

# Synthesis and Crystal Structure of Intramolecularly Hydrogen-Bonded 1-Phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol

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Kansikas, J., Sipilä, K. and Hase, T., 1996. Synthesis and Crystal Structure of Intramolecularly Hydrogen-Bonded 1-Phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol. – Acta Chem. Scand. 50: 1147–1152. © Acta Chemica Scandinavica 1996.

The title compound (C<sub>19</sub>H<sub>22</sub>O<sub>2</sub>S<sub>2</sub>) **1** crystallizes as long colorless needles. The conformation of the molecule is similar to that of 1-phenylthio-1-(tetrahydropyran-2-ylthio)propan-2-ol **2** [Kansikas, J. *et al.*, *Acta Chem. Scand.* 49 (1995) 809]. The main difference is that **1** crystallizes in an acentric space group as a conglomerate of enantiomeric crystals and **2** in a centrosymmetric space group as a racemate. Compounds **1** and **2** both form an intramolecular hydrogen bond. Crystal data for **1**:  $a = 5.402(3)$ ,  $b = 16.807(5)$  and  $c = 19.814(6)$  Å; space group  $P2_12_12_1$ ,  $Z = 4$ ,  $M_r = 346.5$ ,  $D_c = 1.279$  Mg m<sup>-3</sup>,  $\mu = 0.30$  mm<sup>-1</sup> and  $F(000) = 736$ . The data were collected at room temperature up to 53° in  $2\theta$  using Mo K $\alpha$  radiation. 1872 reflections were collected and 977 were regarded as observed [ $I > 2.0\sigma(I)$ ]. Full-matrix least-squares refinement converged to a conventional  $R$ -value of 0.0583 and  $wR$ -value of 0.0457. An intramolecular hydrogen bond O1–H $\cdots$ O2 of 1.828 Å with relative configurations  $S^*$ ,  $S^*$ , and  $R^*$  at atoms C1, C2 and C15, respectively, affects the conformation of the molecule.

We have recently reported the synthesis and X-ray crystal structure of a hydroxyalkylthio-substituted tetrahydropyran **2**, where an intramolecular hydrogen bond is formed between the hydroxy group and the tetrahydropyran oxygen atom.<sup>1</sup> We now describe another, similarly hydrogen bonded crystalline compound **1** in this series. Although the two compounds have very closely related molecular structures it turns out that there is a significant difference in their crystalline forms as discussed below. To our knowledge and according to the Cambridge Structural Database CSD there is no previous example in the literature of any hydrogen bonded structure of this kind where a sulfur atom has been found in the ring. However many disaccharides are similarly intramolecularly hydrogen bonded, but of course they contain an oxygen atom in the place of the sulfur of **1** and **2**.

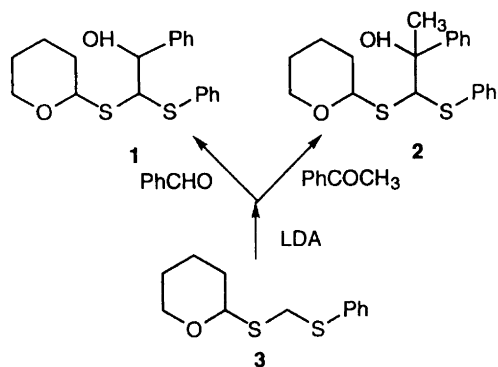
## Experimental

**Syntheses.** For general experimental information, see our previous paper.<sup>1</sup> <sup>1</sup>H, <sup>13</sup>C and DEPT NMR spectra were taken for samples in CDCl<sub>3</sub> with a Varian Gemini-200 and the HMQC spectrum with a Varian INOVA 300

spectrometer with SiMe<sub>4</sub> as an internal reference. The assignments are based on chemical shift data and DEPT and HMQC measurements.

**1-Phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol 1.** A solution of 2-(phenylthiomethylthio)tetrahydropyran **3** (1.0 g, 4.2 mmol) in 10 ml dry tetrahydrofuran was treated with lithium diisopropylamide (5.0 mmol) at –78 °C under Ar (Scheme 1). After 4 h freshly distilled benzaldehyde (0.5 g, 5.0 mmol) was added dropwise and the reaction mixture allowed to reach room temperature with stirring overnight. Water was added and the mixture was extracted several times with diethyl ether. The organic phase was washed with water and brine, dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated off. The residue (1.3 g, containing 20–30% of unreacted starting materials) was purified by flash chromatography. The eluent was allowed to evaporate from the fractions containing **1** as a mixture of diastereomers. The fractions with solid residues were recrystallized from abs. ethanol to give **1** as a conglomerate of enantiomeric crystals (0.17 g, 12%); m.p. 122 °C. <sup>1</sup>H NMR:  $\delta$  1.50–1.95 (6 H, m, CH<sub>2</sub>), 3.58–3.70 (1 H, m, OCH<sub>ax</sub>), 4.05–4.17 (1 H, m, OCH<sub>eq</sub>), 4.42 (1 H, d, 2.7 Hz, SCHS), 5.22 (1 H, dd,  $J = 3.8, 7.5$  Hz, OCHS), 5.20 (1 H, d, 2.7 Hz, CHPh),

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**Scheme 1.** Syntheses of 1-phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol **1** and 2-phenyl-1-phenylthio-1-(tetrahydropyran-2-ylthio)propan-2-ol **2**.

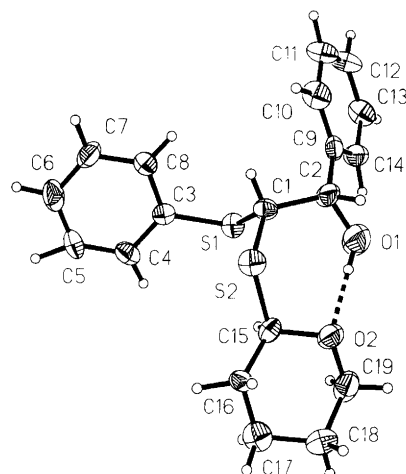
7.20–7.52 (10 H, m, arom. CH).  $^{13}\text{C}$  NMR:  $\delta$  22.48, 22.52, 31.00 ( $\text{CH}_2$ ), 64.78 (SCHS), 65.99 ( $\text{OCH}_2$ ), 79.14 ( $\text{PhCHOH}$ ), 80.05 ( $\text{OCHS}$ ), 126.74–132.53 (arom. C).

**Crystal structure.** Single crystal unit cell determination and X-ray data collection were carried out at room temperature on a Nicolet P3F four-circle diffractometer equipped with a graphite monochromator. Radiation used was Mo K $\alpha$  ( $\lambda = 0.71073 \text{ \AA}$ ). The starting orientation matrix was derived from ten photographic points, which gave a reasonable unit cell. Final unit cell dimensions were obtained by carefully centering 25 reflections within a  $2\theta$  range of  $20\text{--}25^\circ$ . The cell parameters thus obtained were  $a = 5.402(3)$ ,  $b = 16.807(5)$ ,  $c = 19.814(6) \text{ \AA}$  in an orthorhombic crystal system. The data were collected by the  $\omega$ -scan method in the range  $3 < 2\theta < 53^\circ$  totaling 1872 unique reflections. Systematic absences proposed a space group  $P2_12_12_1$  (No. 19), which, being non-centrosymmetric, shows that with a  $Z$  value of 4 only one enantiomer can be present in each crystal.

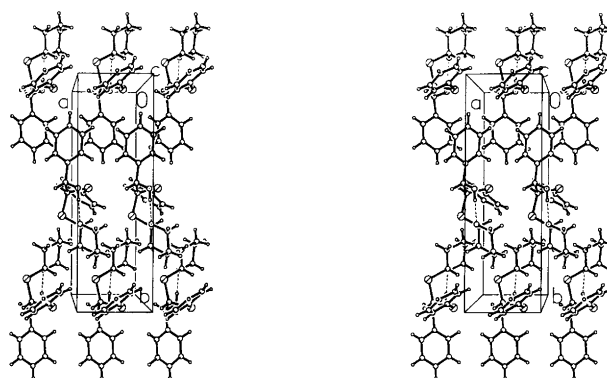
Three test reflections were monitored during the data collection at intervals of one hundred reflections. Intensities of test reflections varied randomly to within 1%. Owing to the weak scattering power of the crystal only 977 reflections of 1872 collected exceeded the criteria  $I > 2\sigma(I)$  and were regarded as observed. Crystal and data collection parameters are listed in Table 1.

Absorption was checked empirically by the  $\psi$ -rotation method measuring four selected reflections differing by approximately ca.  $5^\circ$  in  $2\theta$  at intervals of  $10^\circ$  in  $\psi$ .<sup>2</sup> Transmission based on  $\psi$ -scans was between 0.98 and 1.00 and thus no correction was done. The data were corrected for Lorentz and polarization factors. The isotropic extinction parameter was also refined, but it appeared so negligible that it was omitted from the final refinement.

The structure was solved using direct methods of the program package SHELXTL Plus (PC version)<sup>3</sup> which was also used in drawing the figures. Atomic scattering factors used were those included in the program package. All non-hydrogen atoms were clearly located, including



**Fig. 1.** The structure of 1-phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol **1** with atomic labeling. Anisotropic displacement ellipsoids are drawn at the 30% probability level.



**Fig. 2.** A stereoscopic view of the crystal packing of 1-phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol **1** seen down the  $c$ -axis.

the selection of the enantiomorph, during the first run. After a few least-squares cycles, the difference Fourier map revealed several maxima at reasonable positions to be regarded as hydrogen atoms. However, all hydrogen atoms were positioned at calculated values using a riding atom model with a fixed isotropic displacement parameter. Full-matrix least-squares refinement of scale factor, weighting parameter, positional and anisotropic displacement parameters for non-hydrogen atoms totaling 209 refined parameters converged to a conventional  $R$ -value of 5.83% and weighted  $wR$ -value of 4.57%.

## Results and discussion

A crystal structure determination summary is presented in Table 1. Fractional atomic coordinates with equivalent isotropic displacement parameters for non-hydrogen atoms are listed in Table 2, and bond lengths and angles

Table 1. Structure determination summary of C<sub>19</sub>H<sub>22</sub>O<sub>2</sub>S<sub>2</sub>.

Crystal data	
Empirical formula	C <sub>19</sub> H <sub>22</sub> O <sub>2</sub> S <sub>2</sub>
Color; habit	Colorless; needles
Crystal size/mm	0.1 × 0.1 × 0.3
Crystal system	Orthorhombic
Space group	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub> (No. 19)
Unit cell dimensions	<i>a</i> = 5.402(3) Å <i>b</i> = 16.807(5) Å <i>c</i> = 19.814(6) Å
Volume/Å <sup>3</sup>	1798.9(9)
Formula weight	346.5
Density(calc.)/Mg m <sup>-3</sup>	1.279
Absorption coefficient/mm <sup>-1</sup>	0.303
<i>F</i> (000)	736
Data collection	
Diffractometer used	Nicolet P3F
Radiation	Mo Kα (λ = 0.71073 Å)
<i>T</i> /K	293
Monochromator	Highly oriented graphite crystal
2θ range/°	3.0–53.0
Scan type	ω
Scan speed/°min <sup>-1</sup>	Variable; 1.5–29.30
Scan range, ω/°	1.0
Background measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25% of total scan time
Standard reflections	3 measured every 100 reflections
Index ranges	0 < <i>h</i> < 6, 0 < <i>k</i> < 19, 0 < <i>l</i> < 23
Collected reflections	1872
Independent reflections	1872
Observed reflections	977 [ <i>I</i> > 2.0 σ( <i>I</i> )]
Minimum transmission	0.98
Solution and refinement	
System used	Siemens SHELXTL Plus (PC Version) <sup>4</sup>
Solution	Direct methods
Refinement method	Full-matrix least-squares
Quantity minimized	Σw( <i>F</i> <sub>o</sub> – <i>F</i> <sub>c</sub> ) <sup>2</sup>
Hydrogen atoms	Calculated positions, riding model, fixed isotropic H
Weighting scheme	w <sup>-1</sup> = σ <sup>2</sup> ( <i>F</i> ) + 0.0002 <i>F</i> <sup>2</sup>
No. of parameters refined	209
Final <i>R</i> values (obs. data)	<i>R</i> = 5.83%, <i>wR</i> = 4.57%
<i>R</i> values (all data)	<i>R</i> = 11.99%, <i>wR</i> = 5.11%
Goodness-of-fit	1.51
Largest and mean Δ/σ	0.097, 0.018
Data-to-parameter ratio	4.7:1
Largest difference peak/e Å <sup>-3</sup>	0.40
Largest difference hole/e Å <sup>-3</sup>	–0.29

in Tables 3 and 4, respectively. † Fig. 1 shows the structure of **1** with atomic labeling. The intramolecular hydrogen bond is also shown. Molecular packing is presented in Fig. 2. For determination of the correct enantiomer, the Rogers parameter was calculated, but it did not give a reasonable result [ $\eta = 0.52(0.64)$ ].<sup>4</sup> The Hamilton test was also applied and it showed *R* values of 5.83 and 5.91

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

for the given enantiomer and its inversion, respectively, thus slightly favoring the choice of the enantiomer given by direct methods when solving the structure.

The molecular structure of **1** is very similar to 2-phenyl-1-phenylthio-1-(tetrahydropyran-2-ylthio)propan-2-ol<sup>1</sup> **2**, but crystallographically there is a significant difference. Compound **2** crystallizes as a racemate, i.e., two opposite enantiomers in a centrosymmetric space group *P*2<sub>1</sub>/*c* (No. 14), but **1** crystallizes in a non-centrosymmetric space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (No. 19) as a conglomerate of enantiomeric crystals. The title com-

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters (in  $\text{\AA}^2 \times 10^3$ ) of  $\text{C}_{19}\text{H}_{22}\text{O}_2\text{S}_2$ .

	x	y	z	$U(\text{eq})^a$
S(1)	1960(5)	9766(1)	9804(1)	57(1)
S(2)	-1819(5)	11030(1)	9381(1)	61(1)
O(1)	296(20)	9761(4)	8277(4)	130(5)
O(2)	643(14)	11375(3)	8271(3)	68(3)
C(1)	-1068(15)	9978(4)	9415(4)	49(3)
C(2)	-1413(24)	9532(6)	8747(5)	85(5)
C(3)	1355(17)	10000(4)	10667(4)	45(3)
C(4)	2994(21)	10493(5)	11007(5)	65(4)
C(5)	2713(23)	10633(6)	11680(5)	77(5)
C(6)	681(26)	10306(7)	12023(5)	80(5)
C(7)	-874(21)	9813(7)	11693(5)	73(4)
C(8)	-595(19)	9652(5)	11012(5)	63(4)
C(9)	-1062(22)	8639(6)	8816(4)	57(4)
C(10)	-2805(21)	8231(6)	9182(5)	73(5)
C(11)	-2653(20)	7413(6)	9263(5)	77(5)
C(12)	-795(24)	6993(6)	8964(6)	78(5)
C(13)	979(20)	7393(6)	8607(5)	71(5)
C(14)	855(21)	8214(6)	8532(5)	66(4)
C(15)	819(18)	11495(5)	8983(4)	54(4)
C(16)	824(20)	12365(5)	9157(5)	65(4)
C(17)	3043(22)	12763(5)	8793(5)	76(4)
C(18)	3034(21)	12577(5)	8047(5)	80(4)
C(19)	2788(23)	11693(6)	7927(5)	83(5)

<sup>a</sup> Equivalent isotropic  $U$  is of the form  $U_{\text{eq}} = 1/3(\sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j)$ .

Table 3. Bond lengths (in  $\text{\AA}$ ) for  $\text{C}_{19}\text{H}_{22}\text{O}_2\text{S}_2$ .

S(1)–C(1)	1.844(9)
S(1)–C(3)	1.783(9)
S(2)–C(1)	1.814(7)
S(2)–C(15)	1.807(10)
O(1)–C(2)	1.367(15)
O(2)–C(15)	1.428(11)
O(2)–C(19)	1.447(14)
C(1)–C(2)	1.532(13)
C(2)–C(9)	1.519(14)
C(3)–C(4)	1.388(13)
C(3)–C(8)	1.386(13)
C(4)–C(5)	1.362(15)
C(5)–C(6)	1.404(18)
C(6)–C(7)	1.349(16)
C(7)–C(8)	1.384(15)
C(9)–C(10)	1.372(15)
C(9)–C(14)	1.379(15)
C(10)–C(11)	1.386(14)
C(11)–C(12)	1.362(16)
C(12)–C(13)	1.368(16)
C(13)–C(14)	1.389(15)
C(15)–C(16)	1.502(12)
C(16)–C(17)	1.550(15)
C(17)–C(18)	1.510(15)
C(18)–C(19)	1.511(14)

Table 4. Bond angles (in  $^\circ$ ) for  $\text{C}_{19}\text{H}_{22}\text{O}_2\text{S}_2$ .

C(1)–S(1)–C(3)	101.3(4)
C(1)–S(2)–C(15)	105.1(4)
C(15)–O(2)–C(19)	111.1(7)
S(1)–C(1)–S(2)	113.7(4)
S(1)–C(1)–C(2)	112.0(6)
S(2)–C(1)–C(2)	114.7(6)
O(1)–C(2)–C(1)	111.6(9)
O(1)–C(2)–C(9)	104.8(9)
C(1)–C(2)–C(9)	113.0(8)
S(1)–C(3)–C(4)	118.8(7)
S(1)–C(3)–C(8)	121.3(7)
C(4)–C(3)–C(8)	119.8(9)
C(3)–C(4)–C(5)	120.5(10)
C(4)–C(5)–C(6)	119.6(10)
C(5)–C(6)–C(7)	119.5(10)
C(6)–C(7)–C(8)	121.7(10)
C(3)–C(8)–C(7)	118.8(9)
C(2)–C(9)–C(10)	117.1(10)
C(2)–C(9)–C(14)	124.7(10)
C(10)–C(9)–C(14)	118.2(9)
C(9)–C(10)–C(11)	121.1(10)
C(10)–C(11)–C(12)	120.4(10)
C(11)–C(12)–C(13)	119.2(9)
C(12)–C(13)–C(14)	120.6(10)
C(9)–C(14)–C(13)	120.4(10)
S(2)–C(15)–O(2)	108.5(6)
S(2)–C(15)–C(16)	108.8(7)
O(2)–C(15)–C(16)	111.3(7)
C(15)–C(16)–C(17)	108.3(8)
C(16)–C(17)–C(18)	111.4(9)
C(17)–C(18)–C(19)	110.9(8)
O(2)–C(19)–C(18)	111.1(9)

pound **1** possesses three stereogenic atoms, C1, C2 and C15 (same as found in **2**), the configurations of which, in the present structure, are *S*, *S* and *R*, respectively. The centrosymmetric crystal racemate of **2** has the relative stereochemistry *S*\*, *S*\*, *R*\* at C1, C2 and C16, respectively. The conformation of the tetrahydropyranyl group is a chair with S2 in an equatorial position.

The extent of diastereochemical control in the reaction sequence **3**→lithio-**3**→**1** is not known. It may be based

on the expected equatorial position of the side chain in **3** and possibly on the stereoselective formation of an Li–O coordinated five-membered ring structure for the

Table 5. Some dihedral and interplanar angles (in °) for C<sub>19</sub>H<sub>22</sub>O<sub>2</sub>S<sub>2</sub>.

Angle		Angle		
C1–S2–C15–O2	79.3	S1–C1–C2–O1	–63.6	
C1–S2–C15–C16	–161.3	S1–C1–C2–C9	62.3	
C1–S1–C3–C8	54.7	C1–C2–C9–C10	66.6	
C1–S1–C3–C4	–130.4	O1–C2–C9–C14	9.1	
C3–S1–C1–C2	–158.4	O1–C2–C9–C10	–179.1	
C15–S2–C1–S1	52.1	C1–C2–C9–C14	–114.2	
C15–S2–C1–C2	–77.4			
Plane		Mean deviation of atoms/Å		
(I)	C3,C4,C5,C6,C7,C8	0.013		
(II)	C9,C10,C11,C12,C13,C14	0.008		
(III)	S1,C1,C2,C3	0.141		
(IV)	S2,C1,C2,C9	0.052		
(V)	C1,S2,C15	—		
Angles between planes/°				
(I)	(II)	(III)	(IV)	(V)
	114.1	51.5	112.3	109.8
(II)		88.7	68.0	8.4
(III)			61.2	91.1
(IV)				76.2

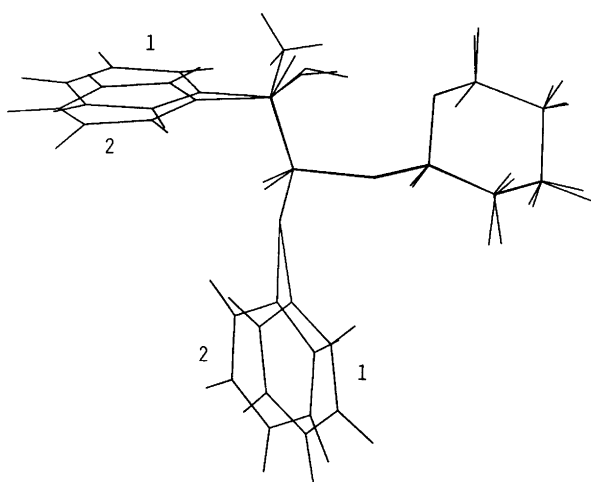


Fig. 3. Superposition of 1-phenyl-2-phenylthio-2-(tetrahydropyran-2-ylthio)ethanol **1** and 2-phenyl-1-phenylthio-1-(tetrahydropyran-2-ylthio)propan-2-ol **2** generated through atoms C1, C2, S1 and S2.

lithio-3 intermediate. Although there are other diastereomers formed in the present reaction, we have observed high stereoselectivities (up to 9:1) in analogous reactions that involve an alkyl halide electrophile in the last step instead of benzaldehyde.<sup>5</sup> In any case, we ascribe the ready crystallizability of **1** to the conformation-locking effect of the hydrogen bond. The geometry of the hydrogen bond is almost linear with the O–H, H···O and O···O distances of 0.894, 1.828 and 2.719 Å, respectively and an angle OHO of 179.1°.

Intramolecular hydrogen bond formation is possible also for other diastereomers, but so far we have not been able to crystallize any others. We are working to deter-

mine their configuration and exact proportion in the crude product.

The corresponding bond lengths in **1** and **2** are practically equal to within a 3σ level. The largest deviation is in bond lengths O1–C2 of 1.367(15) and 1.429(2) for compounds **1** and **2**, respectively. Structural similarities and differences can be seen in Fig. 3 where a superposition of **1** and **2** is shown. The superposition is generated through atoms C1, C2, S1 and S2 of both structures. The fit of the non-hydrogen atoms of the tetrahydropyran-yl groups and hydroxy groups is good. This structural similarity strongly suggests the stabilizing effect of the intramolecular hydrogen-bond. The orientations of the phenyl groups differ more clearly, which can be seen in some interplanar angles (Table 5) and Ref. 1. The angle between the phenyl groups is 114.1° in **1** and is 71.8° in **2**. Packing of the molecules in **1** and **2** is very similar involving only van der Waals forces. Tetrahydropyran-yl groups stack with each other in *b* and *c* axis directions forming a layer, but the distances are too large to allow intermolecular hydrogen bond formation. The other set of layers is formed by phenyl groups.

The calculated coupling constants<sup>6,7</sup> for H(15) (11.2 and 2.5 Hz) compared with those measured in CDCl<sub>3</sub> (7.5 and 3.8 Hz) indicate that the structure is flexible in solution but that the substituent at C(15) is mostly in an equatorial position. The dihedral angle H–C1–C2–H in the crystal is 92.6° which is based on calculated H-atom positions; *J* = 0.9 Hz. The experimental coupling constant 2.7 Hz which corresponds to an average angle of 67° shows that the conformation of **1** is not the same in solution as in the crystal.

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