 = 104°$. The carboxyl group is planar and has normal dimensions. The molecules are arranged into dimers about centres of symmetry, through O—H⋯O hydrogen bonds between carboxyl groups.

The 1,2-dithiolane ring has attracted considerable interest in the later years [1–4] because of its presence in 6-thioctic acid (α-lipoic acid) [5]. From a viewpoint of sulphur stereochemistry the importance of the 1,2-dithiolane ring lies in the circumstance that, due to the geometrical requirements of the five-membered ring, the disulphide group cannot maintain the normal dihedral angle of about 90° [6–9] between the planes of the valencies of the sulphur atoms.

1,2-Dithiolane itself is an unstable yellow substance which readily undergoes polymerization [1,4,10], but beside 6-thioctic acid, some substituted 1,2-dithiolanes have been prepared which are more stable, e.g., the 4,4'-dimethyl, 4,4'-dihydroxymethyl, 3,3'-dimethyl and 3,3',5,5'-tetramethyl derivatives [11,12,4] and the 3,5-dicarboxylic [13] and 3- and 4-carboxylic [14,15] acids. The crystal structure of the last acid is described in this paper.

1,2-Dithiolane-4-carboxylic acid was first isolated by Schotte and Ström [15] in 1956, as yellow prisms with m.p. 76.5—77.5°C, although the corresponding dithiol, β,β'-dithiol*iso*butyric acid, was obtained in 1948 by Jansen [16] on reduction of a sulphur-containing polymeric material isolated from asparagus juice. The UV absorption was measured by Schotte [3] and found to be closely related to that of 1,2-dithiolane itself [1,10]. The unit cell and space group has been published [17], and also a preliminary report on the crystal structure [18].

CRYSTAL DATA

From oscillation and Weissenberg photographs about the three axes and about [1$\bar{1}$0] (of length 6.46 Å) the lattice parameters are, to within 0.5 %: $a = 5.34$ Å, $b = 5.85$ Å, $c = 10.75$ Å, $\alpha = 93\frac{1}{2}°$, $\beta = 89\frac{1}{2}°$, $\gamma = 109\frac{1}{2}°$. There are two molecules per unit cell; density, calc. 1.58, found 1.54 g/cm³. On the basis of the subsequent structure analysis, the space group is C_i^1—$P\bar{1}$. The asymmetric unit is thus one molecule.

The intensities of the $0kl$ and $h0l$ reflections were estimated visually from zero-layer Weissenberg photographs taken with copper radiation. The crystals used for the photographs had cross-sections of about 0.1×0.1 mm or smaller. During the exposures they changed slowly, from the surface inwards, into an oily, presumably polymeric material. Out of 146 $0kl$ reflections within the range $\sin \Theta < 0.985$, 136 were observed, the corresponding figures for the $h0l$ zone being 132 out of 137. Although the absorption is not negligible ($\mu = 70$ cm⁻¹ for Cu$K\alpha$ X-rays) no correction was applied. The intensities were corrected for the Lorentz and polarization factors and converted into relative structure amplitudes in the usual way.

DETERMINATION AND REFINEMENT OF THE STRUCTURE

The approximate y and z coordinates of the sulphur atoms ($y = 0.224$, $z = 0.107$ for S_1 and $y = 0.576$, $z = 0.165$ for S_2) were determined from a Patterson projection along the a axis. A subsequent Fourier synthesis of 77 of the strongest $0kl$ reflections, with signs based on the sulphur contributions, gave the approximate positions of the lighter atoms and allowed refinement by Fourier and Fourier difference methods to be carried out. The b-axis projection was afterwards solved and refined in the same way. Nine cycles
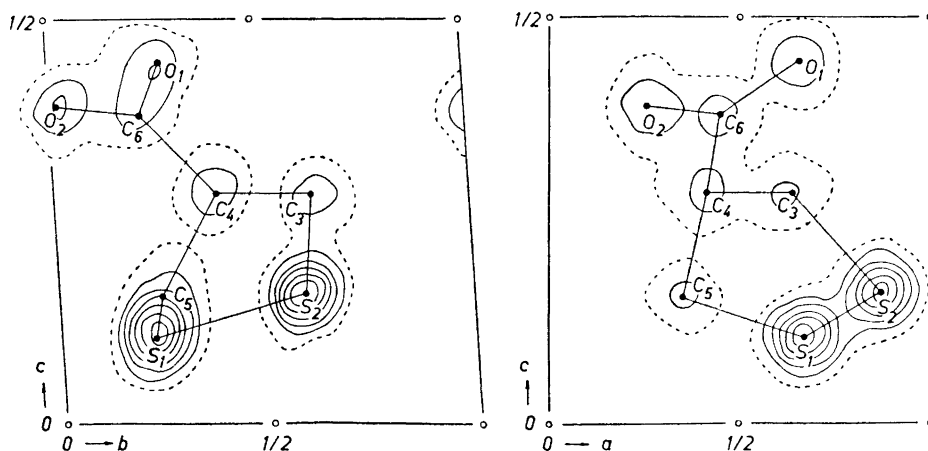
Figs. 1 and 2. Electron density projection of 1,2-dithiolane-4-carboxylic acid along the a axis (left) and along the b axis (right). Contours at intervals of 3 e · Å⁻², beginning with 3 e · Å⁻² (dashed). The final atomic positions are marked with dots.
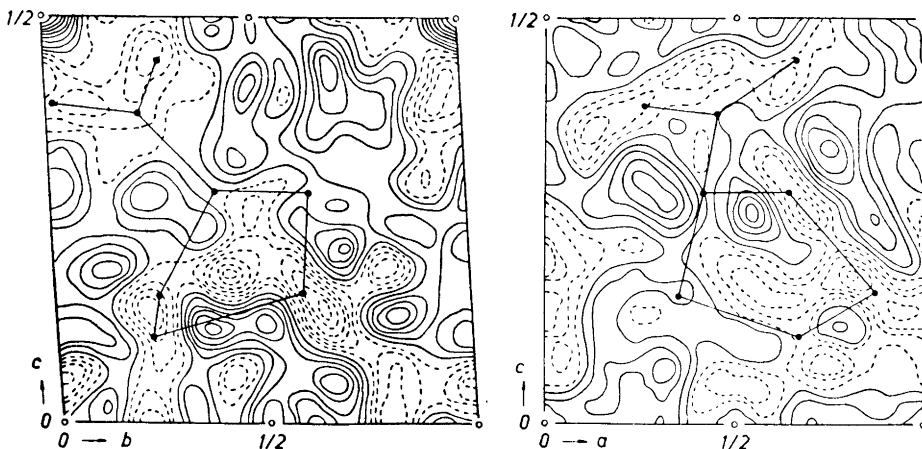
Figs. 3 and 4. Difference projection along the a axis (left) and along the b axis (right). Contours at intervals of 0.15 e $\cdot$ Å^{-2}, with negative dashed, zero and positive fully drawn. The final atomic positions are marked with dots.

of difference refinement were made for the $0kl$ zone and six for the $h0l$ zone. The summations were made by means of Beevers-Lipson strips, using axial subdivisions equal to $a/30$ (0.18 Å), $b/30$ (0.20 Å) and $c/60$ (0.18 Å).

The electron density projections along the a and b axes are shown in Figs. 1 and 2, and the final difference maps in Figs. 3 and 4. The atomic coordinates are listed in Table 1. The two independent sets of z coordinates obtained, one from each zone, differed for the following atoms: $z(S_1) = 0.1060$ and 0.1055, $z(S_2) = 0.1610$ and 0.1605, $z(C_3) = 0.284$ and 0.283, $z(C_4) = 0.286$ and 0.284, $z(C_5) = 0.157$ and 0.156, from the $0kl$ and $h0l$ data, respectively.

Table 1. Atomic coordinates for 1,2-dithiolane-4-carboxylic acid, in fractions of the triclinic axes, and relating to a centre of symmetry.

	x	y	z
S_1	0.669	0.228	0.1057
S_2	0.871	0.593	0.1608
C_3	0.638	0.621	0.284
C_4	0.412	0.392	0.285
C_5	0.349	0.248	0.157
C_6	0.448	0.217	0.381
O_1	0.658	0.270	0.446
O_2	0.254	0.012	0.392

The observed and calculated values of the $0kl$ and $h0l$ structure factors are listed in Table 2. The calculated values are based on the atomic scattering curve of Viervoll and Ögrim for sulphur [19] and of Berghuis et al.[20] for carbon and oxygen. It was not thought worth while to attempt a location of the hydrogen atoms from the X-ray data, although some of the peaks in the

Table 2. Observed and calculated $0kl$ and $h0l$ structure factors for 1,2-dithiolane-4-carboxylic acid.

l	F_o	F_c	l	F_o	F_c	l	F_o	F_c
	$0kl$ zone		7	2.7	− 1.1	4	3.2	− 2.1
	$00l$		8	6.9	− 7.7	5	2.6	+ 2.4
1	5.4	+ 5.8	9	8.0	− 9.7	6	5.1	− 6.5
2	13.4	−13.0	10	2.8	+ 1.4	7	7.5	− 8.9
3	24.2	−24.9	11	<2.2	− 1.0	8	2.9	+ 0.1
4	37.0	−37.5	12	1.8	+ 1.8	9	2.3	+ 3.7
5	7.1	− 5.0				10	2.5	+ 2.2
6	2.0	− 1.4		$0\bar{2}l$				
7	17.2	+17.4	1	12.3	+11.5		$0\bar{4}l$	
8	5.4	+ 3.4	2	6.3	+ 5.4			
9	5.9	− 7.3	3	16.7	+17.9	1	2.4	− 0.3
10	2.2	+ 1.7	4	<1.8	+ 1.6	2	12.3	+12.2
11	4.8	+ 5.3	5	<2.0	− 0.4	3	2.8	− 3.4
12	1.4	− 0.5	6	9.0	+ 5.9	4	18.1	−18.2
13	1.6	+ 2.3	7	2.7	+ 1.0	5	3.2	− 1.8
			8	4.2	+ 3.5	6	7.0	− 7.0
	$01l$		9	8.0	− 7.7	7	2.6	+ 2.5
0	20.7	−19.4	10	5.2	− 4.8	8	9.1	+ 8.1
1	36.1	−38.7	11	4.7	− 4.8	9	6.9	+ 6.7
2	16.3	+20.8	12	2.2	+ 0.8	10	2.1	+ 1.1
3	19.5	−18.8	13	2.2	+ 2.6	11	4.0	− 3.3
4	9.5	− 9.2						
5	4.2	+ 4.2		$03l$			$05l$	
6	2.5	− 4.4	0	8.6	+ 7.7			
7	5.1	+ 0.5	1	13.5	+15.1	0	13.3	+14.7
8	14.4	+14.5	2	15.7	+16.5	1	2.8	− 1.6
9	6.5	+ 6.5	3	17.2	+18.6	2	5.3	− 6.2
10	3.2	+ 2.3	4	4.7	− 6.9	3	7.5	− 7.9
11	6.2	− 6.5	5	5.8	− 6.4	4	6.3	− 6.5
12	4.1	− 4.2	6	6.3	− 7.5	5	2.8	− 0.9
13	1.6	− 0.9	7	3.5	+ 4.3	6	2.6	+ 3.3
			8	2.6	− 0.2	7	4.2	+ 5.2
	$0\bar{1}l$		9	2.5	− 2.0	8	2.9	+ 2.2
1	6.9	+ 7.4	10	2.6	− 2.5			
2	24.6	+24.9	11	2.0	− 1.4		$0\bar{5}l$	
3	45.7	+49.8				1	7.8	+ 9.2
4	6.7	− 8.6		$0\bar{3}l$		2	5.0	− 2.9
5	11.4	+12.6	1	32.8	−33.4	3	3.6	+ 3.3
6	21.9	−22.6	2	24.3	−24.1	4	6.9	− 7.0
7	23.0	−23.3	3	13.5	−15.0	5	2.8	− 1.4
8	3.3	− 3.2	4	14.7	+13.9	6	<2.5	− 2.0
9	4.2	+ 4.8	5	13.8	+14.7	7	<2.3	+ 0.5
10	6.5	+ 6.1	6	9.5	+10.0	8	2.4	+ 1.0
11	4.2	+ 2.9	7	3.0	+ 4.1	9	4.5	− 4.2
12	2.9	+ 1.8	8	4.3	− 4.4	10	1.8	+ 1.4
13	1.9	− 0.5	9	6.4	− 6.4			
			10	2.4	+ 1.3		$06l$	
	$02l$		11	2.5	+ 1.6			
0	21.3	−22.1	12	1.7	− 1.2	0	6.1	− 7.7
1	26.5	−27.4				1	4.8	− 4.7
2	25.2	−27.3		$04l$		2	<2.2	+ 1.9
3	3.3	+ 4.5	0	6.9	+ 7.5	3	<2.1	+ 2.0
4	15.5	+15.8	1	4.3	− 3.2	4	<2.0	+ 1.1
5	21.4	+24.8	2	8.1	+ 9.3	5	<1.7	+ 2.3
6	7.4	+ 8.0	3	3.1	+ 0.3	6	<1.4	− 2.0

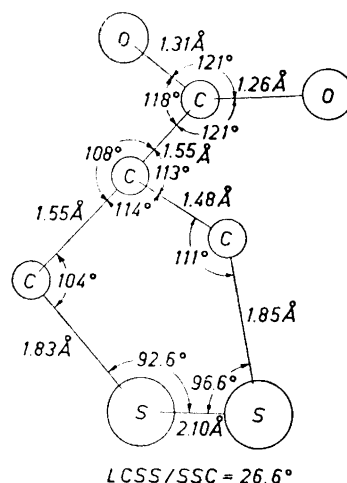| l	F_o	F_c	l	F_o	F_c	l	F_o	F_c
	$0\bar{6}l$			**$20l$**			**$40l$**	
1	2.3	− 2.5	0	22.1	−19.8	0	12.6	−13.1
2	2.7	+ 2.0	1	7.6	+ 7.5	1	2.0	− 1.0
3	7.4	+ 7.9	2	1.2	+ 0.7	2	4.6	+ 5.0
4	4.4	+ 5.2	3	5.5	− 4.4	3	16.0	+14.3
5	2.0	+ 0.9	4	2.3	− 3.0	4	4.2	+ 5.5
6	1.8	− 1.4	5	14.4	−15.3	5	4.4	+ 5.4
7	5.5	− 6.0	6	10.7	+11.6	6	5.6	− 6.9
8	1.4	− 0.9	7	7.5	+ 8.1	7	7.2	− 8.8
			8	11.9	+11.3	8	1.4	− 0.8
	h0l zone		9	1.6	+ 1.6	9	<1.2	+ 0.4
			10	5.4	− 5.7	10	1.6	+ 1.3
	$00l$		11	4.3	− 4.7			
1	5.0	+ 6.4	12	3.9	− 3.9		**$\bar{4}0l$**	
2	12.3	−12.5				1	13.3	−12.9
3	22.2	−24.8		**$\bar{2}0l$**		2	3.3	+ 3.7
4	34.0	−36.2	1	13.0	−11.3	3	4.2	+ 3.3
5	6.5	− 5.0	2	12.6	−13.4	4	<1.6	− 0.6
6	1.8	− 2.0	3	17.0	+17.7	5	2.5	+ 2.2
7	15.8	+15.7	4	22.9	+22.3	6	1.6	0
8	4.9	+ 3.5	5	19.2	+18.8	7	1.5	− 1.3
9	5.4	− 5.8	6	4.0	− 3.4	8	3.4	+ 3.5
10	2.0	+ 1.1	7	11.5	−11.2	9	3.2	+ 2.2
11	4.4	+ 4.2	8	13.4	−14.1	10	1.5	+ 1.6
12	1.3	+ 0.1	9	6.4	− 6.0			
13	1.5	+ 1.5	10	3.7	+ 2.9		**$50l$**	
			11	4.5	+ 4.3	0	3.9	− 3.6
	$10l$		12	4.2	+ 3.4	1	9.1	− 9.7
0	32.0	−32.5	13	<0.8	0	2	2.1	− 2.2
1	29.3	+30.7				3	1.6	− 0.6
2	31.1	+32.6		**$30l$**		4	3.7	+ 4.1
3	1.3	− 1.9	0	12.3	+12.7	5	<1.4	+ 1.0
4	1.7	− 0.3	1	7.1	+ 6.6	6	1.2	+ 1.2
5	11.4	+11.3	2	9.0	+ 8.7	7	1.4	+ 1.4
6	3.8	− 4.7	3	2.9	+ 3.0	8	0.8	− 0.8
7	<1.4	+ 1.5	4	8.8	− 8.2			
8	9.5	− 7.5	5	11.9	−14.5		**$\bar{5}0l$**	
9	3.3	− 3.8	6	7.2	− 8.5	1	3.3	+ 4.0
10	2.3	− 3.6	7	2.3	+ 2.8	2	1.6	+ 0.3
11	2.7	− 3.0	8	2.4	+ 3.9	3	7.9	+ 8.2
12	5.9	+ 5.9	9	5.5	+ 5.8	4	2.7	+ 2.9
13	1.6	+ 2.0	10	1.7	+ 2.3	5	1.8	− 1.0
			11	1.1	+ 0.2	6	2.3	− 2.6
	$\bar{1}0l$					7	1.8	− 1.9
1	4.5	− 4.8		**$\bar{3}0l$**		8	1.0	+ 0.3
2	33.5	−37.0	1	3.8	− 3.2			
3	23.4	−23.7	2	2.7	+ 2.6		**$60l$**	
4	3.5	+ 2.7	3	4.0	− 4.5	0	1.8	− 2.5
5	11.5	+ 9.8	4	5.2	+ 5.1	1	1.1	+ 1.0
6	29.7	+30.8	5	8.1	− 7.5	2	1.9	− 2.3
7	1.3	− 2.8	6	9.0	− 9.6	3	1.6	− 2.2
8	1.5	+ 1.4	7	2.1	− 1.0	4	0.8	+ 0.1
9	3.0	− 2.6	8	1.6	− 1.6			
10	5.9	− 5.2	9	5.7	+ 5.5		**$\bar{6}0l$**	
11	2.4	− 1.5	10	4.4	+ 3.6	1	3.4	+ 3.3
12	1.3	− 0.1	11	3.9	+ 3.1	2	3.5	+ 3.7
13	1.1	+ 0.1	12	1.0	− 0.6	3	1.8	− 2.1
						4	2.8	− 2.7

Fig. 5. 1,2-Dithiolane-4-carboxylic acid as
     seen along the *b* axis.

difference maps (the standard deviation of electron density is about 0.3 e.$\mathring{A}^{-2}$ for both zones) are in the approximate positions expected for hydrogen atoms. In the temperature factor exp $[-B(\sin^2\Theta/\lambda^2)]$ applied in the calculation of structure factors, B (in $\mathring{A}^2$) is 4.5 for sulphur and oxygen and 3.5 for carbon in the $0kl$ zone, and 5.2 for sulphur, 5.5 for oxygen and 4.8 for carbon in the $h0l$ zone. The reliability index $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, with non-observed reflections included when $|F_c|$ exceeds the observeable limit, is 0.122 for the $0kl$ zone and 0.105 for the $h0l$ zone.

Standard deviations of atomic coordinates were estimated from the root-mean-square gradients in the final difference maps and the curvatures of the peaks in the electron density maps [21],[22]. Where overlapping occurred, the s.d. was taken as up to twice that which would otherwise have applied. In this way the following values were obtained and used for calculation of the s.d. of bond lengths and angles: For the sulphur coordinates $\sigma = 0.005$ Å except $\sigma(y)$ for S_1 which was put equal to 0.008 Å. For the light atoms $\sigma = 0.015$ Å for x of C_5 and O_1, y of C_3 and C_4 and z of C_3, C_4 and C_5; 0.02 Å for x of C_3, C_4 and O_2 and for y and z of C_6, O_1 and O_2; 0.025 Å for x of C_6 and 0.03 Å for y of C_5.

CONFIGURATION AND DIMENSIONS OF THE 1,2-DITHIOLANE RING

The bond lengths and angles in the molecule, calculated from the coordinates of Table 1, are listed in Table 3, together with estimated standard deviations. A drawing of the molecule as seen in projection along the *b* crystal axis is shown in Fig. 5.

The data show that the disulphide group differs from non-cyclic disulphides in three distinct ways: The bond angles are smaller and the S—S bond slightly longer, and there is a large decrease in dihedral angle.

Table 3. Dimensions of 1,2-dithiolane-4-carboxylic acid.

$S_1-S_2 = 2.096 \pm 0.009$ Å	$\angle S_1-S_2-C_3 = 96.6 \pm 0.6°$	
$S_1-C_5 = 1.83 \pm 0.02$	$\angle S_2-S_1-C_5 = 92.6 \pm 0.7$	
$S_2-C_3 = 1.85 \pm 0.02$	$\angle S_1-C_5-C_4 = 104.2 \pm 1.3$	
$C_3-C_4 = 1.48 \pm 0.025$	$\angle S_2-C_3-C_4 = 110.6 \pm 1.2$	
$C_4-C_5 = 1.55 \pm 0.03$	$\angle C_3-C_4-C_5 = 114.1 \pm 1.6$	

$$
\left. \begin{array}{l} C_4-C_6 = 1.55 \\ C_6-O_1 = 1.26 \\ C_6-O_2 = 1.31 \end{array} \right\} \pm 0.03 \text{ Å} \qquad \left. \begin{array}{l} \angle O_1-C_6-O_2 = 121.0 \\ \angle C_4-C_6-O_1 = 121.2 \\ \angle C_4-C_6-O_2 = 117.8 \end{array} \right\} \pm 2°
$$

$$\angle C_5-C_4-C_6 = 107.5 \pm 1.5° \qquad\qquad \angle C_3-C_4-C_6 = 113.1 \pm 1.5°$$

Dihedral angle $C_5S_1S_2/S_1S_2C_3 = 26.6 \pm 1°$

The bond angles of the two sulphur atoms, although they appear to differ significantly, are both smaller than the angle of $107 \pm 3°$ in dimethyl disulphide [23], $105.4 \pm 3°$ in *bis*(trifluoromethyl) disulphide [24], $103 \pm 1°$ in N,N'-diglycyl-L-cystine dihydrate [25], and $104 \pm 1°$ and $99 \pm 2°$, respectively, in formamidinium disulphide dibromide and diiodide monohydrates [26]. For all but the last example the angles lie in the range 103—107°.

The observed S—C and C—C bond lengths do not differ significantly from the normal single-bond lengths, 1.82 Å [8] and 1.54 Å. The S—S bond appears to be significantly longer than in non-cyclic disulphides. In the five examples referred to above the mean of the observed lengths is 2.044 Å, with an average deviation of 0.004 Å. In orthorhombic sulphur [27], S—S = 2.037 ± 0.005 Å. The longest bonds between two divalent sulphur atoms, measured with any accuracy, appear to be the two long bonds of 2.10 and 2.13 ± 0.03 Å in cesium hexasulphide [28], and that of 2.088 ± 0.012 Å in the planar thiuret ion, an unsaturated five-membered cyclic disulphide [29]. It has been suggested [8,28,30] that the bonds of length about 2.04 Å possess some double-bond character, and that the single-bond length is in the neighbourhood of 2.08—2.10 Å, as found here. Another view [31] is that the observed variations in S—S bond lengths are due to different degrees of s and p character in the hybrid σ-bond orbitals of sulphur. A smaller bond angle at sulphur would then lead to less s character and a longer bond.

The major change in the disulphide group induced by the geometrical requirements of the ring is the decrease in dihedral angle, from the normal value [8] of about 90° to $26.6 \pm 1°$ in the 1,2-dithiolane ring. The barrier to rotation about the bond between two divalent sulphur atoms, through the planar *cis* and *trans* forms with zero and 180° dihedral angles, has been estimated as 10—14 kcal/mole [32,33]. With the barrier a twofold cosine type the observed dihedral angle in 1,2-dithiolane-4-carboxylic acid corresponds to a S—S torsion energy equal to 80 % of the barrier height. A smaller dihedral angle occurs in thiuret hydroiodide [29] where the angle is zero, and probably in 4-methyl-1,2-dithia-4-*cyclo*pentene-3-thione which according to a short report [34] is approximately planar; these are five-membered cyclic disulphides, but conditions are presumably different because of the unsaturated character of the rings. It appears likely that the decrease in dihedral angle has a bearing on

the increase in S—S bond length, through the increased repulsion between the unshared $p\pi$ electron pairs of sulphur which are thought to be the principal cause of the barrier [6,9], and possibly through less favourable conditions for pd π-bonding.

The 1,2-dithiolane ring is not symmetrical about the disulphide group. Of the bond angles at carbon, that at C_5 appears to be significantly smaller than tetrahedral, and that at C_4 is larger, but not significantly. Here, at C_4, a widening of the angle would result from torsion and bending strain in the disulphide group, the distance between the carbon atoms C_3 and C_5 bonded to sulphur being about 0.2 Å larger in non-cyclic disulphides than the distance, 3.54 Å, observed here. The dihedral angles in the ring, beside that of the disulphide group, are $S_1S_2C_3/S_2C_3C_4 = 20°$, $S_2C_3C_4/C_3C_4C_5 = 26°$, $C_3C_4C_5/C_4C_5S_1 = 54°$, $C_4C_5S_1/C_5S_1S_2 = 49°$. The two large dihedral angles are associated with the carbon atom, C_5, which has the smallest bond angle.

Bergson and Schotte have [35], on the basis of the present structural data, made a conformation analysis of the 1,2-dithiolane ring, and concluded that the total strain in the ring is at least 16 kcal/mole.

The 4-carboxyl group is planar, the maximum deviation of an atom from the least-squares plane through the group being 0.002 Å, in the case of C_6. This carbon atom lies 3.17 Å from S_1 and 3.57 Å from S_2. The dimensions of the group agree reasonably well with values reported for other aliphatic carboxylic acids [36,37]. The carboxyl group is directed towards the symmetry centre at $\frac{1}{2},0,\frac{1}{2}$, which lies 0.11 Å from the plane of the group. Two molecules, one on each side of the symmetry centre, are arranged into dimers through O—H···O hydrogen bonds of length 2.61 Å between the carboxyl groups. This is the structure normally found in monocarboxylic acids [38,39].

A van der Waals contact of length 3.41 Å occurs between two S_1 sulphur atoms across the symmetry centre at $\frac{1}{2},0,0$. In orthorhombic sulphur [27] the shortest intermolecular contact is 3.69 Å and thus longer, but a van der Waals radius for sulphur of about 1.60 Å is indicated in two compounds containing iodine [28,39].

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