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Crystal and Molecular Structure of 5,5-Dimethyl-1,3-dithian-2-ylcarboxylic Acid. Is the Axial Conformer Stabilized by Hydrogen Bonds?

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ABSTRACT

*The crystal structure of the title compound (**3**) was determined by the X-ray diffraction technique from diffractometer intensity measurements:* $C_7H_{12}O_2S_2$, *monoclinic space group* $P2_1/c$, $a = 12.644(1)$ Å, $b = 6.102(1)$ Å, $c = 12.920(2)$ Å, $B = 110.78(1)°$, *2193 reflections, and* $R = 0.043$. *The molecule of **3** adopts a chair conformation in which the carboxyl group occupies an axial position. The contacts between the carbonyl oxygen and axial hydrogens at C(4) and C(6) of 2.564 and 2.697 Å are smaller than the sum of van der Waals radii of this oxygen and hydrogen atoms, indicating a possibility of intramolecular C=O· ·H–C hydrogen bond formation. The acid **3** forms also dimeric structures via intermolecular hydrogen bonds with contact between hydroxyl hydrogen and carbonyl oxygen of 1.439 Å and O–H· · ·O angle of 176.2°.*

INTRODUCTION

The preferred axial conformation and operation of a strong anomeric effect in 2-carbonyl-substituted 1,3-dithianes have been well documented [1,2]. However, the most intriguing finding is that, among the carbonyl containing substituents, the carboxyl group, C(O)OH, shows the strongest anomeric effect, and, as was pointed out by Juaristi *et al.* [1], no simple rationalization can be advanced for this observation.

Although the analogy between the carbonyl group, C(O), and phosphoryl group, P(O), is rather formal (Scheme 1) the latter also shows a strong tendency for the axial orientation in 1,3-di- and 1,3,5-trithiane rings [3]. In 1984, we published the results of X-ray analysis of 2-dimethoxyphosphoryl-1,3,5-trithiane (**1**) [3a], which revealed that the phosphoryl group is axial and its oxygen is almost symmetrically situated above the 1,3,5-trithiane ring and showed two distinctly different contacts between axial hydrogens at C(4) and C(6). Later on, such a situation has been found to be general for other axial 2-phosphoryl-1,3,-diheteroanes **2** (see Scheme 2) and interpreted in terms of intramolecular hydrogen bond formation which, in addition to stereoelectronic factors such as $n_S{-}\sigma^*_{C-P}$ negative hyperconjugation and *through space* interaction, may stabilize the axial conformation.

The results of X-ray crystallographic studies on 2-phosphoryl-1,3-diheteroanes presented above prompted us to synthesize 5,5-dimethyl-1,3-di-

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thian-2-ylcarboxylic acid (**3**) and to determine its crystal and molecular structure with the hope of obtaining better insight into the origin of the strong axial preference of the carboxylic acid group in the 1,3-dithiane ring.

RESULTS AND DISCUSSION

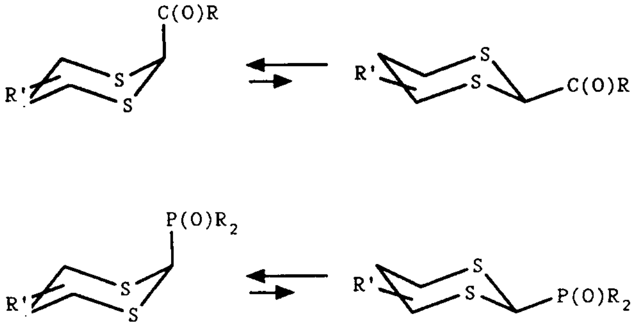
The title acid has been prepared according to the general procedure described by Juaristi *et al.* [1], involving addition of carbon dioxide to the 5.5-dimethyl-1,3-dithianyl carbanion followed by acidification.

The ^1H and ^{13}C NMR spectra of the acid **3** strongly suggest that, in a solution, it exists preferentially in an axial conformation. Thus, the chemical shift difference between axial and equatorial methylene protons $\Delta\delta$ is equal to 1. Such a big difference may arise only from the axial position of the carboxylic acid group and its deshielding effect on the axial protons at C(4) and C(6). Moreover, the strongly negative γ-effect value in the ^{13}C NMR spectra of **3**, $\delta = -3.44$ [6], is also consistent with the prevailing axial position of the 2-carboxylic acid group in the 1,3-dithiane ring.

The axial position of the carboxyl group in the acid **3** was also found in the crystal state. Suitable crystals of **3** for X-ray analysis were obtained by slow crystallization from a solution of methanol and ethyl acetate. The structure has been solved by direct methods and refined by full matrix least squares to the final value $R = 0.043$.

A three-dimensional view of the molecule of **3** and the atom numbering are shown in Figure 1. Figure 2 shows how the molecules of **3** are packed in the unit cell. Positional parameters for all atoms are collected in Table 1. Tables 2 and 3 contain bond distances and bond angles for all atoms. Table 4 gives the temperature factors.

The torsional angles for the 1,3-dithiane ring



SCHEME 1

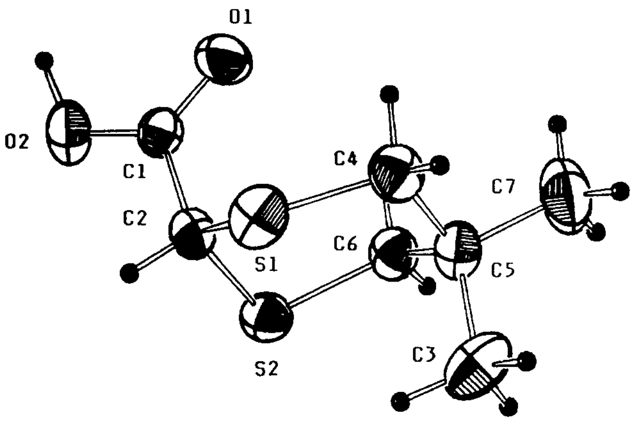
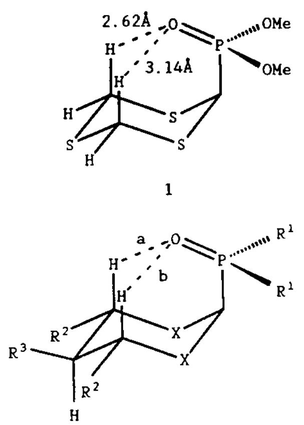


FIGURE 1 Three-Dimensional View of 5,5-dimethyl-1,3-dithian-2-ylcarboxylic Acid (**3**) with Atom Numbering

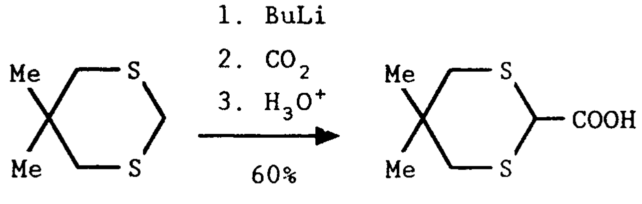


1

2

2a, X = O, R^1 = Ph, R^2 = Me, R^3 = H, a = 2.40Å, b = 2.53Å [4]
2b, X = S, R^1 = OMe, R^2 = H, R^3 = Bu^t, a = 2.49Å, b = 2.57Å [4]
2c, X = S, R^1 = OMe, R^2 = Me, R^3 = H, a = 2.54Å, b = 2.66Å [4]
2d, X = S, R^1 = Ph, R^2 = H, R^3 = Bu^t, a = 2.54Å, b = 2.76Å [4]
2e, X = Se, R^1 = OMe, R^2 = H, R^3 = Bu^t, a = 2.55Å, b = 2.63Å [5]

SCHEME 2



3, mp 155.0-157.5°C

SCHEME 3

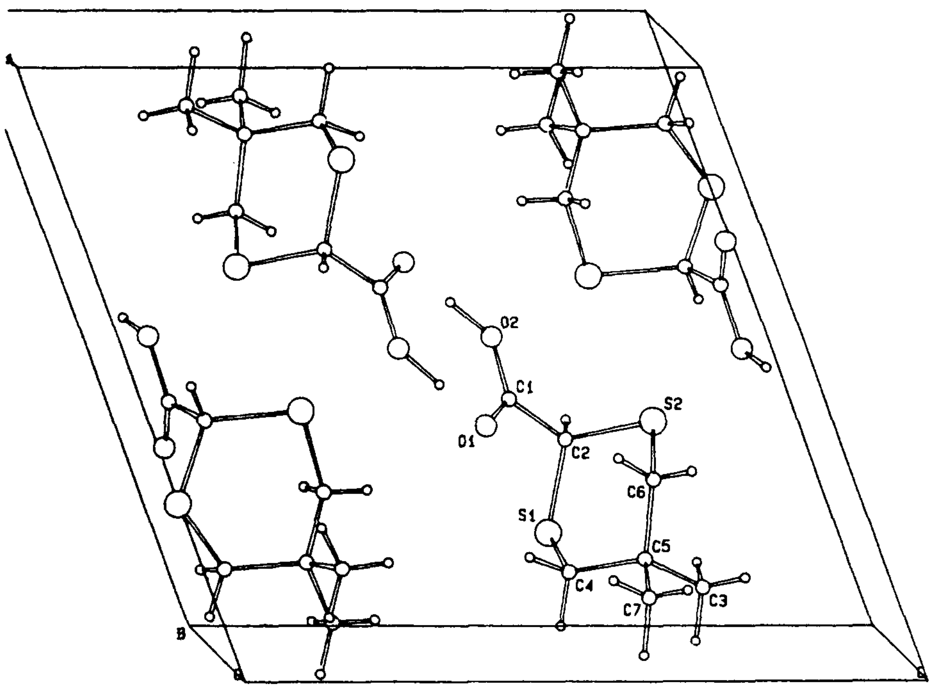


FIGURE 2 Packing of 5,5-dimethyl-1,3-dithian-2-ylcarboxylic Acid (**3**) in Unit Cell

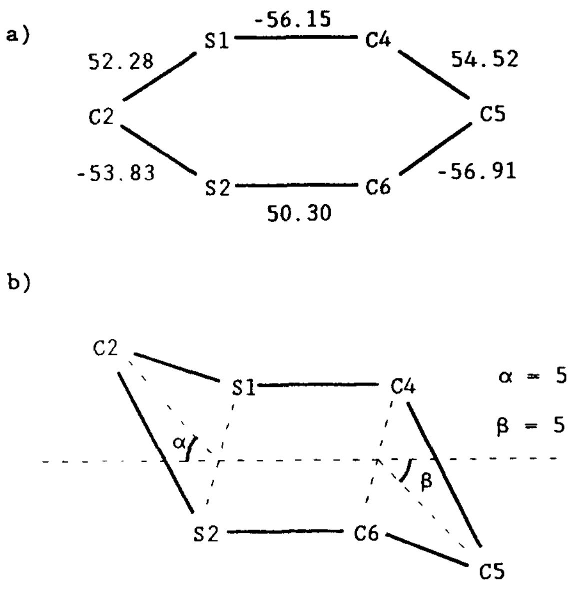
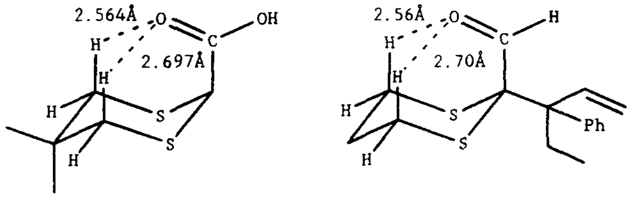


FIGURE 3 Geometrical parameters for 5,5-dimethyl-1,3-dithian-2-ylcarboxylic acid (**3**): (a) torsional angles; (b) angles between planes.



3 4

SCHEME 4

are given in Figure 3a, while the angles α and β (52.34° and 55.67°), describing the chair conformation of this heterocyclic ring, are depicted in Figure 3b. Additionally, the chair conformation of the 1,3-dithiane ring is characterized by the asymmetry parameters, ΔC_s and ΔC_2 listed in Table 5.

They show that the basal plane of the chair is formed by the atoms S1, S2, C4, and C6. The distances of the atoms C2 and C5 from this plane are −0.734 and +0.774 Å, respectively.

The axial position of the carbonyl carbon atom C1 is clearly seen from Figure 1 and evidenced by the angle of 81.04(13)° between the C1-C2 normal and the basal plane of the chair.

With regard to the main question of this work, Figure 2 clearly reveals that the carbonyl group in **3**, like the phosphoryl group in 1,3,5-trithiane **1** and 1,3-dithianes **2**, is situated above the heterocyclic

TABLE 1 Positional Parameters for Atoms of **3** and Their Estimated Standard Deviations

Atom	*x*	*y*	*z*	*B(A2)*
S1	0.24290(6)	−0.0003(1)	0.52410(6)	3.72(2)
S2	0.40595(6)	0.1610(1)	0.74570(6)	3.38(1)
O1	0.3738(2)	0.4312(4)	0.5122(2)	4.07(5)
O2	0.5335(2)	0.2381(4)	0.5574(2)	3.98(4)
C1	0.4313(2)	0.2653(5)	0.5521(2)	2.75(5)
C2	0.3845(2)	0.0865(5)	0.6037(2)	3.04(6)
C3	0.1469(3)	0.0841(7)	0.7255(3)	5.01(8)
C4	0.1590(2)	0.2226(6)	0.5453(2)	3.56(6)
C5	0.1749(2)	0.2794(5)	0.6664(2)	3.45(6)
C6	0.2952(2)	0.3609(5)	0.7255(2)	3.24(6)
C7	0.0949(3)	0.4704(7)	0.6614(3)	5.75(9)
H102	0.577(4)	0.38(1)	0.524(5)	12(2)‡
H21	0.426(3)	−0.042(6)	0.608(2)	2.4(8)‡
H31	0.199(3)	−0.051(7)	0.724(3)	3.8(9)‡
H32	0.063(3)	0.036(7)	0.683(3)	4(1)‡
H33	0.159(3)	0.117(6)	0.795(3)	3.4(9)‡
H41	0.171(2)	0.361(5)	0.502(2)	1.4(6)‡
H42	0.077(3)	0.169(6)	0.501(3)	2.6(8)‡
H61	0.303(2)	0.408(5)	0.788(2)	1.8(7)‡
H62	0.316(2)	0.494(5)	0.692(2)	1.3(6)‡
H71	0.103(3)	0.508(7)	0.724(3)	3.9(9)‡
H72	0.005(3)	0.414(7)	0.618(3)	3.8(9)‡
H73	0.110(3)	0.607(8)	0.625(3)	6(1)‡

Starred atoms were refined isotropically. Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as (4/3)‡[2‡B(1,1) + b2‡B(2,2) + c2‡B(3,3) + ac(cos cacea)‡B(1,2) + ac(cos beta)‡B(1,3) + bc(cos alpha)‡B(2,3)]

ring and placed almost symmetrically between the two axial hydrogens at C4 and C6. The corresponding contacts, i.e., H41· · ·O1 and H62· · ·O1, are 2.564 and 2.697 Å. The distances between the carbonyl oxygen atom O1 and the endocyclic carbon atoms C4 and C6 are 3.163 and 3.272 Å, respectively. In view of the available literature [7,8] data on the C–H· · ·O hydrogen bond in crystals, it is quite reasonable to assume the formation of a weak intramolecular hydrogen bond in **3** between the carbonyl oxygen and at least one axial hydrogen. In this context, it is interesting to note that, in the crystal structure of (R)-3-ethyl-3-phenyl-2,2-(trimethylenedithio)pent-4-enal (**4**) [9], one observes a very similar situation (Scheme 4). The carbonyl group in **4** is axial and its oxygen has close interatomic contacts with axial hydrogens of 2.56 and 2.70 Å, respectively.

In addition to the intramolecular hydrogen bond formation discussed above, Figure 2 shows also that two molecules of the acid **3** form a typical dimeric structure *via* intermolecular hydrogen bonds. The contacts between the hydroxyl hydrogen H102 and the carbonyl oxygen O1 were found to be 1.439 Å, with the O2-H102· · ·O1 angle of 176.2°.

In summary, the crystallographic study of the acid **3** revealed the presence of both intramolecular and intermolecular hydrogen bonds which can enhance effectively the anomeric effect.

EXPERIMENTAL

^1H NMR spectrum of a 0.5% solution in chloroform-*d* containing 0.1% of tetramethylsilane was recorded at 200.13 on a Bruker AC 200 spectrometer. The ^{13}C NMR spectrum of about a 4% solution in chloroform-*d* containing 0.4% of tetramethylsilane was measured at 75.47 MHz on the Bruker MSL 300 instrument. The mass spectrum was recorded with an LKB 2091 spectrometer. The infrared spectrum was taken on a SPECORD M80 instrument.

The melting point was measured using a Boëtius apparatus and is uncorrected. Anhydrous hydrocarbons and tetrahydrofuran were distilled from $LiALH_4$. Chloroform was distilled from P_2O_5. Other compounds, if not described below, were commercially available.

Analytical thin-layer chromatography (TLC) was conducted on precoated plates (silica gel 60F-254, layer thickness 0.25 mm). All chromatographic materials were purchased from Merck.

*5,5-Dimethyl-1,3-dithian-2-ylcarboxylic Acid (**3**)*

A 1.54 M solution of *n*-butyllithium in *n*-hexane (10.0 mL, 15.4 mmol) was added to a stirred, cooled

TABLE 2 Bond Distance (Å) for **3**

Atom 1	*Atom 2*	*Distance*	*Atom 1*	*Atom 2*	*Distance*	*Atom 1*	*Atom 2*	*Distance*
S1	C2	1.799(2)	C2	H21	0.94(3)	C5	C6	1.523(4)
S1	C4	1.805(3)	C3	C5	1.523(5)	C5	C7	1.529(5)
S2	C2	1.814(3)	C3	H31	1.06(4)	C6	H61	0.84(3)
S2	C6	1.805(4)	C3	H32	1.05(3)	C6	H62	1.00(3)
O1	C1	1.247(3)	C3	H33	0.87(4)	C7	H71	0.81(4)
O2	C1	1.280(3)	C4	C5	1.545(4)	C7	H72	1.13(3)
O2	H102	1.21(7)	C4	H41	1.05(3)	C7	H73	1.01(5)
C1	C2	1.506(4)	C4	H42	1.04(3)			

Numbers in parentheses are estimated standard deviations in the least significant digits.

TABLE 3 Bond Angles [°] for **3**

Atom 1	*Atom 2*	*Atom 3*	*Angle*	*Atom 1*	*Atom 2*	*Atom 3*	*Angle*	*Atom 1*	*Atom 2*	*Atom 3*	*Angle*
C2	S1	C4	102.2(1)	C5	C3	H33	110(3)	C4	C5	C7	106.3(2)
C2	S2	C6	101.2(1)	H31	C3	H32	108(3)	C6	C5	C7	107.5(3)
C1	O2	H102	118(3)	H31	C3	H33	108(3)	S2	C6	C5	116.0(2)
O1	C1	O2	123.8(3)	H32	C3	H33	113(3)	S2	C6	H61	106(2)
O1	C1	C2	120.6(3)	S1	C4	C5	116.8(2)	S2	C6	H62	108(2)
O2	C1	C2	115.5(2)	S1	C4	H41	110(2)	C5	C6	H61	111(2)
S1	C2	S2	114.5(2)	S1	C4	H42	102(3)	C5	C6	H62	115(1)
S1	C2	C1	115.3(2)	C5	C4	H41	111(2)	H61	C6	H62	100(3)
S1	C2	H21	102(2)	C5	C4	H42	112(3)	C5	C7	H71	109(3)
S2	C2	C1	109.0(2)	H41	C4	H42	105(2)	C5	C7	H72	109(3)
S2	C2	H21	105(2)	C3	C5	C4	111.2(3)	C5	C7	H73	115(3)
C1	C2	H21	110(2)	C3	C5	C6	111.9(2)	H71	C7	H72	109(3)
C5	C3	H31	110(2)	C3	C5	C7	110.5(3)	H71	C7	H73	105(4)
C5	C3	H32	109(2)	C4	C5	C6	109.2(3)	H72	C7	H73	110(3)

Numbers in parentheses are estimated standard deviations in the least significant digits.

TABLE 4 General Displacement Parameter Expressions—U's

Name	*U(1,1)*	*U(2,2)*	*U(3,3)*	*U(1,2)*	*U(1,3)*	*U(2,3)*
S1	0.0530(3)	0.0415(4)	0.0494(3)	−0.0125(3)	0.0214(3)	−0.0136(3)
S2	0.0403(3)	0.0502(4)	0.0362(3)	0.0033(3)	0.0113(2)	0.0057(3)
O1	0.0464(9)	0.048(1)	0.062(1)	0.0042(9)	0.0212(8)	0.017(1)
O2	0.0449(8)	0.039(1)	0.078(1)	−0.0008(8)	0.0350(7)	−0.007(1)
C1	0.036(1)	0.037(1)	0.033(1)	−0.001(1)	0.0138(8)	−0.005(1)
C2	0.041(1)	0.033(1)	0.045(1)	0.005(1)	0.0198(9)	0.002(1)
C3	0.062(1)	0.075(2)	0.063(2)	−0.022(2)	0.034(1)	−0.004(2)
C4	0.034(1)	0.054(2)	0.044(1)	−0.001(1)	0.009(1)	−0.002(1)
C5	0.039(1)	0.046(2)	0.050(1)	0.002(1)	0.0211(9)	−0.002(1)
C6	0.045(1)	0.038(1)	0.042(1)	−0.000(1)	0.0185(9)	−0.006(1)
C7	0.062(2)	0.081(2)	0.080(2)	0.024(2)	0.031(1)	−0.007(2)

The form of the anisotropic displacement parameter is exp [−2PI2(h2a2U(1,1) + k2b2U(2,2) + 12c2U(3,3) + 2hkabU(1,2) + 2h1acU(1,3) + 2k1bcU(2,3)}], where a, b, and c are reciprocal lattice constants.

TABLE 5 Asymmetry Parameters of a Six-Membered Ring in 1,3-dithiane 3

x	ΔC_s^x	*x*	δC_2^x
C5	2.91	C5-C4	9.49
C4	10.42	C4-S1	12.67
S1	7.59	S1-C2	3.41

(−78°C) solution of 5,5-dimethyl-1,3-dithiane [10] (2.156 g, 14.54 mmol) in tetrahydrofuran (100 mL) maintained under nitrogen. The mixture was stirred at this temperature for 0.5 hour and at −10°C for 0.5 hour. After having been cooled to −78°C, Dry Ice (1.0 g, 23 mmol) was dropped into the flask and the cooling bath was removed. The mixture was stirred at room temperature for 1 hour. Then, 10% hydrochloric acid (10 mL, 27 mmol) was added, and the mixture was concentrated in vacuo. The residue was extracted with chloroform (3 × 30 mL). The combined organic solution was washed with water (25 mL) and dried ($MgSO_4$) and the solvent was evaporated. Crystallization of the residue from chloroform/*n*-pentane afforded 1.695 g (60.6%) of colorless plates, mp 155.0–157.5°C. ^1H NMR (200.13 MHz, $CDCl_3$) δ 1.13 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 2.25 (d, $^2J_{H\text{-}H}$ = 13.8 Hz, 2 H, C*H*H), 3.25 (d, $^2J_{H\text{-}H}$ = 13.8 Hz, 2 H, CH*H*), 4.10 (s, 1 H, CH–CO), 10.88 (s, 1 H, COOH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 23.83 (s, CH_3), 25.95 (s, Me_2C), 30.94 (s, CH_3), 37.82 (s, CH_2), 38.64 (s, CH), 175.38 (s, CO); IR (KBr) 784 (m), 824 (m), 892 (m), 912 (m), 1194 (m), 1280 (m), 1302 (m), 1404 (m), 1694 (vs), 2960 (s) cm^{-1}; MS (70 eV) *m/e* 192(40, $M^{+}\cdot$), 147(100), 69(58), 56(19), 45(55), 41(46), 39(24), 27(18). Anal. Calcd. for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29; S, 33.35. Found: C, 43.64; H, 6.38; S, 33.40.

Structure Determination of **3**

The acid **3** was crystallized from methanol and ethyl acetate solution. Monoclinic, space group $P2_1/c$.

Intensity data were collected using a CAD4 diffractometer in the Θ range $1 \leq \Theta \leq 75°$ with graphite monochromatized Cu-K_α radiation ($\lambda = 1.54178$ Å). Lattice constants were refined by least-squares fit of 25 reflections in the Θ range 16.9–29.7°. Integrated reflections (2198) were collected in $\omega/2\Theta$ scan technique, scan width $(1.32 + 0.14 \tan\Theta)°$; $0<h<15$, $0<k<7$, $-16<l<16$. The decline in the intensities of the three standard reflections (2, −1, 5; −2, −1, 6; −1, −2, −2) was 6.8% during 27.8 hours. For this reason, the collected data were corrected by the CHORT program with correction coefficients: min = 0.9999, max = 1.1090, av = 1.0647. An absorption correction was applied by the DIFABS program with correction coefficients: min = 0.766, max = 1.237, av = 1.008. The 1668 observed reflections ($I>3\sigma(I)$) were used to solve the structure by direct methods and to refine it by full matrix least squares using F's. The H atoms were taken from a difference Fourier map and refined isotropically. Refinement converged to $R = 0.043$ with unit weights for 148 refined parameters. The largest shift/error in the last cycle was 0.001; the largest residual peak in the final difference Fourier map was 0.315 eÅ^{-3}. All calculations were carried out with the Enraf-Nonius SDP crystallographic computing package [11].

Crystal Data

$C_7H_{12}O_2S_2$, monoclinic, $P2_1/c$, $a = 12.644(1)$ Å, $b = 6.102(1)$ Å, $c = 12.920(2)$ Å, $\beta = 110.78(1)°$, $z = 4$, $D_c = 1.370$ g/cm^3, $\mu = 47.4$ mm^{-1}, $V = 932.1(2)$ Å^3. The structure was refined to $R = 0.043$.

Note. Crystal data are deposited with the Cambridge Crystallographic Data Center, United Kingdom.

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