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Synthesis and Structure of an Intramolecularly Hydrogen-Bonded 2-Phenyl-1-phenylthio-1-(2-tetrahydropyranylthio)propan-2-ol Diastereomer

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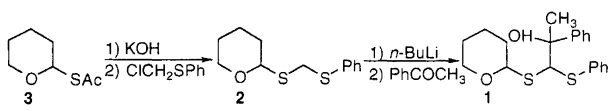
The title compound ($C_{20}H_{24}S_2O_2$) crystallizes in space group $P2_1/c$ (14) with cell dimensions of $a = 5.724(3)$, $b = 19.756(7)$, $c = 16.587(6)$ Å, $\beta = 96.31(3)°$ and $V = 1864.3(9)$ Å^3. $M_r = 360.5$, $F(000) = 768$ and $\mu = 0.295$ mm^{-1}. The data were collected with $3 < 2\Theta < 53°$ totalling 7947 reflections comprising two unique sets with the indices $-8 < h < 8$, $0 < k < 25$ and $-21 < l < 21$. Merging of the equivalent reflections yielded 3870 unique reflections, of which 2724 were regarded as observed [$(I > 2\sigma(I)$] with $R_{int} = 0.031$. Refinement of 289 parameters converged to the R-value of 4.17% and an wR-value of 4.09%. The molecule involves an intramolecular hydrogen bond with the O–O distance of 2.816(3) Å. S–C distances for the propanol carbon are 1.837(2) and 1.829(2) Å and the S–C–S angle is 113.2°.

Dithio- and hemithioacetals are useful as sources of synthetic equivalents[1] of acyl anions or as protective groups.[2] In connection with a study of compounds that are at the same time hemithio- and dithioacetals we synthesized 2-(phenylthiomethylthio)tetrahydropyran (**2**) (Scheme 1). The anion of **2** reacted with acetophenone to produce



Scheme 1. The preparation of 2-phenyl-1-phenylthio-1-(2-tetrahydropyranylthio)propan-2-ol.

2-phenyl-1-phenylthio-1-(2-tetrahydropyranylthio)propan-2-ol (**1**) as a mixture of diastereomers. One of these was isolated by recrystallization from ethanol, and the structure was determined by spectroscopic methods and X-ray crystallography. A characteristic if unusual feature of this structure (Fig. 1) is the presence of a seven-membered ring involving an intramolecular hydrogen bond between the hydroxy group and the ether oxygen. We assume that the easy crystallization of this diastereomer is due to the conformation-locking effect of the intramolecular hydrogen bond.

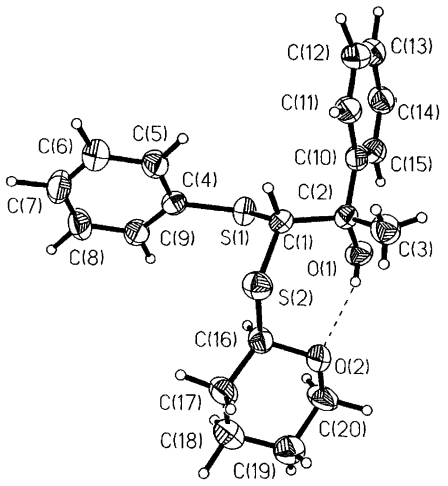


Fig. 1. The structure 2-phenyl-1-phenylthio-1-(2-tetrahydropyranylthio)propan-2-ol with atomic labelling. Anisotropic thermal ellipsoids are drawn at 50% probability level.

Experimental

Syntheses. Tetrahydrofuran (THF) was dried and distilled over CaH_2 before use. Lithium diisopropylamide (LDA) was prepared by adding 1 mol of *n*-BuLi in hexane (Aldrich) as 1.5–2 M solution to 1.2 mol of diisopropylamine in dry THF at 0°C under Ar. The concentration of *n*-BuLi was determined by literature procedures.[3,4] The m.p. was determined in an open cap-

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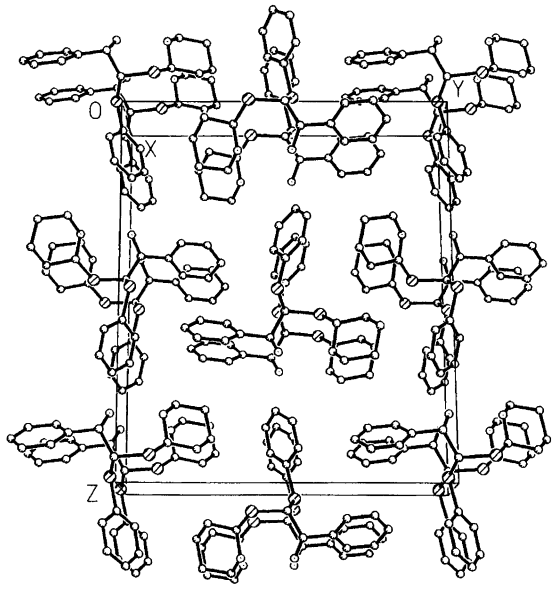

Fig. 2. Unit-cell packing of 2-phenyl-1-phenylthio-1-(2-tetrahydropyranylthio)propan-2-ol seen to the ***a***-axis direction. Hydrogen atoms are omitted for clarity.

illary tube with an Electrothermal apparatus and is uncorrected.

For flash chromatography, Merck Silica gel 60 (0.040–0.063 mm, 230–400 mesh) and CH_2Cl_2 elution were used. NMR spectra were taken in $CDCl_3$ with a Varian Gemini 200 spectrometer. The assignments are based on chemical-shift data and DEPT measurements. Mass spectra were run on a Jeol JMS-SX 102 instrument (70 eV). The IR spectrum was taken on a Perkin-Elmer 1310 spectrometer (KBr pellet) and a Bio-Rad SPC 3200 FT-IR spectrometer (CCl_4).

*2-(Acetylthio)tetrahydropyran (**3**).* For the preparation of **3**, an improved modification of a literature procedure[5] was applied. 3,4-Dihydro(2*H*)pyran (33.6 g, 0.40 mol) was added slowly to a mixture of thioacetic acid (30.4 g, 0.40 mol) and 5 ml of 37 HCl at 0°C. After 2 h at room temperature diethyl ether was added and the mixture was washed with 10% $NaHCO_3$ solution and dried on Na_2SO_4. The solvent was evaporated and the residue distilled to give **3** (38.5 g; 60%), b.p. 79–84°C/2.7 mbar.

MS: no M^+ observed (*m/z* 160).

^{1}H NMR: δ 1.50–1.80 (6H, m; CH_2), 2.36 (1H, s; CH_3), 3.65–3.77 (1H, m; OCH_{ax}), 3.82–3.95 (1H, m; OCH_{eq}), 5.69 (1H, t, 4 Hz; OCHS). ^{13}C NMR: δ 21.3, 24.9, 31.0 (CH_2), 30.7 (CH_3), 65.4 (OCH_2), 80.3 (OCHS), 193.4 (C=O).

*2-(Phenylthiomethylthio)tetrahydropyran (**2**).* 2-(Acetylthio)-tetrahydropyran (**3**) (4.8 g, 30 mmol) was added to a stirred mixture of KOH (3.5 g, 60 mmol), DMSO (45 ml) and water (15 ml) at 0°C, and stirred for 15 min at 0°C and 30 min at room temperature. Chloromethyl phenyl sulfide (4.8 g, 30 mmol) was added during 10 min at 0°C, and the reaction mixture was allowed to reach room temperature with stirring overnight. Water was added and the mixture extracted with diethyl ether. The organic phase was washed with water and brine, dried with Na_2SO_4, and the solvent was evaporated. The residue was purified with flash chromatography to give **2** (5.7 g; 79%).

HRMS: Mol. wt. obs. 240.0627, calc. for $C_{12}H_{16}OS_2$ 240.0642.

^{1}H NMR: δ 1.55–2.05 (6H, m; CH_2), 3.46–3.60 (1H, m; OCH_{ax}), 4.00–4.14 (1H, m; OCH_{eq}), 4.12 (2H, AB_q, 13 Hz; SCH_2S), 5.13–5.20 (1H, m; OCHS), 7.20–7.50 (5H, m; arom. H).

^{13}C NMR: δ 21.93, 26.02, 31.10 (CH_2), 35.59 (SCH_2S), 64.68 (OCH_2), 81.08 (OCS), 127.12, 129.35, 130.46 (arom. C), 135.97 (arom. C–S).

*1-Phenylthio-1-(2-tetrahydropyranylthio)-2-phenylpropan-2-ol (**1**).* A solution of **2** (1.0 g, 4.2 mmol) in 10 ml of dry THF was treated with LDA (4.2 mmol) at −78°C under Ar. After 2 h freshly distilled acetophenone (4.2 mmol) was added dropwise and the reaction mixture was allowed to reach room temperature with stirring overnight. The residue (1.3 g) was a gum containing 25–30% of unreacted **2** and **1** as a mixture of diastereomers. Crystallization from abs. ethanol gave **1** as a single diastereomer (0.2 g; 12%); m.p. 175°C.

MS: no M^+ observed (*m/z* 360).

IR: 3320 cm^{-1} (s) in KBr; 3380 cm^{-1} (s) in CCl_4.

^{1}H NMR: δ 1.50–1.95 (6H, m; CH_2), 1.74 (3H, s; CH_3), 3.58–3.70 (1H, m; OCH_{ax}), 4.00–4.15 (1H, m; OCH_{eq}), 4.50 (1H, s; SCHS), 4.85–5.13 (1H, broad s; OH), 5.23–5.28 (1H, m; OCHS), 7.18–7.60 (10 H, m: arom. CH).

^{13}C NMR: δ 22.28, 24.96, 30.75 (CH_2), 30.66 (CH_3), 65.97 (OCH_2), 69.90 (SCS), 77.20 (CPh), 79.84 (OCS), 124.78, 126.67, 127.32, 127.86, 128.61, 132.37 (arom. C).

Crystal structure. Unit-cell determination and X-ray intensity collection were carried out on a Nicolet P3 four-circle diffractometer using graphite monochromatized Mo*K*α radiation (λ = 0.71073 Å) at room temperature. Unit-cell and data collection summaries are presented in Table 1. The unit-cell dimensions of a monoclinic needle-like crystal with dimensions of 0.11 × 0.11 × 0.25 mm were $a = 5.724(3)$, $b = 19.756(6)$, $c = 16.587(5)$ Å, $\beta = 96.31(3)°$ and $V = 1864.3(9)$ Å^3. The orientation matrix and unit-cell dimensions of the crystal were based on 25 well centered reflections with $20 < 2\Theta < 25°$. Systematic absences proposed the space group to be $P2_1/c$ (14). $Z = 4$, $M_r = 360.50$, $F(000) = 768$ and $\mu = 0.295$ mm^{-1}. The data were collected using a ω-scan method in the range $3 < 2\Theta < 53°$ totalling 7967 reflections, of which 243 were rejected, comprising two unique sets with the indices $-7 < h < 7$, $0 < k < 24$ and $-20 < l < 20$. Merging of the equivalent reflections yielded 3870 unique reflections, of which 2724 were regarded as observed $[(I > 2\sigma(I)]$ with $R_{int} = 3.06\%$.

Table 1. Structure determination summary of $C_{20_{24}}S_2O_2$.

Crystal data	
Empirical formula	$C_{20}H_{24}O_2S_2$
Color; habit	Colorless; needles
Crystal size/mm	0.11×0.11×0.25
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit-cell dimensions	a=5.724(3) Å
	b=19.756(7) Å
	c=16.587(6) Å
	β=96.31(3)°
Volume/Å^3	1864.3(9)
Formula weight	360.50
Density(calc.)/Mg m^{-3}	1.284
Absorption coefficient/mm^{-1}	0.295
F(000)	768
Data collection	
Diffractometer used	Nicolet P3
Radiation	Mo$K\alpha$ (λ=0.71073 Å)
Temperature/K	293
Monochromator	Highly oriented graphite crystal
2θ range	3.0 to 53.0°
Scan type	ω
Scan speed	Variable; 1.5 to 29.30 ° min^{-1} in ω
Scan range, ω	1.0°
Background measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 50% of total scan time.
Standard reflections	3 measured every 100 reflections
Index ranges	$-7<h$, $0<k<24$, $-20<l<20$
Reflections collected	7724
Independent reflections	3870 (R_{int}=3.06%)
Observed reflections	2724 [$I>2.0\sigma(I)$]
Absorption correlation	Empirical, ψ-rotation
Solution and refinements	
System used	Siemens SHELXTL PLUS (PC Version)[6]
Solution	Direct methods
Refinement method	Full-matrix least-squares
Quantity minimized	$\Sigma w(F_O-F_c)^2$
Hydrogen atoms	Refined positional parameters, fixed isotropic U
Weighting scheme	$w^{-1}=\sigma^2(F)+0.0002F^2$
No. of parameters refined	289
Final Rindices (obs. data)	R=4.17%, wR=4.09%
R indices (all data)	R=8.03%, wR=4.70%
Goodness–of–fit	1.20
Largest and mean Δ/σ	0.424, 0.032
Data–to–parameter ratio	9.4:1
Largest difference peak/e Å^{-3}	0.23
Largest difference hole/e Å^{-3}	−0.22

Absorption correction was done empirically measuring five reflections in 36 ψ-settings at 10° intervals at ca. 5° intervals in 2Θ. Maximum differences in I were 8%.

The structure was solved using direct methods of SHELXTL PLUS (PC version) program system.[6] All non-hydrogen atoms were located in the TREF run. After the converged least-squares refinement with isotropic thermal displacement parameters for non-hydrogen atoms, the hydrogen atoms could be detected from a stereoscopic difference Fourier peak list in the XP program.[6] A full-matrix least-squares refinement of scale factor, positional parameters for all atoms, anisotropic thermal displacement parameters for non-hydrogen atoms and fixed isotropic displacement parameters for hydrogen atoms and weighting parameters, totalling 289 parameters, converged to a conventional R-value of 4.17% and a weighted R-value of 4.09%, where the weighting scheme is of the form $w^{-1}=\sigma^2(F)+0.0002F^2$.

Table 2. Atomic coordinates (×10^4) and equivalent isotropic displacement coefficients (in Å×10^{-3}) of $C_{20}H_{24}S_2O_2$.

Atom	x	y	z	U(eq)[a]
S(1)	3402(1)	2753(1)	3316(1)	43(1)
S(2)	274(1)	3000(1)	4670(1)	46(1)
O(1)	2668(3)	4225(1)	3579(1)	45(1)
O(2)	3038(3)	3994(1)	5264(1)	55(1)
C(1)	681(4)	3131(1)	3603(1)	36(1)
C(2)	560(4)	3875(1)	3285(1)	38(1)
C(3)	−1556(5)	4249(2)	3546(2)	50(1)
C(4)	3009(4)	1878(1)	3510(1)	38(1)
C(5)	1036(5)	1519(1)	3200(2)	51(1)
C(6)	912(6)	829(1)	3324(2)	60(1)
C(7)	2761(5)	488(1)	3743(2)	60(1)
C(8)	4728(6)	838(1)	4048(2)	61(1)
C(9)	4854(5)	1531(1)	3943(2)	50(1)
C(10)	447(4)	3859(1)	2356(1)	38(1)
C(11)	−1461(5)	3552(1)	1900(2)	46(1)
C(12)	−1567(5)	3517(1)	1063(2)	54(1)
C(13)	210(5)	3789(1)	665(2)	54(1)
C(14)	2078(5)	4101(1)	1107(2)	51(1)
C(15)	2213(4)	4138(1)	1948(2)	43(1)
C(16)	3019(4)	3268(1)	5224(1)	42(1)
C(17)	3283(5)	2961(2)	6069(2)	55(1)
C(18)	5536(6)	3215(2)	6544(2)	58(1)
C(19)	5613(7)	3977(2)	6545(2)	61(1)
C(20)	5215(7)	4241(2)	5688(2)	64(1)

[a] Equivalent isotropic U is of the form $U_{eq}=1/3(\Sigma_i\Sigma_j U_{ij}a^*_i a^*_j \boldsymbol{a}_i \cdot \boldsymbol{a}_j)$.

Results and discussion

X-Ray crystal structure. A structure-determination summary is presented in Table 1. The isotropic extinction

Table 3. Bond lenghts (in Å) for $C_{20}H_{24}S_2O_2$.

S(1)–C(1)	1.837(2)	C(6)–C(7)	1.376(4)
S(1)–C(4)	1.777(2)	C(7)–C(8)	1.369(4)
S(2)–C(1)	1.829(2)	C(8)–C(9)	1.384(4)
S(2)–C(16)	1.810(2)	C(10)–C(11)	1.397(3)
O(1)–C(2)	1.429(3)	C(10)–C(15)	1.391(3)
O(2)–C(16)	1.436(3)	C(11)–C(12)	1.385(4)
O(2)–C(20)	1.447(4)	C(12)–C(13)	1.381(4)
C(1)–C(2)	1.560(3)	C(13)–C(14)	1.375(4)
C(2)–C(3)	1.522(4)	C(14)–C(15)	1.390(4)
C(2)–C(10)	1.534(3)	C(16)–C(17)	1.520(4)
C(4)–C(5)	1.384(3)	C(17)–C(18)	1.520(4)
C(4)–C(9)	1.390(3)	C(18)–C(19)	1.506(4)
C(5)–C(6)	1.383(4)	C(19)–C(20)	1.508(4)

Table 4. Bond angles (in °) for $C_{20}H_{24}S_2O_2$.

C(1)–S(1)–C(4)	102.8(1)	S(1)–C(4)–C(5)	123.0(2)	C(11)–C(12)–C(13)	120.4(2)
2C(1)–S(2)–C(16)	104.7(1)	S(1)–C(4)–C(9)	117.9(2)	C(12)–C(13)–C(14)	119.3(2)
C(16)–O(2)–C(20)	111.2(2)	C(5)–C(4)–C(9)	118.9(2)	C(13)–C(14)–C(15)	120.9(3)
S(1)–C(1)–S(2)	113.2(1)	C(4)–C(5)–C(6)	120.2(2)	C(10)–C(15)–C(14)	120.3(2)
S(1)–C(1)–C(2)	107.7(2)	C(5)–C(6)–C(7)	120.5(3)	S(2)–C(16)–O(2)	108.5(2)
S(2)–C(1)–C(2)	117.1(2)	C(6)–C(7)–C(8)	119.7(3)	S(2)–C(16)–C(17)	110.1(2)
O(1)–C(2)–C(1)	109.6(2)	C(7)–C(8)–C(9)	120.3(3)	O(2)–C(16)–C(17)	110.8(2)
O(1)–C(2)–C(3)	109.7(2)	C(4)–C(9)–C(8)	120.4(2)	C(16)–C(17)–C(18)	109.8(2)
C(1)–C(2)–C(3)	111.6(2)	C(2)–C(10)–C(11)	119.8(2)	C(17)–C(18)–C(19)	110.7(3)
O(1)–C(2)–C(10)	107.1(2)	C(2)–C(10)–C(15)	121.8(2)	C(18)–C(19)–C(20)	110.1(2)
C(1)–C(2)–C(10)	108.4(2)	C(11)–C(10)–C(15)	118.3(2)	O(2)–C(20)–C(19)	111.9(3)
C(3)–C(2)–C(10)	110.4(2)	C(10)–C(11)–C(12)	120.7(2)		

correction parameter had a negligible value of 0.00005, and it has been omitted from final calculations. The largest difference peak and hole were 0.23 and -0.22 e Å^{-3}, respectively.

Atomic fractional coordinates with equivalent isotropic displacement coefficients are listed in Table 2. Bond lengths and bond angles for non-hydrogen atoms are listed in Tables 3 and 4, respectively.†

The pyranyl group possesses a chair conformation and the hydroxyl group forms an intramolecular hydrogen bond to the oxygen atom of the pyranyl group with an O1–O2 distance of 2.816(3) Å, an O2–H distance of 2.05(3) Å and an O1–H–O2 angle of 153°.

Bond lengths around the sulfur atoms are 1.837(2), 1.777(2), 1.829(2) and 1.810(2) Å for S1–C1, S1–C4, S2–C1 and S2–C16 bonds, respectively. Bond angles around the sulfur atoms are 102.8(1) and 104.7(1)° for the C1–S1–C4 and C1–S2–C16 angles, respectively.

Refined hydrogen-atom distances are 0.76(3) Å for O–H and from 0.86(3) to 1.06(2) Å for C–H.

The title compound **1** possesses three chiral C atoms. The first, C16, is already present in the starting compound **3** and it remains in either configuration during the formation of **2**, in which C1 is not chiral at this stage. In the next step $PhCOCH_3$ can substitute either hydrogen atom at C1, thus fixing the configuration of C1; simultaneously, when the C1–C2 bond is formed, the configuration of C2 will be fixed as well, because $PhCOCH_3$ is not chiral. Only the configuration of each chiral center corresponding to the given coordinates, or their inversion, will produce an internal hydrogen bond.

NMR analysis of the crude product revealed different isomers, but their proportion and configuration could not be defined, and only **1** and its mirror image were crystallized, thus indicating that the hydrogen bond favours crystallization.

A similar combination of configurations has been found in 1-phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol[7] (**4**), i.e. the methyl group, C3 in **1**, is substituted by a hydrogen atom. A dramatic difference between **1** and **4** is that **4** crystallizes as a conglomerate of enantiomeric crystals in an acentric space group.

Table 5. Some dihedral and interplanar angles (in °) for $C_{20}H_{24}S_2O_2$.

Angle		Angle	
C1–S2–C16–O2	79.2	S1–C1–C2–C3	−175.8
C1–S2–C16–C17	−160.0	S1–C1–C2–C10	62.3
C1–S1–C4–C5	52.4	C1–C2–C10–C11	63.0
C1–S1–C4–C9	−132.3	O1–C2–C10–C15	0.8
C4–S1–C1–C2	−168.2	O1–C2–C10–C11	−179.1
C16–S2–C1–S1	50.4	C1–C2–C10–C15	−117.1
C16–S2–C1–O1	−75.8	C3–C2–C10–C11	−59.9
S1–C1–C2–O1	−53.9	C3–C2–C10–C15	120.1

Plane		Mean deviation of atoms/Å
(I)	C4,C5,C6,C7,C8,C9	0.006
(II)	C10,C11,C12,C13,C14,C15	0.006
(III)	S1,C1,C2,C3	0.028
(IV)	C1,S2,C16	–

Angles between planes/°

	(II)	(III)	(IV)
(I)	71.8	55.7	68.9
(II)		90.2	10.2
(III)			80.5

To describe orientations of differ ent fragments in the structure some dihedral and interplanar angles are listed in Table 5.

References

1. Ager, D. J. In Hase, T., Ed., *Umpoled Synthons*, Wiley, New York 1987, Chap. 2.
2. Greene, T. W. and Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Edn., Wiley, New York 1991, pp. 198–210.
3. Kiljunen, H. and Hase, T. A. *J. Org. Chem. 56* (1991) 6950.
4. Juaristi, E., Martinez-Richa, A., Garcia-Rivera, A. and Cruz-Sanches, J. S. *J. Org. Chem. 48* (1983) 2603.
5. Martin, M. Bassery, L. and Leroy, C. *Bull. Soc. Chim. Fr. 12* (1972) 4763.
6. Sheldrick, G. M. *SHELXTL-Plus Version 4.1*, Siemens Analytical X-Ray Instruments, Inc., Madison, WI 1990.
7. Kansikas, J. and Sipilä, K. *14th Nordic Meeting of Structural Chemists, Programme and Abstracts* (1993) p. 71.

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† A list of observed and calculated structure factors, anisotropic displacement parameters for non-hydrogen atoms and hydrogen atom coordinates is obtainable from one author (J. K.).