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Uncovering stereochemical relations in a compound with a stereogenic N—O axis: methyl 2-(4-methyl-2-thioxo-2,3-dihydrothiazol-3-yloxy)-propanoate

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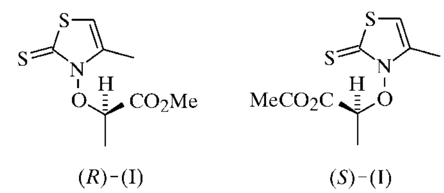
The geometry of racemic methyl 2-(4-methyl-2-thioxo-2,3-dihydrothiazol-3-yloxy)propanoate, $C_8H_{11}NO_3S_2$, (I), is characterized by a distorted heterocyclic five-membered ring and an enantiomorphic *N*-alkoxy substituent, which is inclined at an angle of −68.8° to the thiazolethione plane in (*M*)-(I). The unit cell consists of a 1:1 ratio of *R*,*P*- and *S*,*M*-configured molecules of (I). The combination of a *P* configuration at the N—O axis and an *R* configuration at the asymmetric propanoate C_β atom on one side, and an *S*,*M* configuration on the other side, is considered to originate from steric interactions. The largest substituent at the asymmetric propanoate C_β atom, *i.e.* the methoxycarbonyl group, resides above the methyl substituent; the medium-sized propanoate γ-methyl substituent points in the opposite direction with respect to the N—O bond, whereas the H atom is located above the C═S double bond of the thiazolethione subunit.

Comment

The N—O functionality in *N*-(alkoxy)thiazole-2(3*H*)-thiones constitutes an element of chirality (Fig. 1). The barrier to rotation about this axis is, however, small, thus leading to an almost unhindered topomerization of *N*-alkoxy substituents at room temperature (Hartung, Kneuer, Schwarz *et al.*, 2001). Since *N*-(alkoxy)thiazolethiones have become compounds of significant contemporary interest for investigations of mechanistic and biological aspects of oxyl radical chemistry, for instance, in an early stage of ageing processes or clinical phenomena induced by oxidative stress (Hartung *et al.*, 2002), it was considered essential to uncover the principles of stereocontrol at this axis in the solid state with the aid of a homomorphic ligand. Thus, lactic acid derivatives of *N*-hydroxy-4-methylthiazole-2(3*H*)-thione have been prepared (Hartung, Kneuer, Kopf *et al.*, 2001); both enantiomers of lactic acid occur naturally. Since the synthesis of the title compound starting from methyl (*S*)-lactate provided material that failed to crystallize, racemic methyl 2-(4-methyl-2-thioxo-2,3-dihydrothiazol-3-yloxy)propanoate, (I), was synthesized and investigated by X-ray diffraction.



Compound (I) crystallizes in the triclinic space group $P\overline{1}$. The unit cell contains one molecule each of (*R*,*P*)-(I) and (*S*,*M*)-(I) (Figs. 2 and 3). Ring atoms S2, C6 and O1 are slightly removed from the thiazolethione plane [S2—C2—N3—O1 = 4.0 (2)°, C6—C4—C5—S1 = 176.9 (2)° and O1—N3—C4—C5 = 173.2 (1)°; Table 1]. The heterocyclic core is characterized by a five-membered ring that is distorted because the connectivities between atoms C2 and C5 towards atom S2 [S1—C2 = 1.724 (2) Å and S1—C5 = 1.724 (2) Å] are longer than those between the other endocyclic atoms [N3—C2 = 1.352 (2) Å, N3—C4 = 1.399 (2) Å and C4—C5 = 1.332 (3) Å]. Furthermore, the C2—S1—C5 bond angle [92.50 (8)°] is smaller than 108° (the angle required for a regular five-membered ring). The C2—S2 [1.658 (2) Å] and N3—O8 [1.385 (2) Å] bond lengths are interpreted as C═S and N—O bonds and are in agreement with literature values for related *N*-(alkyl)thiazole-2(3*H*)-thiones (C2—S2; Rochester *et al.*, 1987; Ugozzoli & Andreetti, 1987; Shin & Lim, 1995) and *N*-hydroxy-4-methylthiazole-2(3*H*)-thione (C2—S2 and N3—O8; Bond & Jones, 2000). Three intramolecular contacts were observed for (I) in the solid state [O2···H6*A* = 2.34 (3) Å, S2···H7 = 2.598 (17) Å and C2···H7 = 2.685 (19) Å]. Furthermore, the S2*A*···H6C*B* distance [2.85 (3) Å] between two adjacent molecules in combination with the associated S2*A*—C6*B*—H6C*B* angle [157 (2)°] may be interpreted as a C—H acceptor interaction between C═S and CH_3 groups (Steiner, 1996).

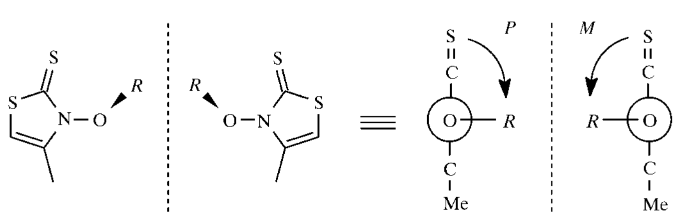


Figure 1
Stereochemical descriptors for an assignment of configurations at the N—O axis in *N*-alkoxy-4-methylthiazole-2(3*H*)-thiones. The descriptor *P* (plus) denotes a clockwise arrangement of substituents of highest priority at a stereogenic axis, whereas *M* (minus) is used for an anticlockwise configuration (*R* = H or alkyl).

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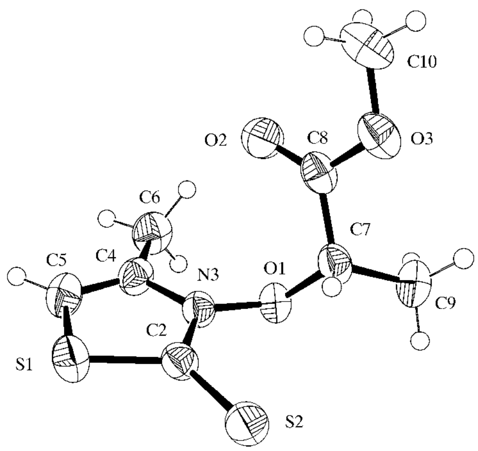

Figure 2
The molecular structure of (I), with the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level.

The substituent on atom O1 is bent from the heterocyclic plane of (I) [C2—N3—O1—C7 = −68.6 (2)° in (*M*)-(I)] for steric and electronic reasons (Hartung, Kneuer, Schwarz *et al.*, 2001). The location of the substituents on atom C7 in (I) may be rationalized by subdividing the heterocyclic plane, as seen in a projection along the N—O axis, into a lower hemisphere (S) and two upper parts (NW/NE) [for (*S*,*M*)-(I) see Fig. 4]. Substituents on atom C7 exhibit the smallest steric repulsion from the 4-methylthiazole-2(3*H*)-thione subunit in (*S*,*M*)-(I) if located in the NE part, which positions the largest substituent (L, *i.e.* the ester functionality) in a synclinal (−*sc*) arrangement [N3—O1—C7—C8 = −70.9 (2)°] and thus in the opposite direction to the heterocyclic plane. If rotated towards the NW area (+*sc* arrangement of L), steric repulsion should arise between (i) the L and C═S groups and (ii) the two CH_3 groups bound to atoms C5 and C7. An increase of conformational energy is also expected if L is located in the southern hemisphere in (*S*,*M*)-(I) [antiperiplanar (*ap*) arrangement of L], since this geometry would incline the C9 methyl group to have a closer proximity to the thiocarbonyl substituent. According to this interpretation, energetically favorable configurations of (I) are restricted to the combinations (*S*,*M*) and (*P*,*R*).

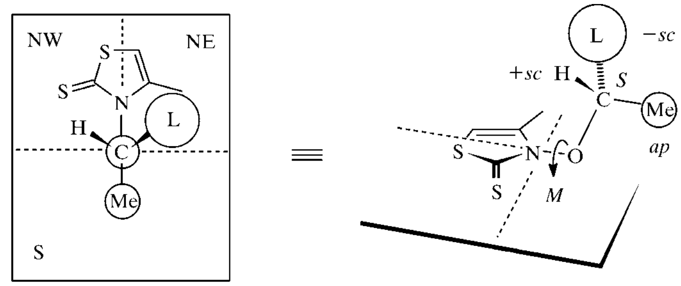

Figure 4
A guideline for predicting a preferred N—O configuration in secondary chiral *N*-(alkoxy)thiazole-2(3*H*)-thiones. The stereochemical descriptors are valid for the following priority of substituents: O1 > L (CO_2CH_3) > Me (CH_3) > H. (+*sc* denotes +synclinal, −*sc* denotes −synclinal and *ap* denotes antiperiplanar.)

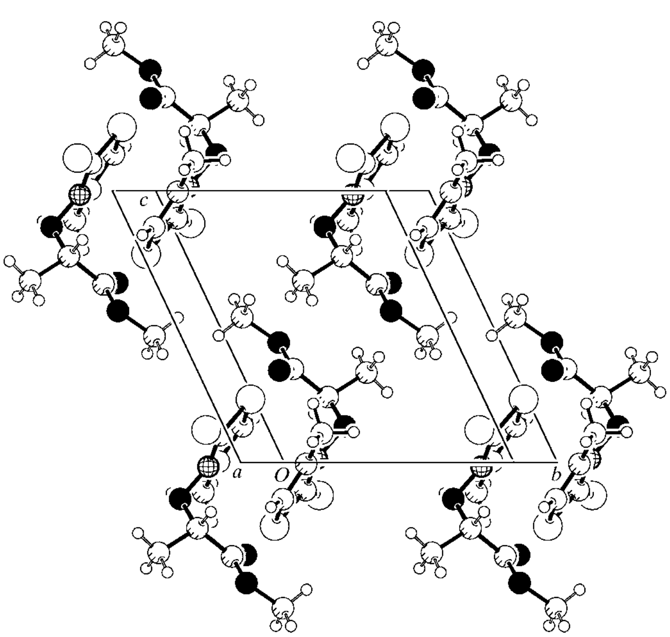

Figure 3
The packing of (*S*,*M*)-(I) and (*R*,*P*)-(I) in the unit cell, viewed along [100].

It is noteworthy that the stereochemical model outlined in Fig. 4 is also applicable for interpreting the observed configuration at the N—O axes in related structures, *i.e.* secondary *N*-(alkoxy)pyridine-2(1*H*)-thiones, *N*-alkoxy-2(1*H*)-pyridones and *N*-alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thiones (Hartung *et al.*, 1996, 1999). As all of these compounds selectively afford oxygen-centered radicals upon photochemical excitation (Hartung *et al.*, 2002), the mnemonic device outlined in Fig. 4 is considered to be useful in order to predict preferred geometries in the vicinity of the reactive N—O bond, thus contibuting to a rationalization of selectivities in future solid-state photochemical experiments.

Experimental

A solution of *N*-hydroxy-4-methylthiazole-2(3*H*)thione (Barton *et al.*, 1986) (783 mg, 5.32 mmol) in anhydrous acetonitrile (11 ml) was treated with K_2CO_3 (2.01 g, 14.5 mmol), NBu_4HSO_4 (180 mg, 532 mmol) and racemic methyl 2-(*p*-toluenesulfonyloxy)propionate (1.25 g, 4.84 mmol) (Hartung *et al.*, 1997). The reaction mixture was stirred for 2 h at 293 K and worked up according to the procedure described by Hartung *et al.* (1999) to furnish (I) (813 mg, 72%). Crystals suitable for X-ray analysis were obtained from a saturated solution of (I) in diethyl ether, which was stored in an atmosphere saturated with *n*-pentane vapor (m.p. 342–344 K). Analysis calculated for $C_8H_{11}NO_3S_2$: C 41.18, H 4.75, N 6.00, S 27.49%; found: C 41.33, H 4.58, N 6.02, S 27.30%. ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.61 (*d*, *J* = 7 Hz, 3H), 2.33 (*q*, *J* = 1 Hz, 3H), 3.72 (*s*, 3H), 6.08 (*q*, 7 Hz, 1H), 6.14 (*q*, *J* = 1 Hz, 1H); ^{13}C NMR (50 MHz,$CDCl_3$): δ_C 13.8, 16.3, 52.3, 77.9, 102.5, 139.4, 180.2.

Crystal data

$C_8H_{11}NO_3S_2$	$Z = 2$
$M_r = 233.30$	$D_x = 1.433$ Mg m^{-3}
Triclinic, $P\overline{1}$	Mo $K\alpha$ radiation
$a = 7.802$ (1) Å	Cell parameters from 25 reflections
$b = 8.622$ (1) Å	$\theta = 2.4$–11.7°
$c = 9.441$ (1) Å	$\mu = 0.47$ mm^{-1}
$\alpha = 113.84$ (1)°	$T = 300$ (2) K
$\beta = 91.18$ (1)°	Prism, colorless
$\gamma = 109.04$ (1)°	0.75 × 0.40 × 0.20 mm
$V = 540.52$ (13) Å^3	

Data collection

Enraf–Nonius CAD-4 diffractometer	$R_{int} = 0.020$
$\omega/2\theta$ scans	$\theta_{max} = 26.0°$
Absorption correction: ψ scan (North *et al.*, 1968)	$h = -9 \rightarrow 3$
$T_{min} = 0.632$, $T_{max} = 0.855$	$k = -10 \rightarrow 10$
3209 measured reflections	$l = -11 \rightarrow 11$
2122 independent reflections	3 standard reflections frequency: 120 min intensity decay: 19.4%
1915 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0632P)^2 + 0.1124P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.037$	$(\Delta/\sigma)_{max} = 0.004$
$wR(F^2) = 0.103$	$\Delta\rho_{max} = 0.30$ e Å^{-3}
$S = 1.10$	$\Delta\rho_{min} = -0.39$ e Å^{-3}
2122 reflections	
147 parameters	
H atoms: see below	

Table 1
Selected geometric parameters (Å, °).

S1—C2	1.724 (2)	N3—C2	1.352 (2)
S1—C5	1.724 (2)	N3—C4	1.399 (2)
S2—C2	1.658 (2)	C4—C5	1.332 (3)
O1—N3	1.385 (2)	C4—C6	1.481 (2)
C2—S1—C5	92.50 (8)	S1—C2—N3	107.0 (1)
N3—O1—C7	113.8 (1)	S2—C2—N3	127.9 (1)
O1—N3—C2	122.2 (1)	N3—C4—C5	110.2 (2)
O1—N3—C4	118.9 (1)	N3—C4—C6	120.9 (2)
C2—N3—C4	117.8 (1)	C5—C4—C6	128.9 (2)
S1—C2—S2	125.1 (1)	S1—C5—C4	112.2 (1)
N3—C4—C5—S1	−1.0 (2)	C6—C4—N3—C2	−173.0 (2)
C6—C4—C5—S1	176.9 (2)	C5—C4—N3—O1	173.2 (1)
S2—C2—N3—O1	4.0 (2)	C6—C4—N3—O1	−4.9 (2)
S1—C2—N3—O1	−174.2 (1)	C2—N3—O1—C7	−68.6 (2)
S2—C2—N3—C4	171.7 (1)	N3—C2—S1—C5	4.7 (1)
S1—C2—N3—C4	−6.5 (2)	S2—C2—S1—C5	−173.6 (1)
C5—C4—N3—C2	5.1 (2)	C4—C5—S1—C2	−2.2 (1)

The H atoms on methyl atoms C9 and C10 were placed in idealized positions, with C—H distances of 0.96 Å. All other H atoms were located from a difference Fourier map and their positions were refined freely, with isotropic displacement parameters.

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1993); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *CAD*-4 *EXPRESS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997) and *PLATON*2002 (Spek, 2002); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1186). Services for accessing these data are described at the back of the journal.

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