

Alan R. Kennedy,<sup>a\*</sup> Abedawn I. Khalaf,<sup>a</sup> Colin J. Suckling<sup>a</sup> and Roger D. Waigh<sup>b</sup><sup>a</sup>Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, Scotland, and <sup>b</sup>Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow G4 0NR, ScotlandCorrespondence e-mail:  
a.r.kennedy@strath.ac.uk

## Key indicators

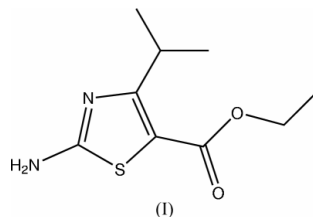
Single-crystal X-ray study  
 $T = 295$  K  
Mean  $\sigma(\text{C}-\text{C}) = 0.003$  Å  
 $R$  factor = 0.038  
 $wR$  factor = 0.109  
Data-to-parameter ratio = 19.4For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.

## Ethyl 2-amino-4-isopropyl-1,3-thiazole-5-carboxylate

Both the molecular and the crystal structures of the title compound,  $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ , are similar to those of its 4-phenyl analogue. The supramolecular network is based upon  $\text{N}-\text{H}\cdots\text{N}$  hydrogen-bonded centrosymmetric dimers linked by  $\text{N}-\text{H}\cdots\text{O}$  contacts.

## Comment

The quest for bioactive compounds led us to the synthesis of a variety of heterocyclic compounds, among them the title compound, (I). There are many compounds in nature incorporating the thiazole moiety in their structure (Ikemoto *et al.*, 2003; Kumar *et al.*, 2002; El-Meligie & El-Awady, 2002), that have useful bioactivities. For example, Leucamide A was first extracted from the Australian marine sponge *Leucetta microraphis* and showed cytotoxicity toward several tumour cell lines (Wang & Nan, 2003). Thiazoles containing an isopropyl group were recently incorporated in the synthesis of minor-groove binders and this has led to a new class of potent antibacterial and antifungal compounds (Khalaf *et al.*, 2004; Antony *et al.*, 2004).



The molecular structure of (I) is unexceptional, with all ring bond lengths and angles (Table 1) close to the mean values obtained from 22 related fragments in the Cambridge Structural Database (Version 5.25, with updates to April 2004; Allen, 2002). Steric repulsion between the adjacent isopropyl and ester groups causes the main deviation from ideal geometry, widening the angles  $\text{C}2-\text{C}3-\text{C}4$  and  $\text{C}3-\text{C}2-\text{C}7$  to  $133.90$  (14) and  $127.20$  (14)°, respectively. However, all geometric parameters are in excellent agreement with those found for the 4-phenyl analogue of (I) (Lynch & McClenaghan, 2000). Indeed, the similarity of these two structures extends to their hydrogen-bonding motifs. Compound (I) mimics its analogue in forming hydrogen-bonded centrosymmetric dimers *via* near-linear  $\text{N}-\text{H}\cdots\text{N}$  contacts (Table 2), the supramolecular network being completed by  $\text{N}-\text{H}\cdots\text{O}$  contacts.

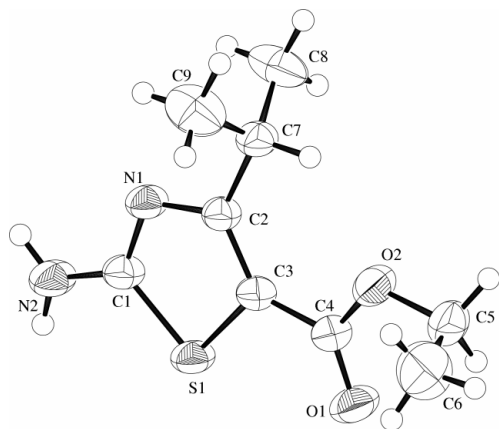
## Experimental

Bromine (10.5 g, 65.3 mmol) was added to a stirred suspension of ethyl 4-methyl-3-oxopentanoate (10.0 g, 63.2 mmol) in water (50 ml)

Received 26 May 2004

Accepted 9 June 2004

Online 19 June 2004



**Figure 1**  
The molecular structure of (I), with 50% probability displacement ellipsoids.

at 273 K over a period of 45 min. After a further 30 min at 273 K, the reaction mixture was extracted with diethyl ether (150 ml). The organic layer was then dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure to give ethyl 2-bromo-4-methyl-3-oxopentanoate as an oil (14.6 g, 61.1 mmol). This oil was added to a solution of thiourea (4.7 g, 61.1 mmol) in ethanol (50 ml). The reaction mixture was kept under reflux for 1 h. Ice-water (250 ml) was added and the mixture was basified with 18 M aqueous ammonia with vigorous stirring. The insoluble material was filtered off, washed with water and dried under reduced pressure at 303 K overnight. This gave the desired product as a pale-yellow crystalline material [6.7 g, 49% yield; m.p. 449–451 K, literature m.p. 449–451 K (Barton *et al.*, 1982)].  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 1.25 (6H, *d*,  $J = 8.0$  Hz), 1.33 (3H, *t*,  $J = 7.1$  Hz), 3.88 (1H, *hept*,  $J = 6.9$  Hz), 4.27 (2H, *q*,  $J = 7.1$  Hz), 5.41 (2H, *s*). IR (KBr): 3393, 3112, 1665, 1531, 1509, 1466, 1307, 1134, 1034  $\text{cm}^{-1}$ .

#### Crystal data

$\text{C}_9\text{H}_{14}\text{N}_2\text{O}_2\text{S}$   
 $M_r = 214.28$   
Monoclinic,  $P2_1/n$   
 $a = 7.8757$  (10) Å  
 $b = 9.1080$  (11) Å  
 $c = 15.8434$  (12) Å  
 $\beta = 100.853$  (9)°  
 $V = 1116.1$  (2) Å<sup>3</sup>  
 $Z = 4$

$D_x = 1.275$  Mg  $\text{m}^{-3}$   
Mo  $K\alpha$  radiation  
Cell parameters from 24 reflections  
 $\theta = 18.7$ – $19.8$ °  
 $\mu = 0.27$   $\text{mm}^{-1}$   
 $T = 295$  (2) K  
Plate, colourless  
 $0.65 \times 0.40 \times 0.18$  mm

#### Data collection

Rigaku AFC-7S diffractometer  
 $\omega/2\theta$  scans  
Absorption correction:  $\psi$  scan  
(North *et al.*, 1968)  
 $T_{\min} = 0.760$ ,  $T_{\max} = 0.950$   
2849 measured reflections  
2674 independent reflections  
2119 reflections with  $I > 2\sigma(I)$

$R_{\text{int}} = 0.023$   
 $\theta_{\max} = 28.0$ °  
 $h = 0 \rightarrow 10$   
 $k = 0 \rightarrow 11$   
 $l = -20 \rightarrow 19$   
3 standard reflections  
every 150 reflections  
intensity decay: none

#### Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.038$   
 $wR(F^2) = 0.109$   
 $S = 1.03$   
2674 reflections  
138 parameters  
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0493P)^2 + 0.2832P]$   
where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\max} < 0.001$   
 $\Delta\rho_{\max} = 0.23$  e Å<sup>-3</sup>  
 $\Delta\rho_{\min} = -0.26$  e Å<sup>-3</sup>

**Table 1**

Selected geometric parameters (Å, °).

S1–C1	1.7350 (15)	N1–C1	1.3226 (18)
S1–C3	1.7468 (15)	N1–C2	1.371 (2)
O1–C4	1.2149 (19)	N2–C1	1.331 (2)
O2–C4	1.3357 (19)	C2–C3	1.3707 (19)
C1–S1–C3	88.68 (7)	C3–C2–C7	127.20 (14)
C1–N1–C2	111.26 (12)	N1–C2–C7	117.60 (12)
N1–C1–N2	123.58 (14)	C2–C3–C4	133.90 (14)
N1–C1–S1	114.78 (12)	C2–C3–S1	110.09 (12)
N2–C1–S1	121.64 (12)	C4–C3–S1	116.01 (11)
C3–C2–N1	115.18 (13)		
C2–N1–C1–S1	−1.08 (18)	N1–C2–C3–S1	0.45 (18)
C3–S1–C1–N1	1.13 (13)	C1–S1–C3–C2	−0.85 (12)
C1–N1–C2–C3	0.4 (2)		

**Table 2**

Hydrogen-bonding geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$\text{N2}-\text{H1}\cdots\text{O1}^{\text{i}}$	0.85 (2)	2.08 (2)	2.902 (2)	163 (2)
$\text{N2}-\text{H2}\cdots\text{N1}^{\text{ii}}$	0.86 (2)	2.15 (2)	3.006 (2)	177 (2)

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

The amine H atoms were located in a difference map and refined isotropically; all other H atoms were constrained to idealized geometry with a riding model, with  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ . C–H distances:  $\text{CH}_3 = 0.96$  Å,  $\text{CH}_2 = 0.97$  Å and  $\text{CH} = 0.98$  Å.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1992); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97*.

#### References

- Allen, F. A. (2002). *Acta Cryst.* **B58**, 380–388.  
Altomare, A., Casciarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.  
Antony, N. G., Fox, K. R., Johnston, B. F., Khalaf, A. I., Mackay, S. P., McGroarty, I. S., Parkinson, J. A., Skellern, G. G., Suckling, C. J. & Waigh, R. D. (2004). *Bioorg. Med. Chem. Lett.* **14**, 1353–1356.  
Barton, A., Breukelman, S. P., Kaye, P. T., Meakins, G. D. & Morgan, D. J. (1982). *J. Chem. Soc. Perkin Trans. 1*, pp. 159–164.  
El-Meligie, S. & El-Awady, R. A. (2002). *J. Heterocycl. Chem.* **39**, 1133–1138.  
Ikemoto, N., Liu, J., Brands, K. M. J., McNamara, J. M. & Reider, P. (2003). *Tetrahedron*, **59**, 1317–1325.  
Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.  
Khalaf, A. I., Waigh, R. D., Drummond, A. J., Pringle, B., McGroarty, I., Skellern, G. G. & Suckling, C. J. (2004). *J. Med. Chem.* **47**, 2133–2156.  
Kumar, R., Rai, D., Ko, S. C. C. & Lown, J. W. (2002). *Heterocycl. Commun.* **8**, 521–530.  
Lynch, D. E. & McClenaghan, I. (2000). *Acta Cryst.* **C56**, e586.  
Molecular Structure Corporation (1988). *MSC/AFC Diffractometer Control Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.  
Molecular Structure Corporation (1992). *TEXSAN*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* **A24**, 351–359.

Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.  
Wang, W. L. & Nan, F. (2003). *J. Org. Chem.* **68**, 1636–1639.

## supporting information

*Acta Cryst.* (2004). E60, o1188–o1190 [https://doi.org/10.1107/S1600536804013984]

## Ethyl 2-amino-4-isopropyl-1,3-thiazole-5-carboxylate

Alan R. Kennedy, Abedawn I. Khalaf, Colin J. Suckling and Roger D. Waigh

(I)

*Crystal data*

$C_9H_{14}N_2O_2S$

$M_r = 214.28$

Monoclinic,  $P2_1/n$

$a = 7.8757$  (10) Å

$b = 9.1080$  (11) Å

$c = 15.8434$  (12) Å

$\beta = 100.853$  (9)°

$V = 1116.1$  (2) Å<sup>3</sup>

$Z = 4$

$F(000) = 456$

$D_x = 1.275$  Mg m<sup>-3</sup>

Mo  $K\alpha$  radiation,  $\lambda = 0.71069$  Å

Cell parameters from 24 reflections

$\theta = 18.7$ – $19.8$ °

$\mu = 0.27$  mm<sup>-1</sup>

$T = 295$  K

Plate, colourless

$0.65 \times 0.40 \times 0.18$  mm

*Data collection*

Rigaku AFC-7S

diffractometer

Radiation source: fine-focus sealed tube

Graphite monochromator

$\omega/2\theta$  scans

Absorption correction:  $\psi$  scan

(North et al., 1968)

$T_{\min} = 0.760$ ,  $T_{\max} = 0.950$

2849 measured reflections

2674 independent reflections

2119 reflections with  $I > 2\sigma(I)$

$R_{\text{int}} = 0.023$

$\theta_{\max} = 28.0$ °,  $\theta_{\min} = 2.6$ °

$h = 0 \rightarrow 10$

$k = 0 \rightarrow 11$

$l = -20 \rightarrow 19$

3 standard reflections every 150 reflections

intensity decay: none

*Refinement*

Refinement on  $F^2$

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.038$

$wR(F^2) = 0.109$

$S = 1.03$

2674 reflections

138 parameters

0 restraints

Primary atom site location: structure-invariant  
direct methods

Secondary atom site location: difference Fourier  
map

Hydrogen site location: inferred from  
neighbouring sites

H atoms treated by a mixture of independent  
and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0493P)^2 + 0.2832P]$

where  $P = (F_o^2 + 2F_c^2)/3$

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

$\Delta\rho_{\max} = 0.23$  e Å<sup>-3</sup>

$\Delta\rho_{\min} = -0.26$  e Å<sup>-3</sup>

*Special details*

**Geometry.** All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

**Refinement.** Refinement of  $F^2$  against ALL reflections. The weighted  $R$ -factor  $wR$  and goodness of fit  $S$  are based on  $F^2$ , conventional  $R$ -factors  $R$  are based on  $F$ , with  $F$  set to zero for negative  $F^2$ . The threshold expression of  $F^2 > \sigma(F^2)$  is used only for calculating  $R$ -factors(gt) *etc.* and is not relevant to the choice of reflections for refinement.  $R$ -factors based on  $F^2$  are statistically about twice as large as those based on  $F$ , and  $R$ -factors based on ALL data will be even larger.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ( $\text{\AA}^2$ )*

	$x$	$y$	$z$	$U_{\text{iso}}^*/U_{\text{eq}}$
S1	0.35390 (5)	0.22977 (5)	0.31256 (2)	0.04375 (14)
O1	0.47481 (17)	-0.03494 (16)	0.23705 (8)	0.0606 (4)
O2	0.70278 (16)	-0.08324 (14)	0.34096 (8)	0.0531 (3)
N1	0.55929 (16)	0.32156 (15)	0.44919 (8)	0.0420 (3)
N2	0.3123 (2)	0.46619 (18)	0.40776 (11)	0.0540 (4)
H1	0.222 (3)	0.483 (2)	0.3702 (13)	0.056 (6)*
H2	0.345 (3)	0.526 (2)	0.4493 (14)	0.061 (6)*
C1	0.41151 (19)	0.35188 (17)	0.39715 (10)	0.0402 (3)
C2	0.63246 (18)	0.19615 (17)	0.42422 (9)	0.0370 (3)
C3	0.54117 (18)	0.12966 (17)	0.35213 (9)	0.0379 (3)
C4	0.5675 (2)	-0.00187 (19)	0.30463 (10)	0.0421 (3)
C5	0.7327 (3)	-0.2197 (2)	0.29860 (13)	0.0588 (5)
H5A	0.8551	-0.2427	0.3109	0.088*
H5B	0.6975	-0.2083	0.2369	0.088*
C6	0.6343 (4)	-0.3418 (3)	0.3283 (2)	0.0880 (8)
H6A	0.6587	-0.3454	0.3900	0.132*
H6B	0.6678	-0.4329	0.3057	0.132*
H6C	0.5128	-0.3261	0.3085	0.132*
C7	0.8035 (2)	0.14796 (19)	0.47675 (10)	0.0446 (4)
H7	0.8388	0.0574	0.4514	0.067*
C8	0.9424 (2)	0.2634 (3)	0.47442 (16)	0.0726 (6)
H8A	0.9522	0.2819	0.4159	0.109*
H8B	1.0511	0.2284	0.5058	0.109*
H8C	0.9115	0.3525	0.5001	0.109*
C9	0.7856 (3)	0.1150 (3)	0.56843 (13)	0.0739 (7)
H9A	0.7498	0.2021	0.5943	0.111*
H9B	0.8949	0.0826	0.6006	0.111*
H9C	0.7008	0.0393	0.5685	0.111*

*Atomic displacement parameters ( $\text{\AA}^2$ )*

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{12}$	$U^{13}$	$U^{23}$
S1	0.0385 (2)	0.0470 (2)	0.0396 (2)	0.00162 (16)	-0.00809 (15)	-0.00464 (16)
O1	0.0576 (7)	0.0646 (8)	0.0504 (7)	0.0054 (6)	-0.0135 (6)	-0.0192 (6)
O2	0.0550 (7)	0.0518 (7)	0.0471 (6)	0.0117 (6)	-0.0041 (5)	-0.0141 (5)
N1	0.0384 (6)	0.0419 (7)	0.0405 (7)	0.0034 (5)	-0.0062 (5)	-0.0049 (5)
N2	0.0453 (8)	0.0508 (9)	0.0565 (9)	0.0124 (6)	-0.0141 (7)	-0.0123 (7)
C1	0.0366 (7)	0.0402 (8)	0.0402 (8)	-0.0005 (6)	-0.0021 (6)	-0.0012 (6)
C2	0.0340 (7)	0.0391 (7)	0.0355 (7)	-0.0006 (6)	0.0006 (5)	-0.0009 (6)
C3	0.0348 (7)	0.0413 (8)	0.0350 (7)	-0.0008 (6)	0.0004 (5)	-0.0003 (6)

C4	0.0401 (7)	0.0461 (8)	0.0386 (7)	-0.0031 (6)	0.0031 (6)	-0.0049 (6)
C5	0.0586 (11)	0.0555 (11)	0.0601 (11)	0.0114 (9)	0.0052 (9)	-0.0196 (9)
C6	0.0876 (17)	0.0597 (14)	0.118 (2)	-0.0006 (13)	0.0237 (16)	-0.0137 (14)
C7	0.0382 (8)	0.0476 (9)	0.0429 (8)	0.0063 (6)	-0.0055 (6)	-0.0062 (7)
C8	0.0383 (9)	0.0989 (17)	0.0746 (14)	-0.0089 (10)	-0.0046 (9)	0.0152 (12)
C9	0.0611 (12)	0.0956 (17)	0.0594 (12)	0.0074 (12)	-0.0033 (9)	0.0329 (12)

*Geometric parameters (Å, °)*

S1—C1	1.7350 (15)	C5—H5A	0.970
S1—C3	1.7468 (15)	C5—H5B	0.970
O1—C4	1.2149 (19)	C6—H6A	0.960
O2—C4	1.3357 (19)	C6—H6B	0.960
O2—C5	1.453 (2)	C6—H6C	0.960
N1—C1	1.3226 (18)	C7—C9	1.516 (3)
N1—C2	1.371 (2)	C7—C8	1.522 (3)
N2—C1	1.331 (2)	C7—H7	0.980
N2—H1	0.85 (2)	C8—H8A	0.960
N2—H2	0.86 (2)	C8—H8B	0.960
C2—C3	1.3707 (19)	C8—H8C	0.960
C2—C7	1.5093 (19)	C9—H9A	0.960
C3—C4	1.450 (2)	C9—H9B	0.960
C5—C6	1.482 (3)	C9—H9C	0.960
C1—S1—C3	88.68 (7)	C5—C6—H6A	109.5
C4—O2—C5	117.46 (13)	C5—C6—H6B	109.5
C1—N1—C2	111.26 (12)	H6A—C6—H6B	109.5
C1—N2—H1	118.9 (14)	C5—C6—H6C	109.5
C1—N2—H2	119.7 (14)	H6A—C6—H6C	109.5
H1—N2—H2	121 (2)	H6B—C6—H6C	109.5
N1—C1—N2	123.58 (14)	C2—C7—C9	110.59 (14)
N1—C1—S1	114.78 (12)	C2—C7—C8	110.90 (15)
N2—C1—S1	121.64 (12)	C9—C7—C8	110.91 (17)
C3—C2—N1	115.18 (13)	C2—C7—H7	108.1
C3—C2—C7	127.20 (14)	C9—C7—H7	108.1
N1—C2—C7	117.60 (12)	C8—C7—H7	108.1
C2—C3—C4	133.90 (14)	C7—C8—H8A	109.5
C2—C3—S1	110.09 (12)	C7—C8—H8B	109.5
C4—C3—S1	116.01 (11)	H8A—C8—H8B	109.5
O1—C4—O2	122.72 (16)	C7—C8—H8C	109.5
O1—C4—C3	122.75 (15)	H8A—C8—H8C	109.5
O2—C4—C3	114.53 (13)	H8B—C8—H8C	109.5
O2—C5—C6	110.80 (18)	C7—C9—H9A	109.5
O2—C5—H5A	109.5	C7—C9—H9B	109.5
C6—C5—H5A	109.5	H9A—C9—H9B	109.5
O2—C5—H5B	109.5	C7—C9—H9C	109.5
C6—C5—H5B	109.5	H9A—C9—H9C	109.5
H5A—C5—H5B	108.1	H9B—C9—H9C	109.5

C2—N1—C1—N2	178.68 (16)	C5—O2—C4—O1	-2.8 (3)
C2—N1—C1—S1	-1.08 (18)	C5—O2—C4—C3	177.58 (15)
C3—S1—C1—N1	1.13 (13)	C2—C3—C4—O1	-174.00 (18)
C3—S1—C1—N2	-178.64 (16)	S1—C3—C4—O1	6.4 (2)
C1—N1—C2—C3	0.4 (2)	C2—C3—C4—O2	5.6 (3)
C1—N1—C2—C7	179.22 (14)	S1—C3—C4—O2	-173.96 (11)
N1—C2—C3—C4	-179.14 (16)	C4—O2—C5—C6	-87.8 (2)
C7—C2—C3—C4	2.2 (3)	C3—C2—C7—C9	-119.71 (19)
N1—C2—C3—S1	0.45 (18)	N1—C2—C7—C9	61.6 (2)
C7—C2—C3—S1	-178.24 (13)	C3—C2—C7—C8	116.8 (2)
C1—S1—C3—C2	-0.85 (12)	N1—C2—C7—C8	-61.8 (2)
C1—S1—C3—C4	178.82 (13)		

*Hydrogen-bond geometry (Å, °)*

<i>D—H...A</i>	<i>D—H</i>	<i>H...A</i>	<i>D...A</i>	<i>D—H...A</i>
N2—H1...O1 <sup>i</sup>	0.85 (2)	2.08 (2)	2.902 (2)	163 (2)
N2—H2...N1 <sup>ii</sup>	0.86 (2)	2.15 (2)	3.006 (2)	177 (2)

Symmetry codes: (i)  $-x+1/2, y+1/2, -z+1/2$ ; (ii)  $-x+1, -y+1, -z+1$ .