Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

5,5-Dimethyl-3-(5-methylisoxazol-3-yl)-cyclohex-2-enone

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Key indicators

Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.005 Å
R factor = 0.059
wR factor = 0.148
Data-to-parameter ratio = 11.3

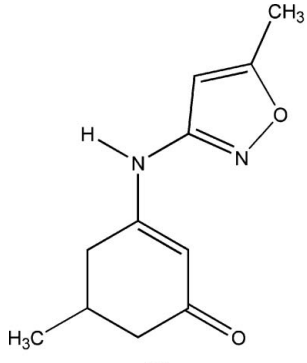
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 29 November 2005
Accepted 6 December 2005
Online 14 December 2005

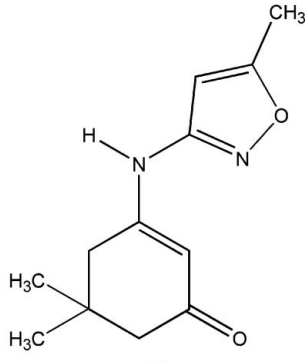
The X-ray crystal structure of the title compound, $C_{12}H_{16}N_2O_2$, has been determined and its structure correlated with its anticonvulsant activity in mice and rats. In each of the two molecules of the asymmetric unit, the two rings are linked by an intramolecular C—H···N hydrogen bond.

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 5-methyl-3-(5-methylisoxazol-3-yl)cyclohex-2-enone, (I) (Hanson *et al.*, 2006), and the title compound, (II), have emerged. Although structurally similar to (I) (Hanson *et al.*, 2006), compound (II) was exclusively MES (maximal electroshock seizure evaluation) 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 4 h). Single-crystal X-ray analyses carried out on (I) (Hanson *et al.*, 2006) and (II) (this work) point to the importance of intramolecular hydrogen bonding.



(I)



(II)

The structure of (II) is shown in Fig. 1. There are two structurally similar molecules, *A* and *B*, in the asymmetric unit. In agreement with our previous studies, hydrogen bonding occurs between the vinyl H atom and the aromatic/heterocyclic ring system (Fig. 2). In (II), this bonding occurs between the H atoms on atoms C2*A* and C2*B* and the lone pairs on atoms N2*A* and N2*B* on the isoxazole rings. 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*

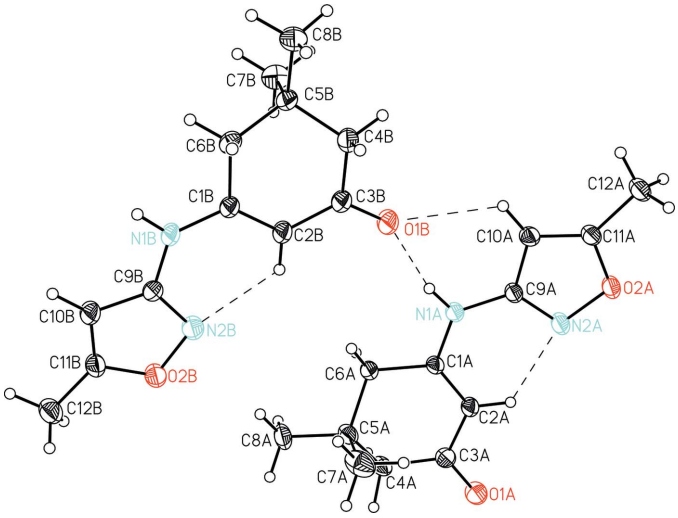


Figure 1
The two independent molecules (suffixes A and B) of the asymmetric unit of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 20% probability level and H atoms are represented by circles of arbitrary size. Dashed lines indicate hydrogen bonds.

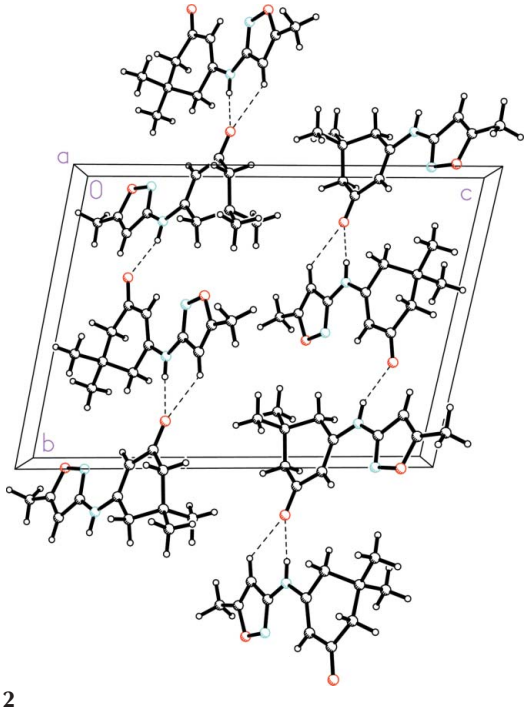


Figure 2
The molecular packing of (II), viewed down the *a* axis. Dashed lines indicate hydrogen bonds.

al., 2002; Anderson *et al.*, 2006; Hanson *et al.*, 2006).

Compared with the packing arrangement in (I) (Hanson *et al.*, 2006), a more complicated structural configuration occurs in the dimethyl analogue, (II). This compound is assembled as a head-to-tail dimer, exhibiting both intramolecular hydrogen bonding (C2*B*···N2*B* and N2*A*···C2*A*) and intermolecular hydrogen bonding with the carbonyl O atom (atom O1*B* and the isoxazole H atom on atom C10*A*, and the H atom on the secondary amine atom N1*A*), producing a pocket between these molecules. Furthermore, this clathrate conformation effectively blocks access to the proposed active site by virtue of the dimethyl substituents at both ends of the pocket. Pauling (1961, 1964*a*,*b*) proposed a molecular theory of general anesthesia, which involved the formation of minute hydrate crystals of the clathrate type that would interfere with nerve impulses. In the structure of (II), a clathrate has, in fact, been shown to occur which, if present in solution, could explain the toxicity of (II).

Experimental

Following the procedure used in the synthesis of 5-methyl-3-(5-methylisoxazol-3-yl)cyclohex-2-enone (Hanson *et al.*, 2006), 5,5-dimethylcyclohexane-1,3-dione (27 mmol) and 3-amino-5-methylisoxazole (33 mmol) produced colourless crystals of (II) (yield 3.1 g, 51%; m.p. 477–480 K). Spectroscopic analysis: ^{1}H NMR (DMSO-d_6, δ, p.p.m.): 1.0 (6H, *s*, gem CH_3), 2.0 (2H, *s*, C_4 CH_2), 2.5 (2H, *s*, C_6 CH_2), 3.3 (3H, *s*, isoxazole CH_3), 6.0 (1H, *s*, ═CH), 6.2 (1H, *s*, isoxazole CH═), 9.4 (1H, *br s*, NH). ^{13}C NMR (DMSO-d_6, δ, p.p.m.): 5.0, 27.3, 42.0, 41.9, 43.4, 45.5, 47.2, 97.1, 102.3, 105.3, 155.3, 197.1; IR (KBr, ν, cm^{-1}): 3340.5 (NH), 3143.7 (5-methylisoxazole stretch), 1678.6 (C═O).

Crystal data

$C_{12}H_{16}N_2O_2$
M_r = 220.27
Triclinic, $P\overline{1}$
a = 6.2647 (4) Å
b = 12.2138 (10) Å
c = 16.459 (2) Å
α = 101.137 (12)°
β = 93.566 (9)°
γ = 100.306 (7)°
V = 1209.6 (2) Å^3
Z = 4
D_x = 1.210 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 36 reflections
θ = 4.2–30.6°
μ = 0.68 mm^{-1}
T = 294 (2) K
Lath, colourless
0.50 × 0.12 × 0.08 mm

Data collection

Bruker *P*4 diffractometer
2θ/ω scans
Absorption correction: none
4192 measured reflections
3342 independent reflections
2017 reflections with $I > 2\sigma(I)$
R_{int} = 0.043
θ_{max} = 58.9°
$h = -6 \rightarrow 1$
$k = -13 \rightarrow 13$
$l = -18 \rightarrow 17$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.059
$wR(F^2)$ = 0.148
S = 1.02
3342 reflections
295 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0588P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N1*A*—H1*AA*···O1*B*	0.86	2.01	2.811 (3)	154
N1*B*—H1*BA*···O1*A*^{i}	0.86	2.05	2.862 (3)	157
C2*A*—H2*AA*···N2*A*	0.93	2.26	2.900 (4)	125
C2*B*—H2*BA*···N2*B*	0.93	2.26	2.898 (5)	125
C10*A*—H10*A*···O1*B*	0.93	2.53	3.148 (4)	124

Symmetry code: (i) $x-1, y-1, z$.

Diffraction data were collected out to d = 0.8 Å. However, data for d = 0.8–0.9 Å were very weak (less than 1σ) and were thus omitted from the refinement. In view of the importance of this compound in comparison and in contrast with that in the previous paper (Hanson *et al.*, 2006), it was felt that it warranted publication in spite of these limitations. 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 U_{iso}(H) = 1.2U_{eq}(N). All other H atoms were placed in geometrically idealized positions 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*.

This research was supported by a grant from the National Institutes of Health (No. 1 R21 GM634940–02), for which KRS is the principal investigator.

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