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Nafimidone monohydrate: an imidazole anticonvulsant

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Key indicators

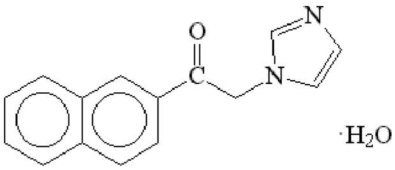
Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.004 Å
R factor = 0.055
wR factor = 0.174
Data-to-parameter ratio = 12.1

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

In the crystal structure of 2-(1*H*-imidazol-1-yl)-1-(2-naphthyl)ethanone monohydrate, $C_{15}H_{12}N_2O\cdot H_2O$, the naphthalene and imidazole rings are essentially planar and the angle between their planes is 77.05 (11)°. The water molecule connects two nafimidone molecules through O—H···N and O—H···O hydrogen bonds [H···N 1.83 (5) and H···O = 2.14 (6) Å], creating centrosymmetric dimer clusters. Weak non-standard hydrogen bonds of the type C—H···O [H···O 2.53–2.60 Å] also contribute to the crystal packing.

Comment

Nafimidone is a member of a group of (arylalkyl)-1*H*-imidazoles, a class of anticonvulsant agents chemically different from phenytoin and carbamazepine but with similar profiles of activity (Walker *et al.*, 1981). Its potent anticonvulsant activity has been documented and structure–activity relationship studies revealed that the pharmacophore in this class of anticonvulsants is the alkylimidazole portion of the molecule, especially when an oxygen functional group (carbonyl, hydroxy, methoxy or acyloxy) is present in the alkylene bridge (Robertson *et al.*, 1986). The present structural study of the compound as the title monohydrate, (I), was undertaken to probe functional and stereochemical determinants responsible for antiepileptic activity, and for stereochemical comparisons with other anticonvulsants.



(I)

The molecular structure of (I) is presented in Fig. 1. Bond distances and angles are consistent with normal values. The naphthalene and imidazole rings are planar and the angle between the planes is 77.05 (11)°. For comparison, the same angle in the oxime derivative is 96.98 (8)° (Kendi *et al.*, 1998). The three atoms of the alkylene bridge are essentially coplanar with the naphthalene moiety, the highest deviation being for atom C17 [0.108 (5) Å]. The sum of the angles around N11 is 359.9°, indicating sp^2 hybridization.

In the crystal structure of (I), the water molecules are hydrogen-bonded to nafimidone molecules, producing centrosymmetric dimer clusters of two nafimidone and two water molecules. Weak non-standard hydrogen bonds of the type C—H···O (Steiner, 1997) and van der Waals interactions also contribute to the crystal packing (Table 1 and Fig. 2). The naphthalene rings are parallel to their symmetry equivalents, with intermolecular distances in the range 3.7–3.8 Å, resulting in distinct hydrophobic areas in the crystal. The distance between the carbonyl O atom and the imidazole atom N13 is 4.194 (5) Å in (I), compared with the carbonyl$\cdots$carbonyl separation of 4.55 Å observed in phenytoin (Camerman & Camerman, 1971) (a small rotation of the imidazole ring about the C16—C17 or N11—C17 bonds would make the distances equal). Molecular superpositions indicate that a folded conformation of nafimidone, rather than the extended one observed in the title crystal structure, is required to approximate the more rigid phenytoin conformation.

Experimental

To obtain crystals of (I) suitable for data collection, nafimidone hydrochloride (Syntex Laboratories Inc., Palo Alto, California, USA) was dissolved in distilled water and the solution allowed to evaporate slowly. Colorless needles of (I) grew in about three weeks.

Crystal data

$C_{15}H_{12}N_2O\cdot H_2O$
$M_r = 254.28$
Monoclinic, $P2_1/c$
$a = 11.597\ (3)$ Å
$b = 14.213\ (3)$ Å
$c = 7.827\ (2)$ Å
$\beta = 90.15\ (2)°$
$V = 1290.1\ (5)$ Å^3
$Z = 4$

$D_x = 1.309$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
$\theta = 28–49°$
$\mu = 0.72$ mm^{-1}
$T = 294\ (2)$ K
Needle, colorless
0.47 × 0.10 × 0.06 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{\min} = 0.911$, $T_{\max} = 0.961$
2310 measured reflections
2197 independent reflections
1328 reflections with $I > 2\sigma(I)$

$R_{\rm int} = 0.008$
$\theta_{\max} = 65.0°$
$h = 0 \rightarrow 13$
$k = -16 \rightarrow 0$
$l = -9 \rightarrow 9$
3 standard reflections every 100 reflections intensity decay: 0.9%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.055$
$wR(F^2) = 0.174$
$S = 0.92$
2197 reflections
181 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0477P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.17$ e Å^{-3}
$\Delta\rho_{\min} = -0.14$ e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0035 (8)

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O19—H191$\cdots$O18	0.78 (6)	2.13 (6)	2.893 (3)	165 (6)
O19—H192$\cdots$N13^{i}	1.02 (5)	1.83 (5)	2.830 (4)	164 (4)
C1—H1$\cdots$O19^{ii}	0.93	2.53	3.458 (4)	175
C15—H15$\cdots$O19^{iii}	0.93	2.59	3.411 (5)	148
C17—H17A$\cdots$O18^{iii}	0.97	2.60	3.491 (4)	153

Symmetry codes: (i) $-x, -y+1, -z+1$; (ii) $x, y, z-1$; (iii) $x, -y+\frac{3}{2}, z-\frac{1}{2}$.

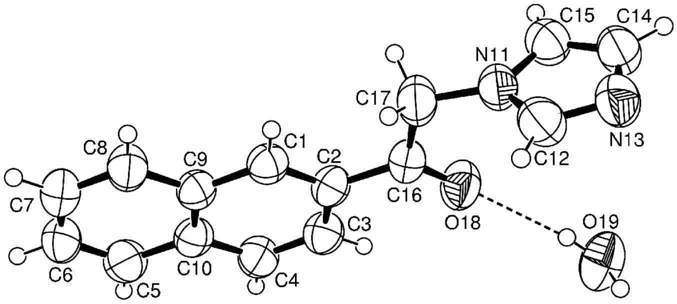


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The dashed line indicates the hydrogen bond.

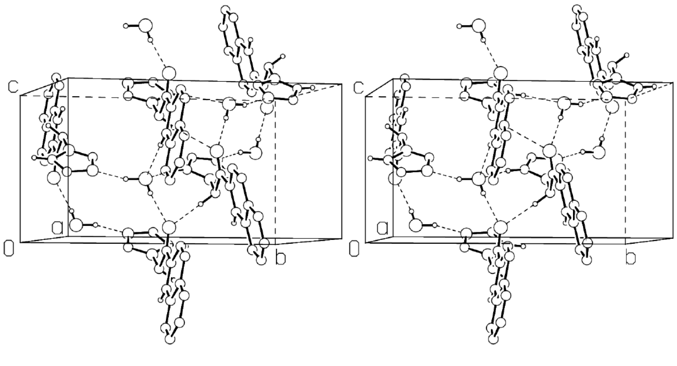


Figure 2
Stereoscopic diagram of the molecular packing and hydrogen-bonding scheme for (I) (hydrogen bonds are shown as dashed lines between atoms). Atoms are drawn as spheres of arbitrary radii.

Water H atoms were found in a difference Fourier map and refined independently with isotropic displacement parameters. The geometric parameters for the water molecule are: O19—H191 = 0.78 (6) Å, O19—H192 = 1.02 (5)Å and H191—O19—H192 = 109 (5)°. All other H atoms were placed in calculated positions, with C—H distances in the range 0.93–0.97 Å, and included in a riding-model approximation, with separate group isotropic displacement parameters refined for both aromatic and methylene H atoms.

Data collection: *Picker Operating Manual* (Picker, 1967); cell refinement: *Picker Operating Manual*; data reduction: *DATRDN* in the *XRAY* system (Stewart, 1978); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELX97*.

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