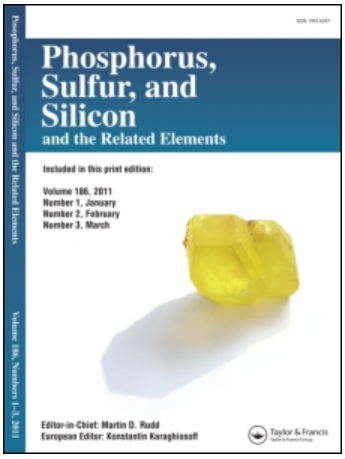

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Strong Axial Preference of 2-S Substituents in 3,4-Dihydro-2 H -1-Benzopyrans

Kaija Sipilä[a]; Jarno Kansikas[b]
[a] Laboratory of Organic Chemistry, Department of Chemistry, University of Helsinki, Finland [b] Laboratory of Inorganic Chemistry, Department of Chemistry, University of Helsinki, Finland

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STRONG AXIAL PREFERENCE OF 2-S SUBSTITUENTS IN 3,4-DIHYDRO-2*H*-1-BENZOPYRANS

Kaija Sipilä[a] *and Jarno Kansikas*[b]
Laboratory of Organic Chemistry, Department of Chemistry, University of Helsinki, PO Box 55, FIN-00014 University of Helsinki, Finland[a] *and Laboratory of Inorganic Chemistry, Department of Chemistry, University of Helsinki, PO Box 55, FIN-00014 University of Helsinki, Finland*[b]

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*The synthesis and crystal structure of a O,S,S-acetal derivative (1*R**,2*R**,2′*S**)-1-(3,4-dihydro-2*H*-1-benzopyran-2-ylthio)-2-phenyl-1-phenylthiopropan-2-ol* ***4*** *are reported. The 2-S-sidechain orientation in solution determined by OCHS signals in* ^{1}*H NMR spectra is mainly axial in all the 3,4-dihydro-2*H*-1-benzopyran derivatives. Compound* ***4*** *crystallizes in the triclinic space group* $P\bar{1}$ *with an axial 2-S-sidechain and an intramolecular hydrogen bond between the OH and the ether oxygen with the O···O distance of 2.799(3)* Å.

Keywords: Conformation; crystal structure; 2-S-3,4-dihydro-2*H*-1-benzopyran synthesis; O,S,S-acetal

INTRODUCTION

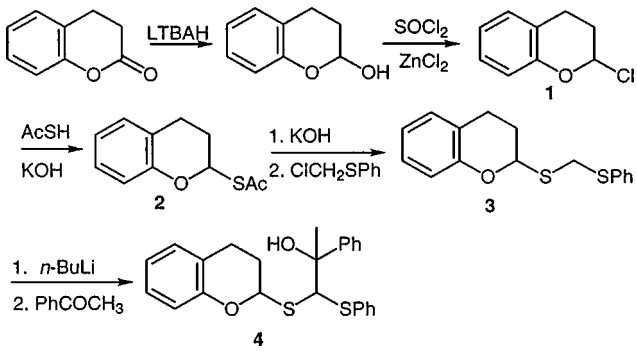
We have studied the syntheses and structures of crystalline O,S,S-acetal derivatives where the O-atom belongs to a tetrahydropyran ring. When 2-(phenylthiomethylthio)tetrahydropyran was lithiated at −78°C in tetrahydrofuran and treated with benzaldehyde, approximately equal amounts of all the four possible diastereoisomers of 1-phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol[1–3] were formed. Conformations and crystallizabilities of these hydroxyalkylation products varied considerably. Crystalline products were also

Address correspondence to Kaija Sipilä, Laboratory of Organic Chemistry, Department of Chemistry, University of Helsinki, PO Box 55, FIN-00014.

obtained in the reaction where acetophenone was used as an electrophile.[4–5] However, in alkylations of lithiated 2-(phenylthiomethylthio)-tetrahydropyran diastereoselectivities up to 90:10 were found but all the products were noncrystalline because of the flexibility of the molecules.[3] The O,S,S-acetal structure was modified by changing the substituent at sulphur from phenyl to naphthyl in order to facilitate the crystallizability. Investigations on 2-(2-naphthylthiomethylthio)tetrahydropyran derivatives are underway.[6] To slow down the conformational exchange the tetrahydropyran ring was replaced by the 3,4-dihydro-2*H*-1-benzopyranyl group. In this article the synthesis and crystal structure of a hydroxyalkylated 2-(phenylthiomethylthio)-3,4-dihydro-2*H*-1-benzopyran derivative, (*1R*,2R*,2'S**)-1-(3,4-dihydro-2*H*-1-benzopyran-2-ylthio)-2-phenyl-1-phenylthiopropan-2-ol **4** are reported.

RESULTS AND DISCUSSION

The syntheses of compounds **1–4** are presented in Scheme 1. The starting material 3,4-dihydro-2*H*-1-benzopyran-2-ol[7] was prepared by applying a slightly modified literature method[8] using commercially available 3,4-dihydro-2*H*-1-benzopyran-2-one and 1 M lithium tri-*tert*-butoxyaluminohydride in tetrahydrofuran at 0°C under argon atmosphere. 3,4-Dihydro-2*H*-1-benzopyran-2-ol was chlorinated with $SOCl_2$ by applying the method of Grob *et al.*[9] for the preparation of glycosyl chlorides to obtain 3,4-dihydro-2-chloro-2*H*-1-benzopyran **1**. Ringom and Benneche[10] have mentioned **1** as an unisolated intermediate product. Indeed, compound **1** was very sensitive and the product was used immediately without further purification for



SCHEME 1 The syntheses of compounds **1–4**.

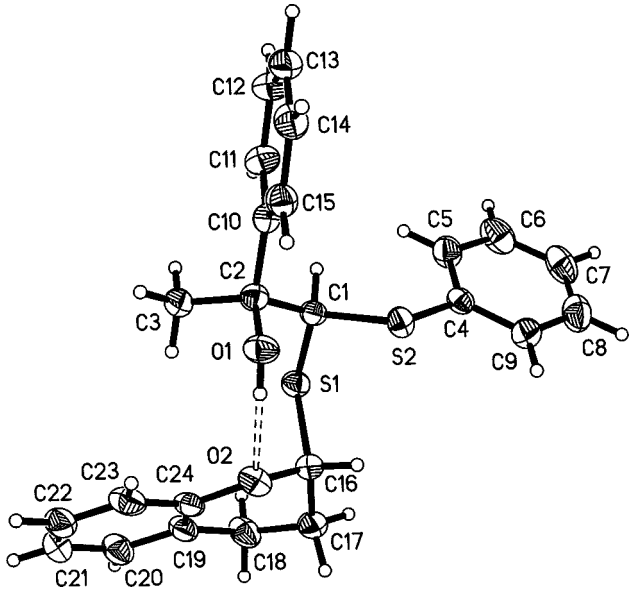


FIGURE 1 The X-ray single-crystal structures of compound **4** with crystallographic atom labels.

the preparation of thioacetic acid *S*-3,4-dihydro-2*H*-1-benzopyran-2-yl ester **2**. The O,S,S-acetal 2-(phenylthiomethylthio)-3,4-dihydro-2*H*-1-benzopyran **3** was prepared from hydrolysed **2** and commercially available chloromethyl phenyl sulfide in a one-pot reaction.[4] In the synthesis of 1-(3,4-dihydro-2*H*-1-benzopyran-2-ylthio)-2-phenyl-1-phenylthiopropan-2-ol **4** from lithiated **3** and acetophenone four diastereomers were formed. One solid diastereomer was obtained from the mixture of products by flash chromatography (Silica gel, CH_2Cl_2) and recrystallized several times from ethanol to obtain crystals suitable for X-ray studies. The crystallographic atom labels for **4** are presented in Figure 1 and crystallographic and refinement data in Table I. Some selected interatomic distances and angles are listed in Table II. Compound **4** crystallizes in the triclinic space group P $\bar{1}$ with an intramolecular hydrogen bond between the hydroxyl group and the O atom of the 3,4-dihydro-1-benzopyran ring with the O···O distance of 2.799(3) Å. The earlier reported, closely related compound 2-phenyl-1-phenylthio-1-(tetrahydropyran-2-ylthio)propan-2-ol **5**[4] has the same relative configuration. This tetrahydropyran derivative also has a similar intramolecular hydrogen bond with the O···O distance of 2.816(3) Å, but however, the 2-S-sidechain is equatorially oriented. We assumed that in **5** the hydrogen bond decreases the electron density at the ether

TABLE I The Crystallographic Data and Data Refinement for **4**

Empirical formula	$C_{24}H_{24}O_2S_2$
Formula weight	408.55
Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, $P\bar{1}$
Unit cell dimensions	$a = 9.7130(19)$ Å
	$b = 10.756(2)$ Å
	$c = 11.312(2)$ Å
	$\alpha = 108.98(3)^\circ$
	$\beta = 109.19(3)^\circ$
	$\gamma = 95.91(3)^\circ$
Volume	1025.9(4) Å^3
Z, Calculated density	2, 1.323 Mg/m^3
Absorption coefficient	0.277 mm^{-1}
$F(000)$	432
Crystal size	0.32 × 0.28 × 0.24 mm
Theta range for data collection	2.69 to 25.50°
Index ranges	$-11 \le h \le 11$, $0 \le k \le 13$, $-13 \le l \le 12$
Reflections collected/unique	3995/3782 [$R_{int} = 0.0332$]
Observed reflections [$I > 2\sigma(I)$]	3078
Completeness to $2\theta = 25.50$	99.1%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3782/0/253
Goodness-of-fit on F^2	1.020
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0547$, w$R_2 = 0.1613$
R indices (all data)	$R_1 = 0.0694$, w$R_2 = 0.1708$
Largest diff. peak and hole	0.559 and −0.454 e.Å^{-3}

oxygen and hinders the *p*-orbital overlap with O—C2 bond thus diminishing the anomeric effect which otherwise would favour the axial orientation.[11] The same effect is evident in 1-phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol where the two intramolecularly hydrogen bonded diastereomers **6**[1] and **7**[3] have equatorial S-sidechains at the anomeric carbon. However, compound **4** shows remarkable preference for the axial S-sidechain orientation in spite of the hydrogen bonding. This phenomenon might be due to the crystal packing forces. The crystal packing of **4** is centrosymmetric triclinic with only two molecules in the unit cell. The molecules form sheets with the thickness of one *b*-axis length parallel to the *a*-*c*-plane. This kind of layer forming is possible when the 2-S-sidechain is axially oriented allowing the two-molecule thick wafer-like packing shown in Figure 2.

Most of the 3,4-dihydro-2*H*-1-benzopyran compounds found in the Cambridge Structural Database (CSD 5.20 October 2000)[12] are multisubstituted. Four compounds where the ring system is monosubstituted

TABLE II Some Selected Interatomic Distances and Angles for **4**

Bond lengths (Å)	
S1—C1	1.836(3)
S1—C16	1.819(3)
S2—C1	1.815(3)
S2—C4	1.770(3)
O2—C16	1.436(4)
O2—C24	1.389(3)
O—H—O	2.799(3)
Bond angles (°)	
C1—S1—C16	104.71(14)
C1—S2—C4	104.51(13)
S1—C1—S2	113.27(14)
Torsion angles (°)	
C1—S1—C16—O2	68.4(2)
C16—S1—C1—S2	52.02(17)
C16—S1—C1—C2	−74.3(2)
C4—S2—C1—S1	73.11(16)
C4—S2—C1—C2	−155.61(18)
S1—C1—C2—O1	81.6(2)
S2—C1—C2—O1	−47.4(2)
C24—O2—C16—S1	77.5(3)

only at C-2 were found[13–15] each of them with a C-sidechain in an equatorial orientation, which is the normal steric preference for a bulky sidechain. In all of these four compounds the 3,4-dihydropyran ring adopts a half-chair conformation. In compound **4** the 3,4-dihydrobenzopyran ring with the half-chair conformation has torsion angles t_1, C18—C19—C24—02 of 0.6(4)° and t_2, O2—C16—C17—C18 of 60.3(3)°. The corresponding torsion angles at the tetrahydropyran group with the chair conformation in compounds **5–7** vary from 52.9(3)° to 56.9(7)° for t_1 and from 52.9(3)° to 58.8(7)° for t_2, respectively.

The axially oriented C16—S1 bond of 1.819(3) Å in **4** is longer for sterical reasons than the corresponding bond of 1.794 (4)–1.810 (2) Å in **5–7** with the equatorial side chain. The distance of S1 from the central carbon atom C1 of 1.836(3) Å is also somewhat longer than that of the comparison compounds.

The conformation of the tetrahydropyran ring with the 2-SR sidechain was reported to slightly favour the axial orientation in solvent due to the anomeric effect.[11] The S-sidechain orientations of 2-alkylthiotetrahydropyrans were approximated from the OCHS signals of ^{1}H NMR spectra by comparing the separation between the outer peaks $J = J_{AX} + J_{BX}$ to that of *trans*- and *cis*-4-methyl-2-methylthiotetrahydropyran, because in these compounds the

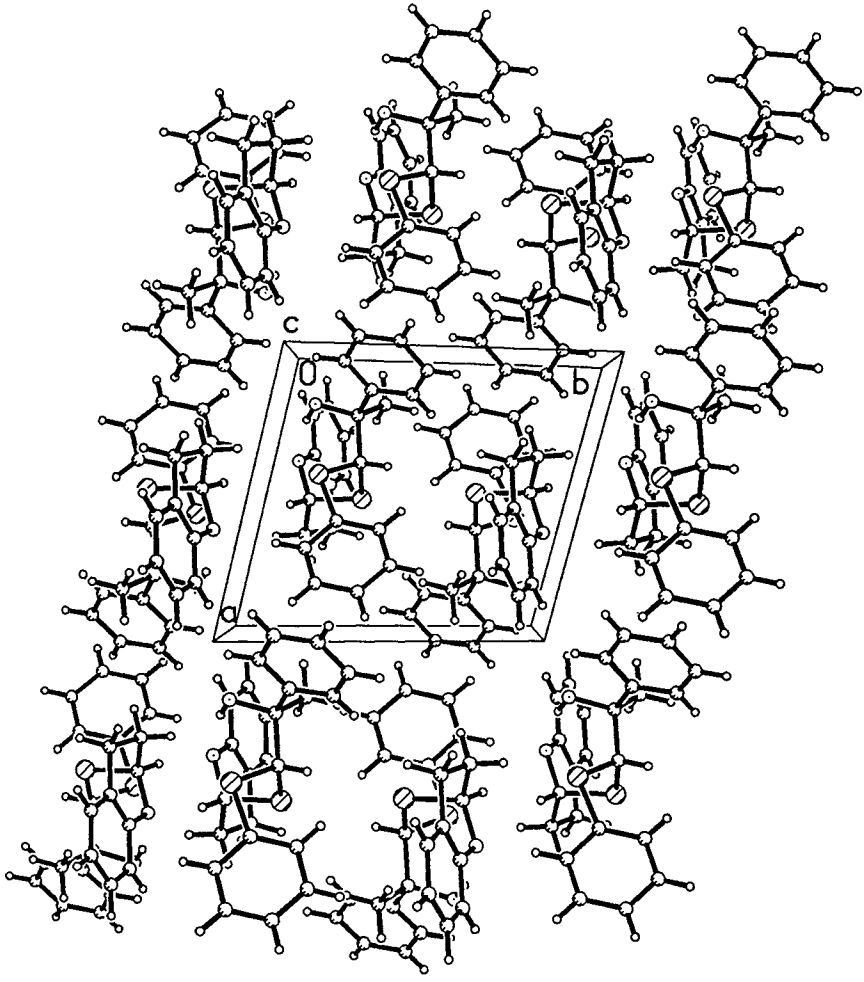


FIGURE 2 The molecular packing scheme for compound **4**.

methylthio group is respectively axially ($J = 5.4$ Hz) and equatorially ($J = 12.7$ Hz) oriented to an extent greater than 98%.[16] In the 200 MHz spectra of compounds **2–4** the OCHS signals resemble a triplet and the sum of the coupling constants varies between 6 Hz in compound **3** to 8 Hz in compound **4**, thus indicating a strong preference for the axial orientation in $CDCl_3$.

It is obvious that the intramolecular hydrogen bond in **4** strongly contributes to the ready crystallizability. The work to separate the rest of the diastereomers formed in the reaction of acetophenone with lithiated

3 and to define their structures and the diastereomeric ratios is underway in our laboratory.

EXPERIMENTAL

Thioacetic acid (97%) was purchased from Fluka and chloromethyl phenyl sulfide (97%) and 3,4-dihydro-*2H*-1-benzopyran-2-one (99%) from Aldrich and used without further purification. Acetophenone was distilled before use. Toluene was dried by azeotropic distillation. Tetrahydrofuran (THF) was dried by refluxing in the presence of sodium and benzophenone and distilled. Dimethyl formamide (DMF) was purified by refluxing with CaH_2 and distilled in vacuo. Flash chromatography was carried out using Merck Silica gel 60 230–400 mesh. The concentration of *n*-BuLi in hexane was determined by a literature procedure.[17] The NMR spectra were recorded on a Varian Gemini 200 spectrometer (chemical shifts in δ; ppm, J; Hz). The assignments are based on chemical shift data and DEPT measurements. The mass spectrum was run on a JEOL JMS-SX 102 instrument (70eV). The melting points were determined in an open capillary tube with an Electrothermal apparatus and are uncorrected.

2-Chloro-3,4-dihydro-2*H*-1-benzopyran 1

Zinc chloride (5.2 g, 0.038 mol) was activated by melting it three times in vacuum and allowing it to cool under argon atmosphere, 3,4-Dihydro-2*H*-1-benzopyran-2-ol[7] (0.55 g, 0.0037 mol) in 40 ml of dry toluene and freshly distilled $SOCl_2$ (3.4 g, 0.029 mol) were added at 0°C and the mixture was stirred at room temperature over night. The precipitation was filtered off with the aid of Celite and the solvent was evaporated to obtain 0.5 g (80%) of **1** as a yellowish liquid.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 2.2–2.3 (m, CH_2), 2.6–2.7, and 3.1–3.3 (m, $PhCH_2$), 6.5 (s-like m, OCHCl), 6.8–7.2 (m, arom. H); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 20.0 (CH_2), 30.4 ($PhCH_2$), 89.9 (OCCl), 118.0, 122.9, 128.2, 130.0, 150.6 (arom. C); MS: no M^+ observed (m/z 168).

Thioacetic acid *S*-3,4-dihydro-2*H*-1-benzopyran-2-yl ester 2

Thioacetic acid (1.7 g, 0.022 mol) was slowly added to the mixture of KOH (1.3 g, 0.023 mol) in 100 ml of DMF. The solution was cooled in an ice bath and 3.5 g (0.021 mol) of 2-chloro-3,4-dihydro-2*H*-1-benzopyran in 2 ml of DMF was added and the mixture was stirred overnight at

room temperature. Water was added and the reaction mixture was extracted with diethyl ether. The organic phase was washed with saturated $NaHCO_3/H_2O$, water, and brine, dried with Na_2SO_4, and the solvent was evaporated. The oily, brownish residue (3.6 g, 82%) was purified with flash chromatography (Silica gel, CH_2Cl_2) to obtain 1.9 g (43%) of **2** as a reddish brown syrup. The crude product was used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 2.10–2.25 and 2.28–2.50 (m, CH_2), 2.36 (s, CH_3), 2.70–3.00 (m, $PhCH_2$), 6.3 (t, *J* 3.8, OCHS), 6.80–6.95 and 7.0–7.15 (m, arom. H); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 22.3 (CH_2), 27.2 ($PhCH_2$), 31.1 (CH_3), 78.3 (OCHS), 117.5, 121.1, 121.3, 127.5, 129.5 (arom. C), 152.2 (arom. C—O), 193.8 (C═O); HRMS: 208.0566, calc. for $C_{11}H_{12}O_2S$ 208.0558.

2-(Phenylthiomethylthio)-3,4-dihydro-2*H*-1-benzopyran 3

Thioacetic acid *S*-3,4-dihydro-2*H*-1-benzopyran-2-yl ester (1.35 g, 6.5 mol) was hydrolyzed by the solution of 0.77 g (14 mmol) of KOH in dimethyl sulfoxide-water (30 + 10 ml) in an ice bath. After stirring for 1 h at the same temperature chloromethyl phenyl sulfide (1.03 g, 6.5 mol) was added and the mixture was allowed to reach room temperature by stirring overnight. After usual work up the evaporation residue (1.35 g) was purified with flash chromatography (Silica gel, CH_2Cl_2 + hexane 1:1) to obtain 0.70 g (37%) of **3**.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 2.00–2.35 (m, CH_2), 2.65–3.00 (m, $PhCH_2$), 4.22 (AB_q, *J* 13.5, SCH_2S), 5.85–5.88 (t-like m, OCHS), 6.8–7.0 and 7.0–7.2 (m, arom. H); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 22.1 (CH_2), 26.6 ($PhCH_2$), 35.3 (SCH_2S), 78.6 (OCHS), 117.5, 121.5, 126.8, 127.3, 128.9, 129.5, 130.2, 152.0 (arom. C); HRMS 288.0632, calc. for $C_{16}H_{16}OS_2$ 288.0643.

1-(3,4-Dihydro-2*H*-1-benzopyran-2-ylthio)-2-phenyl-1-phenylthiopropan-2-ol 4

2-(Phenylthiomethylthio)-3,4-dihydro-2*H*-1-benzopyran (0.25 g, 0.00087 mol) in 7.0 ml of THF under argon atmosphere was treated with 1.4 ml of 1.2 M *n*-BuLi in hexane (0.0017 mol) at −78°C. After stirring for three hours at temperatures −78 – 35°C, 0.104 g (0.00087 mol) of acetophenone was added and the mixture was stirred overnight allowing it slowly to reach the room temperature. The reaction mixture was poured into water, extracted with diethyl ether and washed with saturated $NaHSO_3/H_2O$, $NaHCO_3/H_2O$, and water, dried with NaH_2SO_4, and the solvent was evaporated. The yellowish

evaporation residue was purified with flash chromatography (silica gel, dichloromethane) to obtain 0.18 g (51%) of **4** as a mixture of diastereomers. A solid diastereomer was separated from the mixture of products by flash chromatography (Silica gel, CH_2Cl_2) and recrystallized several times from ethanol.

M.p. 73°C; ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.67 (s, CH_3), 1.95–2.35 (m, CH_2), 2.65–3.05 (m, $PhCH_2$), 4.27 (s, OH), 4.58 (s, SCHS), 5.74 (t, J 4, OCHS), 6.8–7.0 and 7.0–7.2 (m, arom. H); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 22.4, 27.3, 29.4, 69.7 (SCHS), 79.3 (OCHS), 117.5, 121.5, 125.2, 127.1, 127.6, 128.0, 128.8, 129.7, 132.4, 145.4 (arom. C).

Crystal Structure

X-ray data* for compound **4** were collected on a Nicolet AFC-7S four-circle diffractometer at 193 K. The crystal was mounted on a glass fiber using a viscose oil drops method[18] and applying some grease as an adhesive. Data reduction was done using the Texsan program system.[19] The structure was solved by the SHELXS program[20] using direct methods and refinement was done by the SHELXL software.[21] H-atoms were positioned at calculated locations using the XP program package[22] and they were refined using a riding model where their distances and angels to the C- or O-atoms were fixed and their isotropic thermal parameters were 1.2 and 1.5× the equivalent isotropic U-value of C or O, respectively. The XP-program was also used for producing the illustrations.

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*The crystallographic data (no CCDC 173138) is deposited to the Cambridge Crystallographic Data Centre, U.K.

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