

1*H*-2-Benzothiopyran-4(3*H*)-one in Aldol and Mannich Reactions

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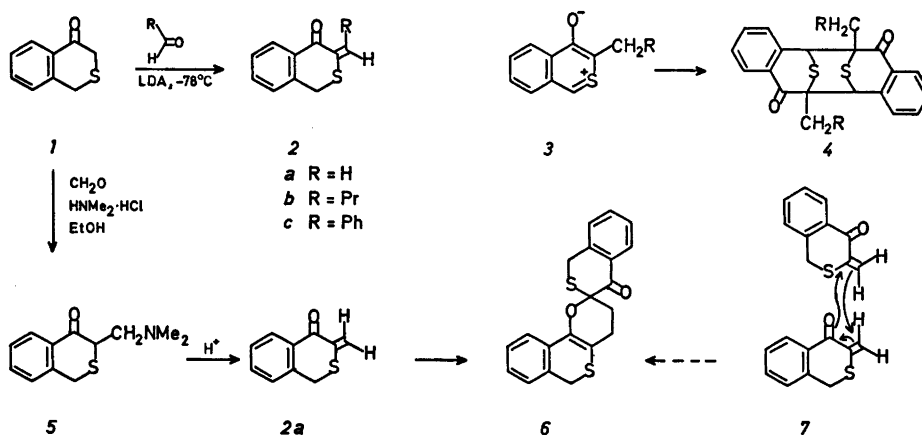
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The title compound (*1*) has been converted to (*Z*)-3-alkylidene derivatives by aldol condensation with butanal or benzaldehyde. The 3-methylene derivative, expected from the reaction with formaldehyde, dimerized spontaneously to a spiro compound (*6*), which was also obtained from *1* through a Mannich reaction. The stereochemistry of *6* has been investigated by *X*-ray techniques.

Hydride abstraction from 1*H*-2-benzothiopyran-4(3*H*)-one *1* (Scheme 1) or its 1-methyl derivative has yielded 4-hydroxy-2-benzothiopyrylium salts.^{1,2} The betaines of the latter are rapidly dimerized to *syn*- and *anti*-5,6,12,13-tetrahydro-5,13:6,12-bisepithiodibenzo[*a,f*]cyclodecene-7,14-diones (*4*). This report describes studies of 3-alkylidene derivatives *2* which are isomeric with the thiopyrylium betaines *3*.

The lithium enolate of 1*H*-2-benzothiopyran-4(3*H*)-one³ was generated at -78°C by means of lithium diisopropylamide (LDA), and the enolate reacted with butanal. The initial aldol

was dehydrated in the strongly basic medium. Acetaldehyde with the enolate gave a heterogeneous reaction product, presumably because of metal-hydrogen exchange between acetaldehyde and the enolate of *1* followed by reactions of the new enolate.^{4a} The aldol condensation proceeded well for benzaldehyde. In IR, the carbonyl band for *2b* was at 1685 cm^{-1} and for *2c* at 1665 cm^{-1} . *M* was the base peak in the mass spectra. The benzylic protons on C-1 appear as a singlet at *ca.* δ 3.8. Among the aromatic protons, H-5 resonates at the lowest field due to the anisotropy effect of the carbonyl group.¹ Spectroscopy and chromatography are consistent with formation of one stereoisomer. The latter is expected to have the β -vinyl substituent *trans* to the carbonyl group.^{4b} *trans* configuration is also supported by comparisons of ¹H NMR spectra. In 2-methylcyclohexanone the *cis* proton with respect to the carbonyl group resonates at δ 5.72 and the *trans* proton at δ 5.04.⁵ In (*E*)-2-butyl-6-butyl-



Scheme 1.

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Table 1. Fractional atomic coordinates and temperature factors. The anisotropic temperature factor is given by: $\exp -2\pi^2\{U_{11}(a^*h)^2 + \dots + 2U_{23}(b^*c^*kl)\}$.

Atom	X	Y	Z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	.7989(3)	.2113(3)	.5352(1)	.0601(17)	.0474(16)	.0356(15)	.0101(14)	.0290(13)	.0021(14)
C1'	.5456(4)	.2472(6)	.5659(2)	.0384(23)	.0599(28)	.0517(25)	.0024(20)	.0197(21)	-.0005(22)
C2(3')	.8137(4)	.1427(4)	.5996(2)	.0440(23)	.0448(24)	.0342(22)	.0070(19)	.0153(19)	.0016(20)
S2'	.6468(1)	.0675(1)	.5902(1)	.0476(6)	.0482(6)	.0516(6)	-.0012(6)	.0265(5)	-.0020(6)
C3	.9183(4)	.0049(5)	.6243(2)	.0485(25)	.0550(26)	.0494(25)	.0093(22)	.0229(21)	.0078(22)
C4	.8684(4)	-.1240(5)	.5678(2)	.0585(27)	.0497(27)	.0620(28)	.0138(22)	.0338(24)	.0031(23)
C4a	.8177(4)	-.0507(5)	.4965(2)	.0472(24)	.0463(26)	.0568(26)	.0046(21)	.0318(21)	-.0078(23)
C4'	.8591(4)	.2855(5)	.6498(2)	.0406(25)	.0570(28)	.0367(23)	.0034(23)	.0182(21)	.0019(22)
C4a'	.7553(4)	.4116(6)	.6407(2)	.0394(23)	.0504(26)	.0270(20)	.0067(22)	.0159(18)	.0043(20)
S5	.8005(1)	-.1807(1)	.4287(1)	.0772(9)	.0578(8)	.0730(9)	-.0019(7)	.0479(7)	-.0186(7)
C5'	.8079(4)	.5522(6)	.6792(2)	.0485(25)	.0626(27)	.0388(23)	.0003(23)	.0182(20)	.0042(22)
C6	.6743(4)	-.0678(6)	.3550(2)	.0727(31)	.0988(38)	.0583(29)	-.0072(30)	.0392(26)	-.0319(29)
C6a	.7223(4)	.1021(5)	.3566(2)	.0603(28)	.0701(34)	.0469(28)	.0116(25)	.0315(23)	-.0031(26)
C6'	.7186(5)	.6712(5)	.6776(2)	.0627(31)	.0502(28)	.0563(28)	.0023(25)	.0242(25)	-.0006(23)
C7	.7112(5)	.1764(7)	.2963(2)	.1089(41)	.0878(40)	.0467(30)	.0254(35)	.0449(29)	-.0087(31)
C7'	.5757(6)	.6494(6)	.6383(2)	.0591(31)	.0522(30)	.0662(30)	.0176(24)	.0266(26)	.0029(25)
C8	.7528(6)	.3318(7)	.2989(3)	.1461(49)	.0882(42)	.0650(36)	.0508(38)	.0744(36)	.0232(33)
C8'	.5213(4)	.5131(6)	.5995(2)	.0445(25)	.0454(26)	.0540(28)	.0088(23)	.0203(22)	.0015(24)
C8a'	.6099(4)	.3919(4)	.5995(2)	.0445(25)	.0454(26)	.0540(28)	.0004(21)	.0183(20)	.0010(19)
C9	.8039(5)	.4170(5)	.3610(3)	.1206(42)	.0570(30)	.0768(34)	.0300(30)	.0709(33)	.0207(30)
O9'	.9804(3)	.2923(3)	.6958(1)	.0446(18)	.0702(21)	.0687(20)	.0123(17)	-.0024(17)	-.0166(17)
C10	.8139(4)	.3458(5)	.4211(2)	.0735(31)	.0527(29)	.0557(29)	.0222(24)	.0425(25)	.0019(23)
C10a	.7738(4)	.1877(5)	.4199(2)	.0477(25)	.0590(29)	.0442(16)	.0167(23)	.0303(21)	.0001(24)
C10b	.7937(4)	.1049(5)	.4845(2)	.0438(24)	.0528(29)	.0411(24)	.0038(21)	.0262(20)	-.0049(23)
Atom	x	y	z	B	Atom	x	y	z	B
H1'1	.448	.230	.551	4.0	H1'2	.531	.266	.506	4.0
H3 1	1.016	.044	.634	4.0	H3 2	.929	-.039	.671	4.0
H4 1	.949	-.202	.679	4.0	H4 2	.790	-.187	.570	4.0
H5'	.915	.566	.708	4.0	H6 1	.657	-.122	.309	4.0
H6 2	.579	-.069	.355	4.0	H6'	.759	.776	.706	4.0
H7	.671	.115	.250	4.0	H7'	.509	.737	.638	4.0
H8	.746	.384	.254	4.0	H8'	.414	.498	.570	4.0
H9	.834	.535	.362	4.0	H10	.851	.412	.467	4.0

Table 2. Deviations from least-squares planes ($\text{\AA} \times 10^3$). The deviations for those atoms used to define a plane is marked with *.

Atom	Plane A	Plane B	Atom	Plane C
O1	-358	-84*	O1	-1054
C2(3')		-287	C1'	-29
C3		525	C2(3')	-131
C4	1021	118*	S2'	777
C4a	627	-11*	C3	321
C4'		116	C4'	119
S5	1115	-35*	C4a'	7*
C6	-38	-885	C5'	1*
C6a	4*	-214	C6'	-8*
C7	-6*		C7'	7*
C8	2*		C8'	1*
C9	3*		C8a'	-8*
C10	-4*	712	O9'	393
C10a	0*	133*		
C10b	99	-33*		

idenecyclohexanone the *cis* proton is at even lower field, *viz.* at δ 6.5,⁶ which compares well with the chemical shifts for the vinyl protons in *2b* and *2c* which overlap with the signals from the aromatic protons at *ca.* δ 7. Hence *2b* and *2c* are assigned the (*Z*)-configuration which structurally corresponds to the (*E*)-configuration in cyclohexane analogues.

The methylene derivative *2a* was not available for comparison of the ¹H NMR data. Attempts to prepare *2a* gave other products. Thus when gaseous formaldehyde, which was generated by pyrolysis of paraformaldehyde, was passed into a solution of the lithium enolate of *1* a dimer of *2a* was obtained. The same

compound was more conveniently made by subjecting *1* to the Mannich reaction with formaldehyde and dimethylamine. The molecular ion in the mass spectrum was at *m/e* 352 ($\text{C}_{20}\text{H}_{16}\text{O}_2\text{S}_2$) with base peak at *m/e* 176 ($\text{C}_{10}\text{H}_8\text{OS}$); the mass spectrum is consistent with a dimer of *2a*. The carbonyl absorption at 1695 cm^{-1} was at the same position as in *1*; a new band at 1630 cm^{-1} indicated a carbon-carbon double bond. In ¹H NMR, one of the eight aromatic protons appeared at δ 8.1, the others in the region δ 7.0–7.5. Two isolated methylene groups were shown by an AB quartet at δ 3.48 and 4.34, *J* 17 Hz, and by a slightly split two-proton signal at δ 3.83. Four unresolved signals in the region δ 1.9–2.8 suggested an ethylene bridge in a complex environment. An X-ray structure determination showed that the compound had the spiro-structure *6*. The compound was difficult to purify because of decomposition reactions which presumably originate in the reactive monothioether function in which the oxygen atom is also part of an enol ether.

The same product *6* was also obtained when the Mannich reaction was run in acetic acid. In the absence of dimethylamine no reaction between *1* and formaldehyde took place. Hence the formation of *6* is rationalized by formation of the Mannich product which subsequently undergoes elimination to *2a*. The latter is dimerized by a Diels-Alder reaction (7) in the regioselective manner expected from the polarization of *2a*. The reaction is analogous to dimerizations of the α,β -unsaturated aldehydes acrolein and methacrolein to 2-formyl-2,3-di-

Table 3. Selected torsional angles ($^\circ$). The angles are positive in a right-hand screw.

Angle	Angle	Angle	
C2(3')-C1'-S2'-C8a'	-52.8(3)	S2'-C1-C8a'-C4a'	29.7(5)
C8a'-C4a'-C2(3')	15.5(5)	C5'-C8a'-C4'-O9'	10.8(5)
C4a'-C4'-C2(3')-S2'	-46.4(4)	C4a'-C4'-C2(3')-O1	72.5(4)
C1'-S2'-C2(3')-O1	-53.2(3)	C1'-S2'-C2(3')-C3	-176.3(3)
S2'-C2(3')-O1-C10b	-79.8(3)	C3-C2(3')-O1-C10b	164.0(3)
O1-C2(3')-C3-C4	-59.6(4)	S2'-C2(3')-C3-C4	178.1(3)
C2(3')-O1-C10b-C10a	178.1(3)	C2(3')-O1-C10b-C4a	-7.9(5)
C4a-C10b-C10a-C6a	26.2(6)	O1-C10b-C10a-C10	24.6(5)
C7-C6a-C6-S5	135.0(4)	C6a-C6-S5-C4a	52.7(3)
C6-S5-C4a-C10b	-26.9(4)	C10b-C4a-C4-C3	-12.7(5)
C4a-C4-C3-C2(3')	43.8(4)		

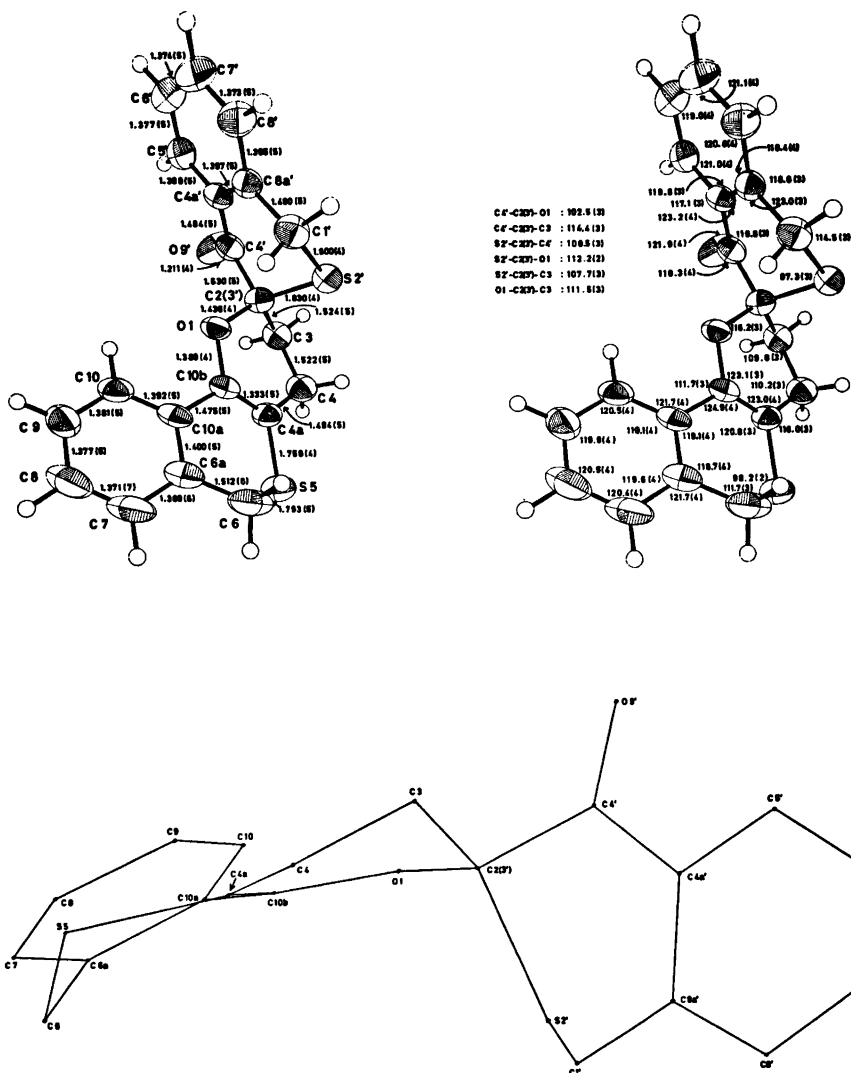


Fig. 1. Bond lengths (Å) and bond angles (°).

hydro-4*H*-pyrans.^{7,8} 2-Methylenecyclohexanone has also been dimerized on heating and the product on the basis of its chemical properties was assigned the spiro structure which corresponds to **6**.⁹

The compounds **2** are isomeric with the thiopyrylium betaines **3**. Our attempts, however, to isomerize **2** to **3** using perchloric acid, boron trifluoride, or lithium tetrafluoroborate were unsuccessful.

The molecular geometry of structure **6**

together with bond lengths, bond angles and numbering of the atoms is given in Fig. 1. The bond lengths are normal. Some bond angles show deviations probably caused by strain in the ring system. The configuration around the double bond C4a-C10b deviates significantly from planarity, and the angle between the plane of the benzene ring C6a-C10a and the plane defined by the atoms around the double bond is 25°. The thiopyranone ring has the sulfur out of the plane through the other

atoms of the ring. The other heterocyclic rings have twisted chair conformations (Tables 2 and 3).

The shortest intermolecular distances are compatible with normal van der Waals' contacts.

EXPERIMENTAL

(*Z*)-3-Butylidene-1*H*-2-benzothiopyran-4(3*H*)-one 2b. Freshly distilled (NaH) diisopropylamine (3.6 ml, 25 mmol) was added by means of a syringe to freshly distilled (LiAlH₄) THF (25 ml), the solution cooled to 0 °C and butyllithium (1.45 M, 17.3 ml, 25 mmol) added by means of a syringe under purified nitrogen gas. The mixture was stirred for 10 min at 0 °C before a solution of 1*H*-2-benzothiopyran-4(3*H*)-one (4.10 g, 25 mmol) in anhydrous THF (50 ml) was added dropwise with stirring at 0 °C. The mixture was stirred for 10 min before the temperature was lowered to -78 °C. A solution of freshly distilled (CaH₂) butanal (2.2 ml, 25 mmol) in anhydrous THF (25 ml) was added dropwise with stirring at this temperature. When the addition was completed, the mixture was left overnight at room temperature before it was poured into ice-cold water (50 ml) and the mixture stirred for 30 min. The mixture was extracted with ether, the dried (MgSO₄) ether extracts evaporated, and the residual oily material subjected to thick-layer chromatography on silica gel 60 PF₂₅₄ (1.5 mm) using dichloromethane to develop the plates. The major band with *R_F* 0.6–0.8 was scraped off, the organic material extracted into dichloromethane, the solution evaporated and the residue subjected to preparative GLC on Apiezon L (10 %; 2.4 m; ret. time *ca.* 8 min) at 250 °C. The product was an oily material; yield 41 %. MS: *M m/e* 218.0771; calc. for C₁₃H₁₄OS: 218.0766. ¹H NMR (CDCl₃): δ 0.95 (3 H-4', t), 1.3–1.9 (2 H-3', m), 2.3 (2 H-2', q), 3.86 (2 H-1, s), 7.0–7.4 (H-6,7,8, 1', m), 8.1 (H-5). IR (CHCl₃): 1685 (α,β-unsat. CO), 1655 cm⁻¹ (C=C). MS [70 eV *m/e* (% rel.int.)]: 218 (100, M), 217 (9), 189 (15), 185 (7), 177 (7), 176 (46), 161 (24), 128 (12), 119 (13), 118 (64).

(*Z*)-3-Benzylidene-1*H*-2-benzothiopyran-4(3*H*)-one 2c. The reaction was carried out as above using freshly distilled (CaH₂) benzaldehyde. The crude product was purified by chromatography on a column of neutral alumina. The title compound was eluted with chloroform; yield 48 %, m.p. 94–95 °C (light petroleum b.p. 80–100 °C). Anal. C₁₉H₁₂OS: C, H. ¹H NMR (CDCl₃): δ 3.88 (2 H-1, s), 7.1–8.2 (10 H). IR (CCl₄): 1665 cm⁻¹ (α,β-unsat. CO). UV [CHCl₃, λ_{max} (log ε)]: 370 (3.59), 280 (4.18) nm. MS [70 eV *m/e* (% rel.int.)]: 252 (100, M), 251 (88), 223 (6), 119 (6), 118 (57), 90 (36), 89 (14).

3,4-Dihydro-2*H*,6*H*-2-benzothiopyrano [4,3-*b*]pyran-2-*spiro*-3'-[1*H*-2]benzothiopyran-4' (3'*H*)-one 6. Method A. 1*H*-2-Benzothiopyran-4(3*H*)-one (3.0 g, 18 mmol), dimethylamine hydrochloride (1.5 g, 20 mmol) and paraformaldehyde (2.0 g, 21 mmol) were dissolved in abs. ethanol (50 ml) and the solution acidified to pH *ca.* 1.5 by ethanolic HCl. The resultant mixture was refluxed for 8 h and then left at room temperature overnight. The precipitate was chromatographed on a column of neutral alumina and the title compound eluted with dichloromethane. The product can be recrystallized from carbon tetrachloride; yield 44 %, m.p. 174–175 °C. The yield of material isolated could be increased by evaporation of the original reaction mixture and subjecting the total residue to chromatographic separation as above. MS: *M m/e* 352.0600; calc. for C₂₀H₁₆O₂S₂: 352.0591. ¹H NMR (CHCl₃): δ 2.0–2.8 (4 H, CH₂-CH₂, m), 3.48 and 4.34 (2 H, AB, *J* 17 Hz), 3.83 (2 H, broad s), 7.0–7.5 (7 H, m), 8.1 (H-8, m). IR (CHCl₃): 1695 (CO), 1630 cm⁻¹ (C=C). UV [CHCl₃, λ_{max} (log ε)]: 295 (3.71), 330 (3.67) nm. MS [70 eV *m/e* (% rel.int.)]: 352 (3, M), 202 (4), 177 (11), 176 (100), 147 (6), 119 (10), 118 (97), 91 (5), 90 (56).

Method B. Paraformaldehyde, dried over P₂O₅, was thermally depolymerized and the gaseous formaldehyde passed into a solution of one equivalent of the lithium enolate of 1*H*-2-benzothiopyran-4(3*H*)-one in THF, which was prepared as above, at -20 °C under an atmosphere of purified nitrogen. When the addition was completed, the mixture was kept at 0 °C for 2 h and then stirred at room temperature overnight. Water was added and the stirring continued for 30 min. The organic layer was collected, evaporated and the residue dissolved in chloroform and chromatographed on a silica gel column. Elution with chloroform gave the title compound in 23 % yield.

Crystallographic section

The compound was recrystallized from carbon tetrachloride. Oscillation and Weissenberg diagrams showed monoclinic symmetry and the systematic absences characteristic of the space group *P*2₁/*c*.

The crystallographic work was carried out on a Syntex P1 diffractometer with graphite monochromatized MoK_α radiation. Cell dimensions were determined from diffractometer measurements of fifteen reflections with 2θ-values between 20 and 30°. The temperature was maintained within 1° at 19 °C.

Three-dimensional intensity data were collected by the ω-2θ scanning mode with scan speeds variable from 3 to 12° min⁻¹ (2θ) depending on the peak intensity of the reflection. Background counting time was 0.35 s scan time on each side of the scan area which was

from $2\theta(\alpha_1) - 0.75^\circ$ to $2\theta(\alpha_2) + 0.9^\circ$. The intensities of three standard reflections which were remeasured after every sixty reflections, were stable throughout the run. The standard deviations were based on counting statistics with a 2% addition of the net intensity. Of the 2570 reflections measured ($2\theta_{\max} = 45^\circ$) 1552 had intensities larger than twice their standard deviations. These were regarded as observed, whereas the remaining were excluded from further calculations. The intensities were corrected for Lorentz and polarization effects. The computer program used as well as programs subsequently employed, is part of a local library.¹⁰ Literature values for the atomic form factors for sulfur, oxygen and carbon,¹¹ and for hydrogen¹² were used. In the full matrix least-squares program the quantity minimized was $\sum w\Delta F^2$ where w is the inverse of the variance of the observed structure factor.

The phase problem was solved by the program assembly MULTAN 77.¹³ The structure model was refined to an R of 0.11. Introduction of anisotropic temperature factors for all non-hydrogen atoms and least-squares refinements lowered R to 0.07. The hydrogen atoms were placed in calculated positions and included in the structure factor calculations with isotropic temperature factors of 4.0 \AA^2 . The least-squares refinements of all parameters involving nonhydrogen atoms converged to an R of 0.043 and an R_w of 0.037. A difference Fourier synthesis showed only small spurious peaks. Final atomic parameters are given in Table 1. The experimental data may be obtained from the authors upon request.

CRYSTAL DATA

3,4-Dihydro-2H,6H-2-benzothiopyrano[4,3-b]-pyran-2-spiro-3'-[1H-2]benzothiopyran-4'(3'H)-one, $C_{20}H_{16}O_2S_2$, $M = 352.48$; space group $P2_1/c$, $a = 10.773(2) \text{ \AA}$, $b = 8.394(2) \text{ \AA}$, $c = 21.475(2) \text{ \AA}$, $\beta = 118.21^\circ(1)$, $V = 1711.2(5) \text{ \AA}^3$, $Z = 4$, $D_{\text{calc}} = 1.367 \text{ g cm}^{-3}$, $F(000) = 432$.

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