

Crystal structures of two chiral piperidine derivatives: 1-[(1*R*)-2-hydroxy-1-phenylethyl]-piperidin-4-one and 8-[(1*S*)-1-phenylethyl]-1,4-dioxa-8-azaspiro[4.5]decane-7-thione

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Keywords: crystal structure; piperidine; piperidone; thione; ring conformation

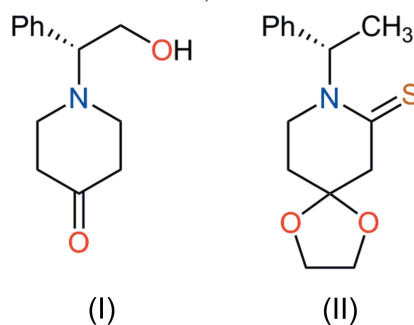
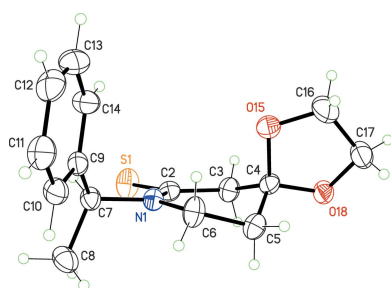
CCDC references: 1424094; 1424093

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The crystal structures of the two title piperidine derivatives show different conformations for the six-membered heterocycle. The *N*-substituted 4-piperidinone 1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidin-4-one, C₁₃H₁₇NO₂, (I), has a chair conformation, while the piperidine substituted in position 2 with a thiocarbonyl group, 8-[(1*S*)-1-phenylethyl]-1,4-dioxa-8-azaspiro[4.5]decane-7-thione, C₁₅H₁₉NO₂S, (II), features a half-chair conformation. Comparison of the two structures, and data retrieved from the literature, suggests that the conformational flexibility is mainly related to the hybridization state of the C atom α to the piperidinic N atom: a *Csp*³ atom favours the chair conformer, while a *Csp*² atom distorts the ring towards a half-chair conformer. In the crystal structure of (I), weak C—H...O hydrogen bonds link the molecules into supramolecular chains propagating along the *b*-axis direction. In the crystal of (II), the molecules are linked by weak C—H...S contacts into supramolecular chains propagating along the *b*-axis direction.

1. Chemical context

The 4-piperidone scaffold has been used as a building block for the synthesis of more complex heterocyclic compounds. An example is the one-pot three-step synthesis of fentanyl [*N*-(1-phenethyl-4-piperidyl) propionanilide], a strong agonist of μ -opioid receptors, used for its potent analgesic activity. This industrial synthesis, patented by Janssen Pharmaceutica (Gupta *et al.*, 2010) employs 4-piperidone hydrochloride monohydrate as the starting material. The range of biological activity for 4-piperidone derivatives is quite broad, including anti-inflammatory, anticancer, antibacterial and antifungal properties. For this reason, new synthetic methods are being sought proactively in this field (*e.g.* Tortolani & Poss, 1999; Davis *et al.*, 2001; Das *et al.*, 2010). For our part, our emphasis is on the synthesis of chiral *N*-substituted piperidone derivatives (*e.g.* Romero *et al.*, 2007).



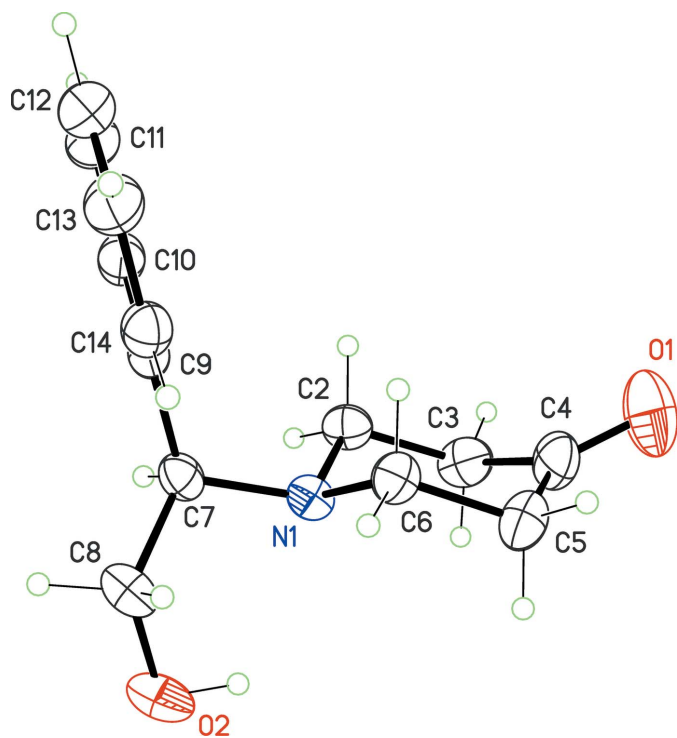


Figure 1
The molecular structure of (I), with displacement ellipsoids for non-H atoms at the 30% probability level.

In this context, X-ray crystallography is a potent tool to assess the conformational modifications experienced by the piperidine heterocycle while its substitution pattern is altered along a synthetic route. The pair of structures reported here illustrates such conformational flexibility in this chemistry.

2. Structural commentary

The first piperidin-4-one derivative [(I), Fig. 1] is a non-sterically hindered molecule, and thus adopts the most stable chair conformation for the six-membered heterocycle. The total puckering amplitude is $Q = 0.553(3) \text{ \AA}$, and the Cremer parameters are $\theta = 168.8(3)^\circ$ and $\varphi = 171.8(18)^\circ$. The deviation from the ideal conformation, $\theta = 180^\circ$, may be related to the heterocyclic nature of the ring, with short C–N bond lengths and longer C–C bond lengths, as expected. Moreover, atom C4 has a geometry consistent with its sp^2 hybridization state, while N1 is essentially tetrahedral, with the lone pair occupying the axial position. The equatorial group substituting this N atom is rigid, as a result of its chiral character. However, the spatial orientation of this group allows the hydroxyl group to interact with the nitrogen lone pair, stabilizing the observed molecular conformation.

The chair conformation for the piperidone in (I) was previously observed in related compounds based on the same heterocycle (Vijayakumar *et al.*, 2010; Rajesh *et al.*, 2010a, 2012). Apparently, the only significant variation allowed for this system is for the N atom, which may approach a planar–trigonal geometry (Shahani *et al.*, 2010; Rajesh *et al.*, 2010b).

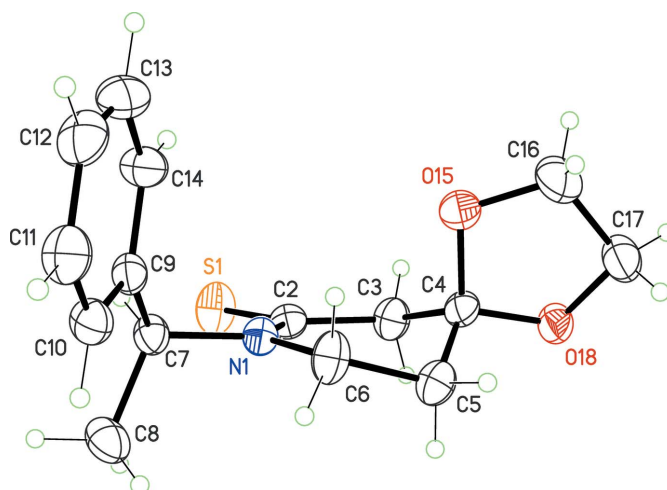


Figure 2
The molecular structure of (II), with displacement ellipsoids for non-H atoms at the 30% probability level.

The chair conformation of (I) is, however, different from that observed for (II), derived from piperidine-2-thione (Fig. 2). In that case, the half-chair form is found in the crystal structure, characterized by a puckering amplitude $Q = 0.513(3) \text{ \AA}$, and Cremer parameters $\theta = 127.5(3)^\circ$ and $\varphi = 29.29(5)^\circ$ (ideal values: $\theta = 129.2^\circ$ and $\varphi = 30^\circ$). The N atom has a planar environment, the sum of angles about this center being 360° . This conformer is identical to one of the stable forms reported for piperidin-2-one (known as δ -valerolatcam): microwave spectroscopy indicated that for δ -valerolatcam, two conformers are stabilized in the gas phase, the half-chair form and the twist form (Kuze *et al.*, 1999). δ -Valerolatcam is actually comparable to (II), because in both molecules C4 has the same sp^3 hybridization. In (II), the spiro atom C4 is part of the 1,3-dioxolane ring. The slightly twisted half-chair conformation for this ring is common. The two rings are almost perpendicular, as reflected in the dihedral angle between their mean-planes of $76.4(2)^\circ$.

3. Effect of hybridization on ring conformation

Since the ring conformation in (II) seems not to be related to any intramolecular strong interaction nor the hybridization modification from sp^2 to sp^3 at C4, it should be a consequence of the presence of the thiocarbonyl functionality at C2. This center is in a state very close to pure sp^2 hybridization. This is reflected in the bond length for the C=S group, $1.677(3) \text{ \AA}$, close to the mean value of 1.669 \AA computed from almost 10000 thiocarbonyl bonds retrieved from the organics subset of the CSD (Version 5.36 with all updates; Groom & Allen, 2014). The restriction to sp^2 -C centers is applied by requiring the C atom to be linked to exactly three atoms and the S atom to be linked to exactly one atom). Indeed, long C=S bonds, above 1.75 \AA , are found in compounds including molecules having a propensity to form hydrogen bonds, like thiourea (Weber, 1984), thiourea derivatives (Busschaert *et al.*, 2011;

Table 1

Hydrogen-bond geometry (Å, °) for (I).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$C3-H3A\cdots O1^i$	0.97	2.49	3.246 (4)	135

 Symmetry code: (i) $-x + 2, y - \frac{1}{2}, -z + 1$.

Table 2

Hydrogen-bond geometry (Å, °) for (II).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$C16-H16B\cdots S1^i$	0.97	2.85	3.709 (5)	148

 Symmetry code: (i) $-x + 2, y + \frac{1}{2}, -z + \frac{3}{2}$.

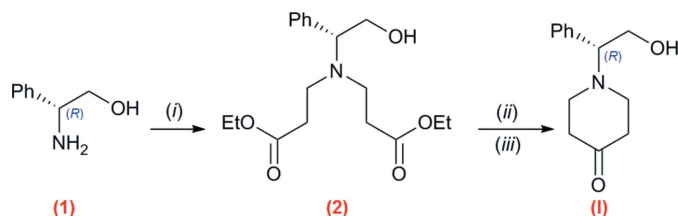
Chumakov *et al.*, 2006), and trithiocarbonic acid (Krebs & Gattow, 1965), among others. In the case of a single C–S bond based on a sp^3 -hybridized C atom, the bond length is sharply distributed around 1.81 Å.

The other factor contributing to the ring conformation in (II) is the absence of the hydroxyl group in the chiral moiety, making the heterocyclic N atom inert towards potential interactions. The lone pair should thus be oriented randomly above and below the piperidine mean plane, through nitrogen inversion, characterized by a low energy barrier in the gas and solution phases. Both features, the planar N atom and the neighboring sp^2 -C atom, generate the half-chair conformation observed for the piperidine-2-thione core. In the present case, it is difficult to determine whether one feature dominates, or both are of importance for stabilizing the half-chair conformation. However, for the 25 hits corresponding to piperidine-2-ones deposited in the CSD, 21 of them present the same conformation as in (II), with C4 as the flap atom for the half-chair. In three cases, the puckering amplitude of the half-chair is close to 0 Å (Woydt *et al.*, 1991; Bolla *et al.*, 2014), and in one case, the ring presents a twist-boat conformation (Sanfilippo *et al.*, 1992). In contrast, piperidine derivatives are stabilized almost universally in the chair conformation, with very few exceptions in some disordered structures (Thirumaran *et al.*, 2009). These rules hold regardless of the substituent on the N atom. Applying these general rules to compounds (I) and (II), we thus infer that the ring conformation is mainly determined by the hybridization state of the C atom in position α to the piperidinic N atom.

4. Supramolecular features

In the crystal of (I), weak C–H \cdots O hydrogen bonds link the molecules into supramolecular chains propagating along the *b*-axis direction (Table 1).

The crystal structure of (II) is based on weak intermolecular C–H \cdots S contacts involving one methylene group of the dioxolane ring and the thiocarbonyl functionality (Table 2), which forms chains along the 2_1 symmetry axis parallel to [010].

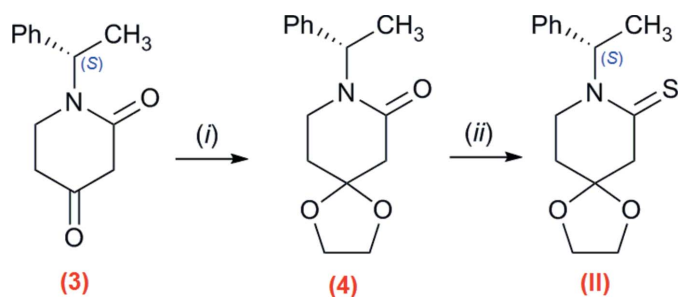

Figure 3

Synthesis of (I). Reaction conditions: (i) ethyl acrylate, MeOH, 298 K, 12 h; (ii) Na/MeOH, benzene, reflux, 5 h; (iii) AcOH/H₂O (30% v/v), reflux.

5. Synthesis and crystallization

Compound (I). The synthesis is illustrated in Fig. 3. A solution of compound (1), (*R*)-(-)-2-phenylglycinol (5.65 g, 41.2 mmol) with an excess of ethyl acrylate in methanol (60 mL), was stirred overnight at 298 K. The reaction mixture was concentrated, and the crude purified by column chromatography (SiO₂, CH₂Cl₂:MeOH, 97:3), to afford (2) as a colorless oil (98%). An amount of (2) (40.6 mmol) was added to a mixture of MeONa in anhydrous benzene. After refluxing the mixture for 5 h, a solid was obtained, which was filtered and dried in air. This solid was treated with AcOH:water (30%, v/v) until pH = 1, initiating the decarboxylation process. The mixture was refluxed until gas evolution stopped. After cooling down to 298 K, pH was adjusted to 7 with NaHCO₃, and the mixture was washed with CH₂Cl₂ (3 × 50 mL). The organic phase was dried over Na₂SO₄, and concentrated. Compound (I) was purified by column chromatography (SiO₂, CH₂Cl₂:MeOH, 95:5). Compound (I) was obtained in 80% yield, and was recrystallized from an AcOEt:*n*-hexane mixture (1:1).

Compound (II). The synthesis is illustrated in Fig. 4. The synthesis of compound (3), (*S*)-(-)-phenylethylpiperi-2,4-dione, has been reported previously (Romero *et al.*, 2013; see compound 5 in Fig. 1 of this report). To a solution of (3) in 50 mL of dry benzene, was added ethylene glycol (0.2 mL, 3.4 mmol) and a catalytic amount of *p*-TSA. The mixture was refluxed until water formation, collected with a Dean–Stark trap, stopped. Then, the reaction mixture was cooled down to room temperature, treated with brine, and washed with CH₂Cl₂ (3 × 50 mL). The organic phase was dried over


Figure 4

Synthesis of (II). Reaction conditions: (i) ethylene glycol, *p*-TSA, anhydrous benzene, reflux, 4 h; (ii) Lawesson's reagent in anhydrous toluene, 313 K, 1 h.

Table 3
Experimental details.

	(I)	(II)
Crystal data		
Chemical formula	C ₁₃ H ₁₇ NO ₂	C ₁₅ H ₁₉ NO ₂ S
<i>M_r</i>	219.27	277.37
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁	Orthorhombic, <i>P</i> 2 ₁ 2 ₁ 2 ₁
Temperature (K)	296	296
<i>a</i> , <i>b</i> , <i>c</i> (Å)	9.7590 (11), 6.8952 (10), 9.7980 (14)	5.9731 (13), 14.948 (3), 16.127 (3)
α , β , γ (°)	90, 114.348 (9), 90	90, 90, 90
<i>V</i> (Å ³)	600.67 (15)	1439.9 (5)
<i>Z</i>	2	4
Radiation type	Mo <i>K</i> α	Mo <i>K</i> α
μ (mm ⁻¹)	0.08	0.22
Crystal size (mm)	0.60 × 0.17 × 0.12	0.60 × 0.38 × 0.36
Data collection		
Diffractometer	Bruker P4	Bruker P4 diffractometer
Absorption correction	–	ψ scan (<i>XSCANS</i> ; Fait, 1996)
<i>T</i> _{min} , <i>T</i> _{max}	–	0.760, 0.922
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	2700, 1341, 1050	3886, 2631, 2007
<i>R</i> _{int}	0.021	0.029
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.595	0.650
Refinement		
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.036, 0.083, 1.04	0.044, 0.120, 1.06
No. of reflections	1341	2631
No. of parameters	146	174
No. of restraints	1	0
H-atom treatment	H-atom parameters constrained	H-atom parameters constrained
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.11, -0.11	0.19, -0.24
Absolute structure	Assigned from the synthesis	Flack <i>x</i> determined using 483 quotients [(<i>I</i> ⁺) - (<i>I</i> ⁻)] / [(<i>I</i> ⁺) + (<i>I</i> ⁻)] (Parsons <i>et al.</i> , 2013)
Absolute structure parameter	–	0.08 (7)

Computer programs: *XSCANS* (Fait, 1996), *SHELXS97* and *SHELXTL* (Sheldrick, 2008) and *SHELXL2014* (Sheldrick, 2015).

Na₂SO₄, and then concentrated under reduced pressure. The crude reaction was purified by column chromatography (SiO₂, AcOEt:petroleum benzine), to afford compound (4) as a white oil, in 95% yield. Next, a suspension of Lawesson's reagent (0.234 g, 0.578 mmol) in dry toluene (60 mL) was refluxed until complete dissolution of the reagent. The solution was cooled to 313 K, and a solution of (4) in anh. toluene (0.151 g, 0.578 mmol, 20 mL) was added (Romero *et al.*, 2007). The reaction mixture was stirred for 1 h to give (II) in 90% yield, after purification by column chromatography (SiO₂, petroleum ether:dichloromethane). The product was recrystallized from CH₂Cl₂:*n*-hexane (1:1).

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 3. All C-bound H atoms were placed in calculated positions, and refined as riding on their carrier atoms, and with C–H bond lengths fixed at 0.93 (aromatic CH), 0.96 (methyl CH₃), 0.97 (methylene CH₂), or 0.98 Å (methine CH). For (I), the hydroxyl H atom, H2, was first found in a difference map. Its position was fixed in the last least-squares cycles, with O2–H2 = 0.91 Å. For all H atoms, the isotropic displacement parameters were calculated as $U_{\text{iso}}(\text{H}) = xU_{\text{eq}}(\text{carrier atom})$, where $x = 1.5$ for methyl and

hydroxyl H atoms, and $x = 1.2$ otherwise. The absolute configuration for chiral centers C7 in (I) and (II) was assumed from the chirality of starting materials used for the synthesis (see previous section). In the case of (II), which contains one site producing anomalous scattering, the expected enantiomer was confirmed by the refinement of the Flack parameter (Parsons *et al.*, 2013).

Acknowledgements

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supporting information

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Crystal structures of two chiral piperidine derivatives: 1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidin-4-one and 8-[(1*S*)-1-phenylethyl]-1,4-dioxo-8-azaspiro-[4.5]decane-7-thione

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Computing details

For both compounds, data collection: *XSCANS* (Fait, 1996); cell refinement: *XSCANS* (Fait, 1996); data reduction: *XSCANS* (Fait, 1996); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXL2014* (Sheldrick, 2015).

(I) 1-[(1*R*)-2-Hydroxy-1-phenylethyl]piperidin-4-one

Crystal data

C₁₃H₁₇NO₂
M_r = 219.27
 Monoclinic, *P*2₁
a = 9.7590 (11) Å
b = 6.8952 (10) Å
c = 9.7980 (14) Å
 β = 114.348 (9)°
V = 600.67 (15) Å³
Z = 2

F(000) = 236
D_x = 1.212 Mg m⁻³
 Mo *K*α radiation, λ = 0.71073 Å
 Cell parameters from 53 reflections
 θ = 3.7–11.1°
 μ = 0.08 mm⁻¹
T = 296 K
 Plate, pale yellow
 0.60 × 0.17 × 0.12 mm

Data collection

Bruker P4
 diffractometer
 Radiation source: fine-focus sealed tube
 Graphite monochromator
 2 θ / ω scans
 2700 measured reflections
 1341 independent reflections
 1050 reflections with *I* > 2 σ (*I*)

*R*_{int} = 0.021
 θ_{\max} = 25.0°, θ_{\min} = 2.3°
h = -11→4
k = -1→8
l = -10→11
 3 standard reflections every 97 reflections
 intensity decay: 0.5%

Refinement

Refinement on *F*²
 Least-squares matrix: full
R [*F*² > 2 σ (*F*²)] = 0.036
wR(*F*²) = 0.083
S = 1.04
 1341 reflections
 146 parameters
 1 restraint

0 constraints
 Primary atom site location: structure-invariant
 direct methods
 Secondary atom site location: difference Fourier
 map
 Hydrogen site location: inferred from
 neighbouring sites
 H-atom parameters constrained

$$w = 1/[\sigma^2(F_o^2) + (0.0372P)^2 + 0.0246P]$$

$$\text{where } P = (F_o^2 + 2F_c^2)/3$$

$$(\Delta/\sigma)_{\max} < 0.001$$

$$\Delta\rho_{\max} = 0.11 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.11 \text{ e } \text{\AA}^{-3}$$

Extinction correction: *SHELXL2014* (Sheldrick, 2015), $F_c^* = kFc[1 + 0.001x Fc^2 \lambda^3 / \sin(2\theta)]^{-1/4}$

Extinction coefficient: 0.040 (6)

Absolute structure: Assigned from the synthesis

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
N1	0.8276 (2)	0.3211 (3)	0.1078 (2)	0.0427 (5)
O1	0.9225 (3)	0.7423 (5)	0.4197 (3)	0.1214 (11)
O2	0.7952 (2)	-0.0767 (3)	0.0760 (3)	0.0797 (7)
H2	0.8389	0.0052	0.1543	0.120*
C2	0.9480 (3)	0.4619 (4)	0.1324 (3)	0.0502 (7)
H2B	0.9068	0.5750	0.0700	0.060*
H2C	1.0229	0.4047	0.1036	0.060*
C3	1.0222 (3)	0.5237 (5)	0.2969 (3)	0.0629 (9)
H3A	1.0773	0.4150	0.3575	0.075*
H3B	1.0934	0.6273	0.3082	0.075*
C4	0.9084 (4)	0.5914 (6)	0.3506 (3)	0.0708 (10)
C5	0.7746 (3)	0.4646 (5)	0.3102 (3)	0.0613 (9)
H5A	0.6983	0.5313	0.3318	0.074*
H5B	0.8025	0.3476	0.3705	0.074*
C6	0.7102 (3)	0.4101 (4)	0.1448 (2)	0.0491 (7)
H6A	0.6277	0.3196	0.1226	0.059*
H6B	0.6716	0.5252	0.0840	0.059*
C7	0.7704 (3)	0.2371 (4)	-0.0447 (3)	0.0461 (7)
H7A	0.8596	0.2074	-0.0631	0.055*
C8	0.6978 (3)	0.0421 (4)	-0.0420 (3)	0.0626 (8)
H8A	0.6054	0.0634	-0.0296	0.075*
H8B	0.6726	-0.0237	-0.1368	0.075*
C9	0.6741 (3)	0.3692 (4)	-0.1714 (2)	0.0460 (7)
C10	0.7397 (3)	0.4820 (5)	-0.2455 (3)	0.0570 (8)
H10A	0.8428	0.4733	-0.2180	0.068*
C11	0.6544 (4)	0.6079 (6)	-0.3602 (3)	0.0737 (9)
H11A	0.7010	0.6837	-0.4072	0.088*
C12	0.5013 (4)	0.6203 (6)	-0.4042 (3)	0.0786 (10)
H12A	0.4440	0.7028	-0.4819	0.094*
C13	0.4338 (4)	0.5101 (5)	-0.3326 (3)	0.0684 (9)
H13A	0.3304	0.5181	-0.3620	0.082*
C14	0.5188 (3)	0.3872 (4)	-0.2169 (3)	0.0541 (7)
H14A	0.4716	0.3151	-0.1684	0.065*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0361 (11)	0.0413 (12)	0.0519 (12)	0.0012 (11)	0.0192 (9)	0.0002 (11)
O1	0.130 (2)	0.119 (2)	0.104 (2)	-0.022 (2)	0.0365 (16)	-0.062 (2)
O2	0.0924 (15)	0.0412 (12)	0.1027 (14)	0.0085 (13)	0.0374 (12)	0.0124 (13)

C2	0.0445 (14)	0.0492 (17)	0.0558 (14)	-0.0064 (15)	0.0194 (11)	0.0027 (14)
C3	0.0533 (16)	0.068 (2)	0.0566 (15)	-0.0138 (18)	0.0114 (13)	0.0026 (17)
C4	0.080 (2)	0.077 (3)	0.0418 (14)	0.003 (2)	0.0114 (15)	-0.0097 (18)
C5	0.0580 (16)	0.080 (2)	0.0481 (14)	0.0064 (19)	0.0243 (13)	-0.0025 (17)
C6	0.0442 (13)	0.0563 (18)	0.0487 (13)	0.0012 (16)	0.0210 (11)	-0.0009 (15)
C7	0.0480 (14)	0.0403 (14)	0.0555 (15)	0.0030 (14)	0.0270 (12)	-0.0042 (14)
C8	0.0660 (19)	0.0403 (16)	0.0795 (19)	-0.0022 (16)	0.0281 (16)	-0.0061 (16)
C9	0.0559 (15)	0.0404 (17)	0.0435 (13)	-0.0022 (15)	0.0222 (12)	-0.0068 (14)
C10	0.0677 (17)	0.0555 (18)	0.0520 (15)	-0.0106 (17)	0.0287 (14)	-0.0061 (16)
C11	0.104 (3)	0.061 (2)	0.0584 (17)	-0.011 (2)	0.0357 (18)	0.0015 (19)
C12	0.101 (3)	0.065 (2)	0.0548 (17)	0.008 (2)	0.0177 (19)	0.0020 (19)
C13	0.0633 (18)	0.071 (2)	0.0594 (17)	0.0094 (19)	0.0132 (15)	-0.0004 (18)
C14	0.0546 (15)	0.0540 (19)	0.0515 (14)	-0.0038 (16)	0.0195 (13)	-0.0051 (15)

Geometric parameters (Å, °)

N1—C2	1.466 (3)	C6—H6B	0.9700
N1—C6	1.469 (3)	C7—C9	1.514 (4)
N1—C7	1.481 (3)	C7—C8	1.525 (4)
O1—C4	1.217 (4)	C7—H7A	0.9800
O2—C8	1.416 (3)	C8—H8A	0.9700
O2—H2	0.9051	C8—H8B	0.9700
C2—C3	1.530 (4)	C9—C10	1.387 (4)
C2—H2B	0.9700	C9—C14	1.398 (3)
C2—H2C	0.9700	C10—C11	1.392 (5)
C3—C4	1.487 (5)	C10—H10A	0.9300
C3—H3A	0.9700	C11—C12	1.376 (4)
C3—H3B	0.9700	C11—H11A	0.9300
C4—C5	1.483 (5)	C12—C13	1.373 (5)
C5—C6	1.524 (3)	C12—H12A	0.9300
C5—H5A	0.9700	C13—C14	1.385 (4)
C5—H5B	0.9700	C13—H13A	0.9300
C6—H6A	0.9700	C14—H14A	0.9300
C2—N1—C6	109.7 (2)	N1—C7—C9	116.1 (2)
C2—N1—C7	111.57 (19)	N1—C7—C8	108.1 (2)
C6—N1—C7	113.85 (17)	C9—C7—C8	114.2 (2)
C8—O2—H2	104.7	N1—C7—H7A	105.9
N1—C2—C3	110.9 (2)	C9—C7—H7A	105.9
N1—C2—H2B	109.5	C8—C7—H7A	105.9
C3—C2—H2B	109.5	O2—C8—C7	111.4 (2)
N1—C2—H2C	109.5	O2—C8—H8A	109.4
C3—C2—H2C	109.5	C7—C8—H8A	109.4
H2B—C2—H2C	108.0	O2—C8—H8B	109.4
C4—C3—C2	111.2 (2)	C7—C8—H8B	109.4
C4—C3—H3A	109.4	H8A—C8—H8B	108.0
C2—C3—H3A	109.4	C10—C9—C14	117.2 (2)
C4—C3—H3B	109.4	C10—C9—C7	120.1 (2)

C2—C3—H3B	109.4	C14—C9—C7	122.7 (2)
H3A—C3—H3B	108.0	C9—C10—C11	121.4 (3)
O1—C4—C5	122.6 (3)	C9—C10—H10A	119.3
O1—C4—C3	122.3 (4)	C11—C10—H10A	119.3
C5—C4—C3	115.1 (3)	C12—C11—C10	120.2 (3)
C4—C5—C6	111.1 (2)	C12—C11—H11A	119.9
C4—C5—H5A	109.4	C10—C11—H11A	119.9
C6—C5—H5A	109.4	C13—C12—C11	119.5 (3)
C4—C5—H5B	109.4	C13—C12—H12A	120.2
C6—C5—H5B	109.4	C11—C12—H12A	120.2
H5A—C5—H5B	108.0	C12—C13—C14	120.4 (3)
N1—C6—C5	110.09 (19)	C12—C13—H13A	119.8
N1—C6—H6A	109.6	C14—C13—H13A	119.8
C5—C6—H6A	109.6	C13—C14—C9	121.4 (3)
N1—C6—H6B	109.6	C13—C14—H14A	119.3
C5—C6—H6B	109.6	C9—C14—H14A	119.3
H6A—C6—H6B	108.2		
C6—N1—C2—C3	61.7 (3)	N1—C7—C8—O2	-50.9 (3)
C7—N1—C2—C3	-171.2 (2)	C9—C7—C8—O2	178.2 (2)
N1—C2—C3—C4	-52.6 (4)	N1—C7—C9—C10	91.9 (3)
C2—C3—C4—O1	-131.9 (3)	C8—C7—C9—C10	-141.3 (2)
C2—C3—C4—C5	46.5 (4)	N1—C7—C9—C14	-86.8 (3)
O1—C4—C5—C6	130.5 (3)	C8—C7—C9—C14	40.1 (3)
C3—C4—C5—C6	-47.9 (4)	C14—C9—C10—C11	0.1 (4)
C2—N1—C6—C5	-62.8 (3)	C7—C9—C10—C11	-178.6 (3)
C7—N1—C6—C5	171.4 (2)	C9—C10—C11—C12	-1.1 (5)
C4—C5—C6—N1	55.1 (4)	C10—C11—C12—C13	1.0 (5)
C2—N1—C7—C9	-73.2 (3)	C11—C12—C13—C14	0.0 (5)
C6—N1—C7—C9	51.5 (3)	C12—C13—C14—C9	-1.0 (5)
C2—N1—C7—C8	157.0 (2)	C10—C9—C14—C13	1.0 (4)
C6—N1—C7—C8	-78.3 (3)	C7—C9—C14—C13	179.6 (3)

Hydrogen-bond geometry (Å, °)

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O2—H2...N1	0.91	2.22	2.764 (3)	118
C2—H2B...O2 ⁱ	0.97	2.65	3.460 (4)	142
C3—H3A...O1 ⁱⁱ	0.97	2.49	3.246 (4)	135

Symmetry codes: (i) *x*, *y*+1, *z*; (ii) -*x*+2, *y*-1/2, -*z*+1.**(II) 8-[(1S)-1-Phenylethyl]-1,4-dioxa-8-azaspiro[4.5]decane-7-thione**

Crystal data

C₁₅H₁₉NO₂S*M_r* = 277.37Orthorhombic, *P*2₁2₁2₁*a* = 5.9731 (13) Å*b* = 14.948 (3) Å*c* = 16.127 (3) Å*V* = 1439.9 (5) Å³*Z* = 4

$F(000) = 592$
 $D_x = 1.279 \text{ Mg m}^{-3}$
 Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$
 Cell parameters from 58 reflections
 $\theta = 4.7\text{--}12.5^\circ$

$\mu = 0.22 \text{ mm}^{-1}$
 $T = 296 \text{ K}$
 Irregular, colourless
 $0.60 \times 0.38 \times 0.36 \text{ mm}$

Data collection

Bruker P4
 diffractometer
 Radiation source: fine-focus sealed tube
 Graphite monochromator
 $2\theta/\omega$ scans
 Absorption correction: ψ scan
 (XSCANS; Fait, 1996)
 $T_{\min} = 0.760$, $T_{\max} = 0.922$
 3886 measured reflections

2631 independent reflections
 2007 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.029$
 $\theta_{\max} = 27.5^\circ$, $\theta_{\min} = 1.9^\circ$
 $h = -7 \rightarrow 3$
 $k = -19 \rightarrow 19$
 $l = -20 \rightarrow 20$
 3 standard reflections every 97 reflections
 intensity decay: 1.5%

Refinement

Refinement on F^2
 Least-squares matrix: full
 $R[F^2 > 2\sigma(F^2)] = 0.044$
 $wR(F^2) = 0.120$
 $S = 1.06$
 2631 reflections
 174 parameters
 0 restraints
 0 constraints
 Primary atom site location: structure-invariant
 direct methods
 Secondary atom site location: difference Fourier
 map

Hydrogen site location: inferred from
 neighbouring sites
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0668P)^2 + 0.0631P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.19 \text{ e \AA}^{-3}$
 $\Delta\rho_{\min} = -0.24 \text{ e \AA}^{-3}$
 Extinction correction: SHELXL2014 (Sheldrick,
 2015), $F_c^* = kF_c[1 + 0.001x F_c^2 \lambda^3 / \sin(2\theta)]^{-1/4}$
 Extinction coefficient: 0.014 (4)
 Absolute structure: Flack x determined using
 483 quotients $[(I^-) - (I^+)] / [(I^-) + (I^+)]$ (Parsons *et al.*,
 2013)
 Absolute structure parameter: 0.08 (7)

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
S1	0.90206 (18)	0.38336 (6)	0.64284 (6)	0.0676 (3)
N1	0.5705 (4)	0.49810 (13)	0.61607 (13)	0.0409 (6)
C2	0.7114 (5)	0.46066 (19)	0.66903 (18)	0.0435 (7)
C3	0.6996 (6)	0.4875 (2)	0.75975 (18)	0.0522 (8)
H3A	0.6350	0.4383	0.7909	0.063*
H3B	0.8509	0.4964	0.7800	0.063*
C4	0.5660 (6)	0.57054 (18)	0.77730 (17)	0.0459 (7)
C5	0.3483 (6)	0.5637 (2)	0.73219 (19)	0.0532 (8)
H5A	0.2547	0.6147	0.7456	0.064*
H5B	0.2702	0.5098	0.7490	0.064*
C6	0.3927 (6)	0.5612 (2)	0.63970 (17)	0.0564 (8)
H6A	0.2557	0.5447	0.6113	0.068*
H6B	0.4342	0.6207	0.6213	0.068*
C7	0.5849 (6)	0.47717 (17)	0.52588 (16)	0.0454 (7)
H7A	0.7363	0.4545	0.5156	0.054*
C8	0.4240 (8)	0.40247 (19)	0.5035 (2)	0.0663 (10)

H8A	0.4611	0.3498	0.5346	0.099*
H8B	0.4353	0.3898	0.4453	0.099*
H8C	0.2738	0.4205	0.5164	0.099*
C9	0.5595 (6)	0.56255 (18)	0.47498 (16)	0.0434 (7)
C10	0.3737 (6)	0.5799 (2)	0.42688 (18)	0.0525 (8)
H10A	0.2566	0.5390	0.4250	0.063*
C11	0.3612 (8)	0.6593 (2)	0.38083 (18)	0.0635 (10)
H11A	0.2348	0.6712	0.3490	0.076*
C12	0.5336 (8)	0.7192 (2)	0.3824 (2)	0.0689 (11)
H12A	0.5256	0.7714	0.3512	0.083*
C13	0.7186 (8)	0.7023 (2)	0.4302 (2)	0.0684 (11)
H13A	0.8356	0.7433	0.4319	0.082*
C14	0.7310 (6)	0.6238 (2)	0.4760 (2)	0.0559 (8)
H14A	0.8576	0.6125	0.5079	0.067*
O15	0.6883 (5)	0.64740 (15)	0.75095 (14)	0.0743 (8)
C16	0.6637 (12)	0.7128 (3)	0.8120 (3)	0.120 (2)
H16A	0.5799	0.7632	0.7902	0.144*
H16B	0.8095	0.7341	0.8297	0.144*
C17	0.5447 (8)	0.6734 (2)	0.8821 (2)	0.0666 (11)
H17A	0.6241	0.6845	0.9335	0.080*
H17B	0.3948	0.6979	0.8865	0.080*
O18	0.5371 (4)	0.57972 (13)	0.86428 (12)	0.0553 (6)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0725 (6)	0.0688 (6)	0.0615 (5)	0.0339 (5)	-0.0020 (5)	-0.0005 (4)
N1	0.0465 (14)	0.0369 (11)	0.0393 (11)	0.0038 (12)	0.0012 (12)	0.0018 (10)
C2	0.0438 (16)	0.0412 (14)	0.0456 (15)	0.0002 (14)	-0.0005 (14)	0.0061 (12)
C3	0.0563 (19)	0.0588 (18)	0.0414 (15)	0.0078 (18)	-0.0023 (15)	0.0039 (14)
C4	0.0578 (19)	0.0404 (14)	0.0393 (13)	-0.0059 (16)	0.0102 (15)	0.0043 (12)
C5	0.054 (2)	0.0551 (17)	0.0501 (16)	0.0096 (17)	0.0064 (16)	0.0031 (14)
C6	0.065 (2)	0.0605 (18)	0.0440 (15)	0.0239 (18)	0.0021 (18)	0.0016 (14)
C7	0.0583 (19)	0.0392 (13)	0.0386 (13)	0.0007 (16)	0.0001 (16)	0.0003 (11)
C8	0.093 (3)	0.0462 (17)	0.0593 (18)	-0.013 (2)	-0.008 (2)	0.0002 (13)
C9	0.0552 (19)	0.0385 (13)	0.0365 (12)	0.0012 (15)	0.0025 (14)	-0.0025 (11)
C10	0.059 (2)	0.0548 (16)	0.0431 (14)	-0.0025 (17)	-0.0062 (17)	0.0039 (13)
C11	0.074 (3)	0.071 (2)	0.0461 (16)	0.010 (2)	-0.0115 (18)	0.0122 (16)
C12	0.099 (3)	0.0540 (18)	0.0543 (17)	0.003 (2)	0.008 (2)	0.0160 (16)
C13	0.084 (3)	0.0496 (19)	0.072 (2)	-0.015 (2)	0.003 (2)	0.0105 (16)
C14	0.0551 (19)	0.0547 (18)	0.0580 (18)	-0.0086 (18)	-0.0075 (17)	0.0077 (16)
O15	0.108 (2)	0.0544 (12)	0.0601 (13)	-0.0289 (14)	0.0275 (15)	-0.0022 (11)
C16	0.200 (7)	0.062 (2)	0.097 (3)	-0.060 (4)	0.057 (4)	-0.022 (2)
C17	0.100 (3)	0.0484 (17)	0.0516 (17)	-0.005 (2)	0.006 (2)	-0.0045 (14)
O18	0.0793 (17)	0.0454 (10)	0.0412 (10)	-0.0079 (12)	0.0118 (11)	0.0009 (8)

Geometric parameters (Å, °)

S1—C2	1.677 (3)	C8—H8B	0.9600
N1—C2	1.323 (4)	C8—H8C	0.9600
N1—C6	1.471 (4)	C9—C14	1.375 (5)
N1—C7	1.490 (3)	C9—C10	1.379 (5)
C2—C3	1.519 (4)	C10—C11	1.402 (4)
C3—C4	1.503 (4)	C10—H10A	0.9300
C3—H3A	0.9700	C11—C12	1.365 (6)
C3—H3B	0.9700	C11—H11A	0.9300
C4—O18	1.420 (3)	C12—C13	1.370 (6)
C4—O15	1.426 (3)	C12—H12A	0.9300
C4—C5	1.493 (5)	C13—C14	1.388 (5)
C5—C6	1.515 (4)	C13—H13A	0.9300
C5—H5A	0.9700	C14—H14A	0.9300
C5—H5B	0.9700	O15—C16	1.395 (4)
C6—H6A	0.9700	C16—C17	1.459 (5)
C6—H6B	0.9700	C16—H16A	0.9700
C7—C8	1.517 (4)	C16—H16B	0.9700
C7—C9	1.525 (4)	C17—O18	1.430 (3)
C7—H7A	0.9800	C17—H17A	0.9700
C8—H8A	0.9600	C17—H17B	0.9700
C2—N1—C6	124.3 (2)	C7—C8—H8B	109.5
C2—N1—C7	120.3 (3)	H8A—C8—H8B	109.5
C6—N1—C7	115.4 (2)	C7—C8—H8C	109.5
N1—C2—C3	118.7 (3)	H8A—C8—H8C	109.5
N1—C2—S1	124.1 (2)	H8B—C8—H8C	109.5
C3—C2—S1	117.1 (2)	C14—C9—C10	118.8 (3)
C4—C3—C2	115.1 (2)	C14—C9—C7	118.5 (3)
C4—C3—H3A	108.5	C10—C9—C7	122.7 (3)
C2—C3—H3A	108.5	C9—C10—C11	120.0 (3)
C4—C3—H3B	108.5	C9—C10—H10A	120.0
C2—C3—H3B	108.5	C11—C10—H10A	120.0
H3A—C3—H3B	107.5	C12—C11—C10	120.3 (4)
O18—C4—O15	106.2 (2)	C12—C11—H11A	119.8
O18—C4—C5	112.5 (3)	C10—C11—H11A	119.8
O15—C4—C5	110.8 (3)	C11—C12—C13	119.9 (3)
O18—C4—C3	109.3 (2)	C11—C12—H12A	120.0
O15—C4—C3	109.7 (3)	C13—C12—H12A	120.0
C5—C4—C3	108.3 (3)	C12—C13—C14	119.8 (4)
C4—C5—C6	109.2 (3)	C12—C13—H13A	120.1
C4—C5—H5A	109.8	C14—C13—H13A	120.1
C6—C5—H5A	109.8	C9—C14—C13	121.1 (3)
C4—C5—H5B	109.8	C9—C14—H14A	119.4
C6—C5—H5B	109.8	C13—C14—H14A	119.4
H5A—C5—H5B	108.3	C16—O15—C4	107.5 (3)
N1—C6—C5	113.4 (2)	O15—C16—C17	108.3 (3)

N1—C6—H6A	108.9	O15—C16—H16A	110.0
C5—C6—H6A	108.9	C17—C16—H16A	110.0
N1—C6—H6B	108.9	O15—C16—H16B	110.0
C5—C6—H6B	108.9	C17—C16—H16B	110.0
H6A—C6—H6B	107.7	H16A—C16—H16B	108.4
N1—C7—C8	110.5 (3)	O18—C17—C16	104.8 (3)
N1—C7—C9	110.1 (2)	O18—C17—H17A	110.8
C8—C7—C9	115.2 (3)	C16—C17—H17A	110.8
N1—C7—H7A	106.9	O18—C17—H17B	110.8
C8—C7—H7A	106.9	C16—C17—H17B	110.8
C9—C7—H7A	106.9	H17A—C17—H17B	108.9
C7—C8—H8A	109.5	C4—O18—C17	106.8 (2)
C6—N1—C2—C3	-3.5 (4)	C8—C7—C9—C14	-163.6 (3)
C7—N1—C2—C3	176.7 (3)	N1—C7—C9—C10	-110.5 (3)
C6—N1—C2—S1	175.5 (2)	C8—C7—C9—C10	15.2 (4)
C7—N1—C2—S1	-4.3 (4)	C14—C9—C10—C11	-0.6 (5)
N1—C2—C3—C4	-14.3 (4)	C7—C9—C10—C11	-179.4 (3)
S1—C2—C3—C4	166.7 (2)	C9—C10—C11—C12	0.9 (5)
C2—C3—C4—O18	170.4 (3)	C10—C11—C12—C13	-0.9 (6)
C2—C3—C4—O15	-73.6 (4)	C11—C12—C13—C14	0.8 (6)
C2—C3—C4—C5	47.6 (4)	C10—C9—C14—C13	0.5 (5)
O18—C4—C5—C6	175.7 (2)	C7—C9—C14—C13	179.3 (3)
O15—C4—C5—C6	57.1 (3)	C12—C13—C14—C9	-0.5 (5)
C3—C4—C5—C6	-63.4 (3)	O18—C4—O15—C16	-19.9 (5)
C2—N1—C6—C5	-13.5 (4)	C5—C4—O15—C16	102.5 (4)
C7—N1—C6—C5	166.3 (3)	C3—C4—O15—C16	-137.9 (4)
C4—C5—C6—N1	47.2 (4)	C4—O15—C16—C17	6.2 (6)
C2—N1—C7—C8	94.8 (4)	O15—C16—C17—O18	9.6 (6)
C6—N1—C7—C8	-85.0 (3)	O15—C4—O18—C17	26.1 (4)
C2—N1—C7—C9	-136.8 (3)	C5—C4—O18—C17	-95.3 (3)
C6—N1—C7—C9	43.4 (4)	C3—C4—O18—C17	144.4 (3)
N1—C7—C9—C14	70.7 (4)	C16—C17—O18—C4	-21.9 (5)

Hydrogen-bond geometry (Å, °)

<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
C7—H7A \cdots S1	0.98	2.51	3.019 (3)	112
C16—H16B \cdots S1 ⁱ	0.97	2.85	3.709 (5)	148

Symmetry code: (i) $-x+2, y+1/2, -z+3/2$.