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5-Methyl-3-(5-methylisoxazol-3-yl)cyclohex-2-enone

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
Disorder in main residue
R factor = 0.052
wR factor = 0.143
Data-to-parameter ratio = 13.4

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

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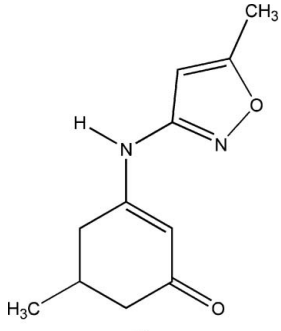
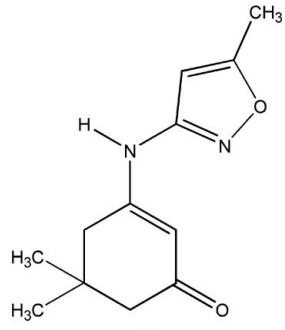
The X-ray crystal structure of the title compound, $C_{11}H_{14}N_2O_2$, has been determined and its structure correlated with its anticonvulsant activity in mice and rats. An intramolecular C—H···N hydrogen bond links the two rings.

Comment

Our research on the anticonvulsant activity of the enaminones has been augmented by X-ray analysis (Kubicki & Codding, 1993; Laws *et al.*, 1998; Foster *et al.*, 1999; Kubicki *et al.*, 2000; Eddington *et al.*, 2002; Anderson *et al.*, 2006; Hanson *et al.*, 2006). Recently, our investigation has led to the evaluation of various isoxazoles from which the title compound, (I), and 3-(5-methylisoxazol-3-yl)-5,5-dimethylcyclohex-2-enone, (II) (Hanson *et al.*, 2006), have emerged (Hanson, 2005).



(I)



(II)

Although structurally similar to (II) (Hanson *et al.*, 2006), (I) was active in the maximal electroshock seizure evaluation (MES) in mice, indicative of protection against tonic–clonic convulsions in humans (1/3 animals protected at 100 mg kg^{-1} at 15 min, and 2/3 protected at 300 mg kg^{-1} at 1 h). Compound (I) also displayed activity in the subcutaneous pentylenetetrazole assessment (scPTZ), indicative of protection against absence seizures. This activity was shown in mice [3/4 animals protected at 300 mg kg^{-1} at 30 min, with toxicity noted at 100 mg kg^{-1} at 30 min (3/8 animals showed neurotoxicity at 100 mg kg^{-1} and 3/4 displayed toxicity at 300 mg kg^{-1} at 15 min)]. In rats, (I) provided an MES ED_{50} (median effective dose) of 66 mg kg^{-1} and a TD_{50} (median toxic dose) of >120 mg kg^{-1}, providing a protective index PI (defined as the ratio of the median toxic dose to the median effective dose) of >1.8. The dimethyl compound, (II) (Hanson *et al.*, 2006), produced a compound that was exclusively MES active and more toxic (3/7 animals protected at 100 mg kg^{-1} at 30 min, 4/5 animals protected at 300 mg kg^{-1} at 30 min and at 4 h; toxicity evaluation: 2/8 toxic at 100 mg kg^{-1} at 30 min, 3/4 toxic at 300 mg kg^{-1} at 30 min and 1/2 toxic at 300 mg kg^{-1} at

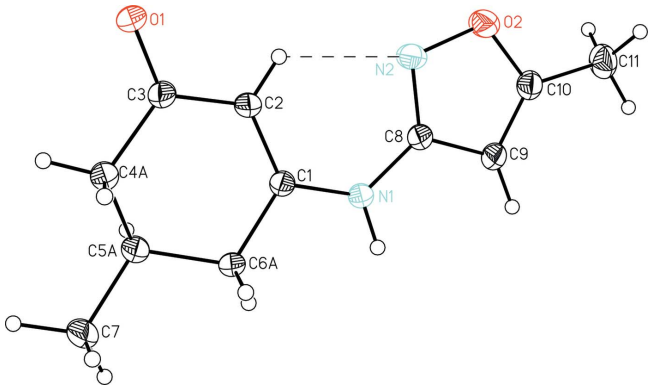


Figure 1
View of the molecule of (I), showing the atom-labelling scheme. Only the major disorder component is shown. Displacement ellipsoids are drawn at the 20% probability level and H atoms are represented by circles of arbitrary size. The dashed line indicates the intramolecular hydrogen bond.

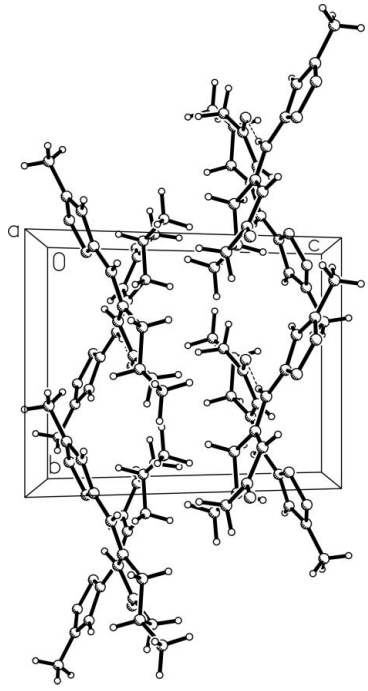


Figure 2
The molecular packing of (I), viewed down the *a* axis. Dashed lines indicate hydrogen bonds.

4 h). Single-crystal X-ray analyses carried out on (I) (this work) and (II) (Hanson *et al.*, 2006) point to the importance of intramolecular hydrogen bonding.

The molecular structure of (I) is shown in Fig. 1. In agreement with our previous studies, hydrogen bonding occurs between the vinyl H atom and the aromatic/heterocyclic ring system (Fig. 2). In (I), this bonding occurs between the H atom on atom C2 and the lone pair on atom N2 on the isoxazole ring. Geometric parameters for this compound are similar to those observed in other related enaminones (Kubicki & Codding, 1993; Laws *et al.*, 1998; Foster *et al.*, 1999; Kubicki *et al.*, 2000; Eddington *et al.*, 2002; Anderson *et al.*, 2006; Hanson *et al.*, 2006).

Experimental

5-Methylcyclohexane-1,3-dione (27 mmol) and 3-amino-5-methylisoxazole (33 mmol) were added to a mixture of absolute ethanol (100 ml) and ethyl acetate (100 ml) and the solution was refluxed and stirred for 6 h. During that time, one-half of the solvent was slowly removed *via* a Dean–Stark trap and, after cooling, replaced with an equal volume of anhydrous diethyl ether. The mixture became cloudy while stirring was continued overnight, whereupon crystals of (I) spontaneously deposited. Recrystallization from ethyl acetate produced colourless crystals (yield 2.81 g, 51%; mp 478–479 K). Spectroscopic analysis: ^{1}H NMR (DMSO-d_6, δ, p.p.m.): 1.0 (3H, *d*, J = 6.4 Hz, CH_3), 1.9–2.4 (5H, *m*, cyclohexene ring), 3.3 (3H, *s*, CH_3 on isoxazole ring), 6.0 (1H, *s*, =CH), 6.3 (1H, *s*, isoxazole CH=), 9.4 (1H, *br s*, NH); ^{13}C NMR (DMSO-d_6, δ, p.p.m.): 11.2, 32.1, 42.0, 42.0, 46.0, 50.0, 53.4, 95,5, 102.9, 105.2, 168.8, 197.4; IR (KBr, ν, cm^{-1}): 3342.8 (NH), 3139.8 (5-methylisoxazole stretch), 1680.2 (C=O).

Crystal data

$C_{11}H_{14}N_2O_2$
M_r = 206.24
Monoclinic, $P2_1/a$
a = 11.1239 (10) Å
b = 9.0159 (7) Å
c = 11.9664 (9) Å
β = 113.970 (7)°
V = 1096.63 (18) Å^3
Z = 4
D_x = 1.249 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 63 reflections
θ = 6.4–27.9°
μ = 0.71 mm^{-1}
T = 293 (2) K
Needle, colourless
0.95 × 0.25 × 0.20 mm

Data collection

Bruker *P*4S diffractometer
$2\theta/\omega$ scans
Absorption correction: part of the refinement model (ΔF) (*SHELXA* in *SHELXTL*; Bruker, 1997)
T_{min} = 0.551, T_{max} = 0.871
2641 measured reflections
2017 independent reflections
1698 reflections with $I > 2\sigma(I)$
R_{int} = 0.028
θ_{max} = 69.1°
$h = -1 \rightarrow 13$
$k = -1 \rightarrow 10$
$l = -14 \rightarrow 13$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.143
S = 1.07
2017 reflections
151 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0609P)^2 + 0.3446P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.018
$\Delta\rho_{max}$ = 0.51 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Extinction correction: *SHELXTL* (Bruker, 1997)
Extinction coefficient: 0.0037 (16)

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1*A*···O1^{i}	0.86	1.99	2.816 (2)	160
C2—H2*A*···N2	0.93	2.22	2.865 (3)	126

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

Atoms C4–C7 with attached H atoms are disordered over two conformations, with occupancies of 0.61 (3) and 0.39 (3). All H atoms were initially located in a difference Fourier map. The methyl H atoms were then constrained to an ideal geometry, with C—H distances of 0.98 Å and U_{iso}(H) = 1.5U_{eq}(C), but each group was allowed to rotate freely about its C—C bond. The position of the amine H atom was idealized, with an N—H distance of 0.86 Å and with U_{iso}(H) = 1.2U_{eq}(N). All other H atoms were positioned

geometrically and constrained to ride on their parent atoms, with C—H distances in the range 0.95–1.00 Å and $U_{iso}(H) = 1.2U_{eq}(C)$.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL* (Bruker, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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