

Methyl 2-amino-5-isopropyl-1,3-thiazole-4-carboxylate

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Key indicators

Single-crystal X-ray study
 $T = 295$ K
Mean $\sigma(\text{C}-\text{C}) = 0.003$ Å
 R factor = 0.041
 wR factor = 0.125
Data-to-parameter ratio = 18.6For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.The title compound, $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2\text{S}$, forms a supramolecular network based on $\text{N}-\text{H}\cdots\text{N}$ hydrogen-bonded centrosymmetric dimers that are linked in turn by $\text{N}-\text{H}\cdots\text{O}$ contacts.

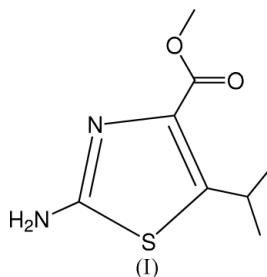
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Comment

To improve the sequence selectivity of the DNA-binding drugs distamycin and netropsin (lexitropsins), a variety of heterocyclic compounds were used in replacing *N*-methyl pyrroles, the main components of the natural products (Khalaf *et al.*, 2000; Khalaf *et al.*, 2002). The title compound, (I), was chosen among others to improve the binding of these compounds to the wall of the minor groove by forming hydrophobic bonds as well as selecting guanine/cytosine over adenine/thiamine base pairs. Thiazoles containing the isopropyl group were recently incorporated in the synthesis of minor groove binders and this process has led to a new class of potent antibacterial and antifungal compounds (Khalaf *et al.*, 2004; Anthony *et al.*, 2004).



The molecular structure of (I) (Fig. 1) 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 $\text{C}2-\text{C}3-\text{C}6$ and $\text{C}3-\text{C}2-\text{C}4$ angles to $130.7(2)$ and $124.07(18)^\circ$, respectively. However, these deviations are smaller than those found in an analogue with the positions of the isopropyl and ester groups reversed [$133.90(14)$ and $127.20(14)^\circ$ in ethyl 2-amino-4-isopropyl-1,3-thiazole-5-carboxylate, (II) (Kennedy *et al.*, 2004)]. This alleviation of steric strain is connected to a rotation of the ester group so that in (I) the smaller $\text{C}=\text{O}$ group contacts the isopropyl group, rather than the OR group as in (II). Detailed comparison of (I) and (II) also shows that (I) has a more exaggerated diene conformation of short and long bonds. This difference is attributed to the effect of removing the ester group from resonance with the NCN fragment. Despite these

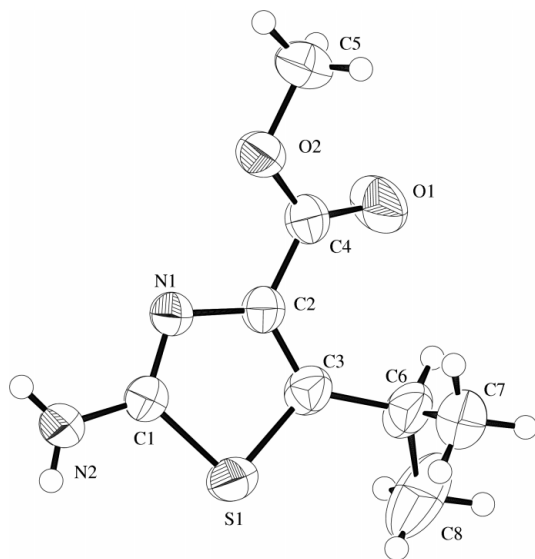


Figure 1
Molecular structure of (I), with 50% probability displacement ellipsoids.

differences, (I) retains a similar supramolecular network to that observed in (II) and other 5-carboxylate species (Lynch & McClenaghan, 2000). This is based on forming hydrogen-bonded centrosymmetric dimers *via* N—H...N contacts (Table 2), the network being completed by N—H...O contacts. In (I), these contacts are longer and thus presumably weaker than in (II).

Experimental

A solution prepared from Na (3.0 g, 0.130 mol) and dry methanol (50 ml) was added over a 45 min period to a solution of methyl dichloroacetate (20.0 g, 0.139 mol) and isobutyraldehyde (14 ml, 0.194 mol) in dry ether (50 ml). The resulting mixture was stirred vigorously at 273 K. After 1 h, diethyl ether (50 ml) and brine were added, and the layers were separated. The ether solution was dried and evaporated to give 16.2 g of material, which was dissolved in dry methanol (60 ml) containing thiourea (8.5 g, 0.112 mol). The solution was boiled under reflux for 4 h, concentrated under reduced pressure and neutralized with 18 M aqueous ammonia. Extraction with dichloromethane gave the title compound as pale-yellow crystals after recrystallization from ethanol–water (16.1 g, 41% yield). M.p. 424–425 K [literature m.p. 423–424 K (Barton *et al.*, 1982)]. ¹H NMR (CDCl₃): δ 1.27 (6H, *d*, *J* = 6.8 Hz), 3.87 (3H, *s*), 4.05 (1H, hept, *J* = 6.8 Hz), 5.15 (2H, *s*). IR (KBr): 3432, 3275, 3136, 2961, 1694, 1627, 1555, 1446, 1338, 1223, 1060, 987 cm⁻¹.

Crystal data

C₈H₁₂N₂O₂S
M_r = 200.26
Monoclinic, *P*2₁/*n*
a = 8.4219 (13) Å
b = 9.9620 (12) Å
c = 12.4307 (15) Å
β = 90.916 (11)°
V = 1042.8 (2) Å³
Z = 4

D_x = 1.276 Mg m⁻³
Mo Kα radiation
Cell parameters from 25 reflections
θ = 13.7–20.1°
μ = 0.28 mm⁻¹
T = 295 (2) K
Plate, colourless
0.55 × 0.55 × 0.05 mm

Data collection

Rigaku AFC-7S diffractometer
ω/2θ scans
Absorption correction: ψ scan
(North *et al.*, 1968)
*T*_{min} = 0.806, *T*_{max} = 0.986
2552 measured reflections
2395 independent reflections
1423 reflections with *I* > 2σ(*I*)

*R*_{int} = 0.040
θ_{max} = 27.5°
h = 0 → 10
k = 0 → 12
l = -16 → 16
3 standard reflections
every 150 reflections
intensity decay: none

Refinement

Refinement on *F*²
R[*F*² > 2σ(*F*²)] = 0.041
wR(*F*²) = 0.125
S = 1.01
2395 reflections
129 parameters
H atoms treated by a mixture of independent and constrained refinement

w = 1/[σ²(*F*_o²) + (0.053*P*)² + 0.0985*P*]
where *P* = (*F*_o² + 2*F*_c²)/3
(Δ/σ)_{max} < 0.001
Δρ_{max} = 0.18 e Å⁻³
Δρ_{min} = -0.17 e Å⁻³

Table 1
Selected geometric parameters (Å, °).

S1—C3	1.739 (2)	N1—C2	1.389 (2)
S1—C1	1.748 (2)	N2—C1	1.342 (3)
O1—C4	1.203 (2)	C2—C3	1.358 (3)
O2—C4	1.322 (3)	C2—C4	1.472 (3)
N1—C1	1.300 (3)		
C3—S1—C1	89.68 (10)	C3—C2—C4	124.07 (18)
C1—N1—C2	110.21 (17)	N1—C2—C4	118.63 (17)
N1—C1—N2	124.6 (2)	C2—C3—C6	130.7 (2)
N1—C1—S1	114.50 (15)	C2—C3—S1	108.41 (15)
N2—C1—S1	120.93 (18)	C6—C3—S1	120.60 (18)
C3—C2—N1	117.19 (18)		

Table 2
Hydrogen-bonding 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>
N2—H1...O1 ⁱ	0.82 (3)	2.21 (3)	2.975 (3)	155 (2)
N2—H2...N1 ⁱⁱ	0.83 (3)	2.20 (3)	3.020 (3)	171 (3)

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

The amine H atoms were located in a difference map and refined freely. All other H atoms were included in the riding-model approximation, with C—H distances of 0.96 (CH₃) and 0.98 Å (CH), and with *U*_{iso}(H) = 1.5*U*_{eq}(C).

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*.

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supporting information

Acta Cryst. (2004). E60, o1510–o1512 [https://doi.org/10.1107/S1600536804019282]

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Crystal data

$C_8H_{12}N_2O_2S$

$M_r = 200.26$

Monoclinic, $P2_1/n$

Hall symbol: $P\ 2_1/n$

$a = 8.4219$ (13) Å

$b = 9.9620$ (12) Å

$c = 12.4307$ (15) Å

$\beta = 90.916$ (11)°

$V = 1042.8$ (2) Å³

$Z = 4$

$F(000) = 424$

$D_x = 1.276$ Mg m⁻³

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

Cell parameters from 25 reflections

$\theta = 13.7$ – 20.1 °

$\mu = 0.28$ mm⁻¹

$T = 295$ K

Plate, colourless

$0.55 \times 0.55 \times 0.05$ mm

Data collection

Rigaku AFC-7S

diffractometer

Radiation source: fine-focus sealed tube

Graphite monochromator

$\omega/2\theta$ scans

Absorption correction: ψ scan

(North et al., 1968)

$T_{\min} = 0.806$, $T_{\max} = 0.986$

2552 measured reflections

2395 independent reflections

1423 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.040$

$\theta_{\max} = 27.5$ °, $\theta_{\min} = 2.6$ °

$h = 0 \rightarrow 10$

$k = 0 \rightarrow 12$

$l = -16 \rightarrow 16$

3 standard reflections every 150 reflections

intensity decay: none

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.041$

$wR(F^2) = 0.125$

$S = 1.01$

2395 reflections

129 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

$w = 1/[\sigma^2(F_o^2) + (0.053P)^2 + 0.0985P]$

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

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

$\Delta\rho_{\max} = 0.18$ e Å⁻³

$\Delta\rho_{\min} = -0.17$ e Å⁻³

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 (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
S1	0.35650 (8)	0.16130 (6)	0.11493 (5)	0.0623 (2)
O1	0.6386 (3)	0.36598 (18)	0.39165 (14)	0.0830 (6)
O2	0.5943 (2)	0.54159 (15)	0.28610 (12)	0.0640 (5)
N1	0.4959 (2)	0.39136 (17)	0.12017 (13)	0.0480 (4)
N2	0.3785 (3)	0.3405 (3)	−0.04668 (16)	0.0706 (6)
H1	0.328 (3)	0.285 (3)	−0.082 (2)	0.061 (7)*
H2	0.409 (3)	0.411 (3)	−0.074 (2)	0.083 (9)*
C1	0.4155 (3)	0.3124 (2)	0.05626 (17)	0.0507 (5)
C2	0.5124 (2)	0.3334 (2)	0.22139 (15)	0.0458 (5)
C3	0.4476 (3)	0.2099 (2)	0.23525 (18)	0.0539 (5)
C4	0.5890 (2)	0.4118 (2)	0.30810 (16)	0.0492 (5)
C5	0.6541 (4)	0.6271 (3)	0.3716 (2)	0.0780 (8)
H5A	0.5852	0.6213	0.4322	0.117*
H5B	0.6578	0.7183	0.3467	0.117*
H5C	0.7590	0.5986	0.3926	0.117*
C6	0.4336 (3)	0.1245 (3)	0.3346 (2)	0.0743 (8)
H6	0.5219	0.1476	0.3835	0.111*
C7	0.2811 (4)	0.1554 (3)	0.3910 (2)	0.0929 (10)
H7A	0.2762	0.2498	0.4064	0.139*
H7B	0.2772	0.1056	0.4570	0.139*
H7C	0.1927	0.1307	0.3455	0.139*
C8	0.4451 (5)	−0.0257 (3)	0.3091 (4)	0.1255 (15)
H8A	0.3580	−0.0513	0.2627	0.188*
H8B	0.4411	−0.0763	0.3747	0.188*
H8C	0.5434	−0.0436	0.2738	0.188*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0743 (4)	0.0500 (3)	0.0620 (4)	−0.0169 (3)	−0.0118 (3)	0.0068 (3)
O1	0.1178 (16)	0.0670 (11)	0.0628 (10)	0.0064 (10)	−0.0404 (10)	0.0097 (9)
O2	0.0920 (12)	0.0486 (9)	0.0509 (9)	−0.0089 (8)	−0.0167 (8)	0.0020 (7)
N1	0.0591 (10)	0.0429 (9)	0.0418 (8)	−0.0042 (8)	−0.0052 (7)	0.0030 (7)
N2	0.1028 (18)	0.0646 (13)	0.0438 (10)	−0.0314 (13)	−0.0160 (11)	0.0056 (10)
C1	0.0606 (13)	0.0454 (11)	0.0462 (11)	−0.0051 (9)	−0.0021 (9)	0.0052 (9)
C2	0.0490 (11)	0.0449 (10)	0.0434 (10)	0.0021 (9)	−0.0030 (9)	0.0058 (9)

C3	0.0530 (12)	0.0521 (11)	0.0564 (12)	-0.0030 (10)	-0.0059 (10)	0.0111 (10)
C4	0.0504 (12)	0.0520 (12)	0.0451 (11)	0.0042 (10)	-0.0037 (9)	0.0047 (9)
C5	0.103 (2)	0.0658 (16)	0.0646 (16)	-0.0156 (14)	-0.0106 (15)	-0.0136 (13)
C6	0.0773 (17)	0.0737 (17)	0.0712 (16)	-0.0209 (13)	-0.0172 (13)	0.0336 (14)
C7	0.126 (3)	0.089 (2)	0.0648 (16)	-0.0303 (19)	0.0139 (17)	0.0062 (16)
C8	0.149 (3)	0.076 (2)	0.153 (4)	0.019 (2)	0.035 (3)	0.064 (2)

Geometric parameters (Å, °)

S1—C3	1.739 (2)	C5—H5A	0.9600
S1—C1	1.748 (2)	C5—H5B	0.9600
O1—C4	1.203 (2)	C5—H5C	0.9600
O2—C4	1.322 (3)	C6—C7	1.505 (4)
O2—C5	1.446 (3)	C6—C8	1.533 (5)
N1—C1	1.300 (3)	C6—H6	0.9800
N1—C2	1.389 (2)	C7—H7A	0.9600
N2—C1	1.342 (3)	C7—H7B	0.9600
N2—H1	0.82 (3)	C7—H7C	0.9600
N2—H2	0.83 (3)	C8—H8A	0.9600
C2—C3	1.358 (3)	C8—H8B	0.9600
C2—C4	1.472 (3)	C8—H8C	0.9600
C3—C6	1.506 (3)		
C3—S1—C1	89.68 (10)	O2—C5—H5C	109.5
C4—O2—C5	115.89 (18)	H5A—C5—H5C	109.5
C1—N1—C2	110.21 (17)	H5B—C5—H5C	109.5
C1—N2—H1	118.6 (18)	C7—C6—C3	110.1 (2)
C1—N2—H2	120 (2)	C7—C6—C8	110.7 (2)
H1—N2—H2	121 (3)	C3—C6—C8	112.0 (3)
N1—C1—N2	124.6 (2)	C7—C6—H6	107.9
N1—C1—S1	114.50 (15)	C3—C6—H6	107.9
N2—C1—S1	120.93 (18)	C8—C6—H6	107.9
C3—C2—N1	117.19 (18)	C6—C7—H7A	109.5
C3—C2—C4	124.07 (18)	C6—C7—H7B	109.5
N1—C2—C4	118.63 (17)	H7A—C7—H7B	109.5
C2—C3—C6	130.7 (2)	C6—C7—H7C	109.5
C2—C3—S1	108.41 (15)	H7A—C7—H7C	109.5
C6—C3—S1	120.60 (18)	H7B—C7—H7C	109.5
O1—C4—O2	122.5 (2)	C6—C8—H8A	109.5
O1—C4—C2	125.0 (2)	C6—C8—H8B	109.5
O2—C4—C2	112.52 (17)	H8A—C8—H8B	109.5
O2—C5—H5A	109.5	C6—C8—H8C	109.5
O2—C5—H5B	109.5	H8A—C8—H8C	109.5
H5A—C5—H5B	109.5	H8B—C8—H8C	109.5
C2—N1—C1—N2	179.4 (2)	C1—S1—C3—C6	175.3 (2)
C2—N1—C1—S1	-0.7 (2)	C5—O2—C4—O1	-3.9 (3)
C3—S1—C1—N1	0.20 (18)	C5—O2—C4—C2	174.3 (2)

C3—S1—C1—N2	-179.9 (2)	C3—C2—C4—O1	19.6 (4)
C1—N1—C2—C3	1.0 (3)	N1—C2—C4—O1	-164.5 (2)
C1—N1—C2—C4	-175.22 (18)	C3—C2—C4—O2	-158.6 (2)
N1—C2—C3—C6	-175.0 (2)	N1—C2—C4—O2	17.4 (3)
C4—C2—C3—C6	1.0 (4)	C2—C3—C6—C7	89.7 (3)
N1—C2—C3—S1	-0.9 (3)	S1—C3—C6—C7	-83.9 (3)
C4—C2—C3—S1	175.16 (16)	C2—C3—C6—C8	-146.6 (3)
C1—S1—C3—C2	0.36 (18)	S1—C3—C6—C8	39.8 (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>
N2—H1...O1 ⁱ	0.82 (3)	2.21 (3)	2.975 (3)	155 (2)
N2—H2...N1 ⁱⁱ	0.83 (3)	2.20 (3)	3.020 (3)	171 (3)

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