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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 σ(C–C) = 0.003 Å
R factor = 0.041
wR factor = 0.125
Data-to-parameter ratio = 18.6

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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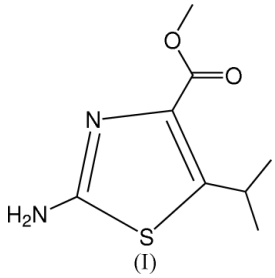
The title compound, $C_8H_{12}N_2O_2S$, forms a supramolecular network based on N—H···N hydrogen-bonded centrosymmetric dimers that are linked in turn by N—H···O contacts.

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).



(I)

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 C2—C3—C6 and C3—C2—C4 angles to 130.7 (2) and 124.07 (18)°, 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)° 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 C=O group contacts the isopropyl group, rather than the O*R* 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

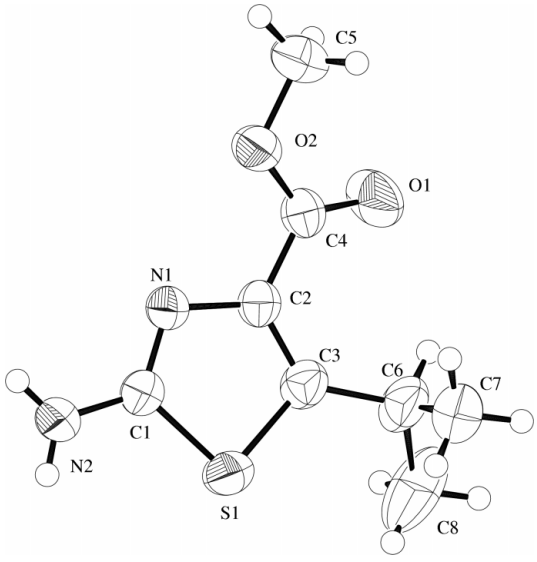


Figure 1
Molecular structure of (I), with 50% probability displacement ellipsoids.

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)]. ^{1}H NMR ($CDCl_3$): 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

$C_8H_{12}N_2O_2S$
M_r = 200.26
Monoclinic, $P2_1/n$
a = 8.4219 (13) Å
b = 9.9620 (12) Å
c = 12.4307 (15) Å
β = 90.916 (11)°
V = 1042.8 (2) Å^3
Z = 4
D_x = 1.276 Mg m^{-3}
Mo $K\alpha$ 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-7*S* diffractometer
$\omega/2\theta$ 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_{int} = 0.040
θ_{max} = 27.5°
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 12$
$l = -16 \rightarrow 16$
3 standard reflections
every 150 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 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
$w = 1/[\sigma^2(F_o^2) + (0.053P)^2 + 0.0985P]$ 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}

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, °).

D—H···A	D—H	H···A	D···A	D—H···A
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 (CH_3) and 0.98 Å (CH), and with U_{iso}(H) = 1.5U_{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: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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