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Oxcarbazepine: structure and anticonvulsant activity

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Key indicators

Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.003 Å
R factor = 0.037
wR factor = 0.124
Data-to-parameter ratio = 9.4

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

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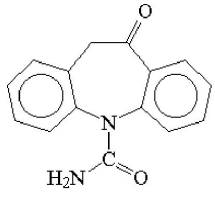
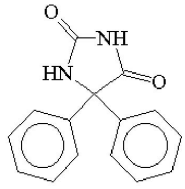
In the crystal structure of the title compound, 10-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide, $C_{15}H_{12}N_2O_2$, the azepine seven-membered ring adopts a classical but slightly twisted boat conformation, forcing the molecule to adopt a butterfly shape. In addition to one normal hydrogen bond, two non-standard weak hydrogen bonds of the C—H···O type also contribute to the molecular arrangement in the crystal structure. Stereochemical comparison with phenytoin indicates that oxcarbazepine may utilize the same mechanism for its anticonvulsant activity.

Comment

The title compound, (I), belongs to a family of iminostilbenes, analogues of carbamazepine, with similar anti-epileptic activity (Walker & Patsalos, 1995). The structural study of (I) was undertaken to probe functional and stereochemical determinants responsible for anti-epileptic activity, and for structural comparison with other anticonvulsants. The molecular structure of oxcarbazepine (ketotegretol) is presented in Fig. 1. Bond distances and angles are consistent with normal values. The two benzene rings are planar, with r.m.s. deviations of 0.005 and 0.004 Å; the planes through the benzene rings intersect at an angle of 62.91 (6)°. Except for the five atoms of the carboxamide group and H111 at C11, all the remaining atoms lie in those two planes.



(I)



(II)

The puckering parameters (Cremer & Pople, 1975) of the azepine ring are q_2 = 0.831 (2), q_3 = 0.271 (2) Å, φ_2 = 209.02 (12), φ_3 = 125.2 (3)°, and the total puckering amplitude Q_T = 0.874 (2) Å, indicating a twist-boat conformation TB (Boeyens, 1978), similar to the crystal structure of hydroxycarbazepine (Lisgarten *et al.*, 1989). As a result of the twist-boat conformation of the azepine ring, the molecule adopts a butterfly shape. A stereoscopic view of the crystal packing is provided in Fig. 2. The hydrogen-bond interactions are summarized in Table 1. When the only normal hydrogen bond is considered (N18—H181···O17), the molecules form infinite one-dimensional ribbons parallel to the *b* axis. However, when non-standard weak hydrogen bonds of the type C—H···O (Steiner, 1997) are also considered, then a three-dimensional hydrogen-bonding system is created, with some van der Waals

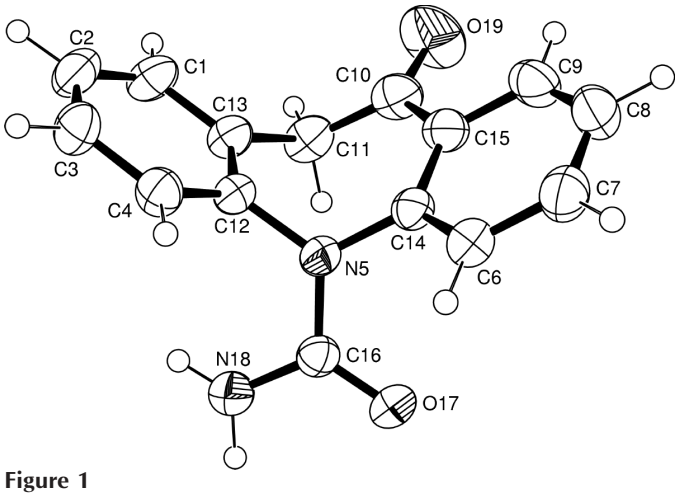


Figure 1
The molecular structure of ketotegretol, showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

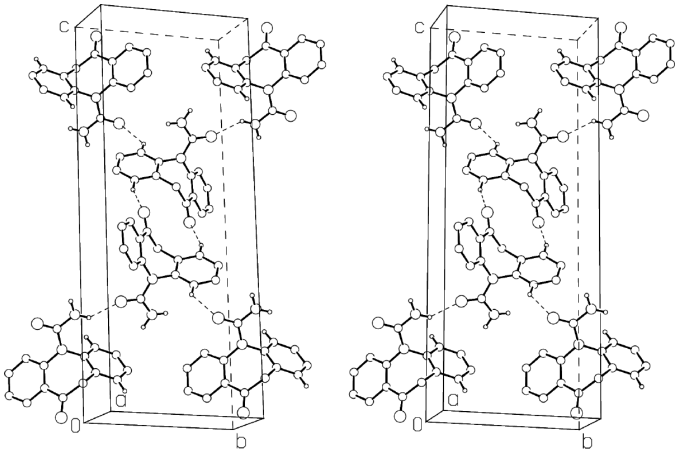


Figure 2
A stereoscopic view of the molecular packing and the hydrogen-bonding scheme. All atoms are drawn as circles of arbitrary radii and hydrogen bonds are shown as dashed lines.

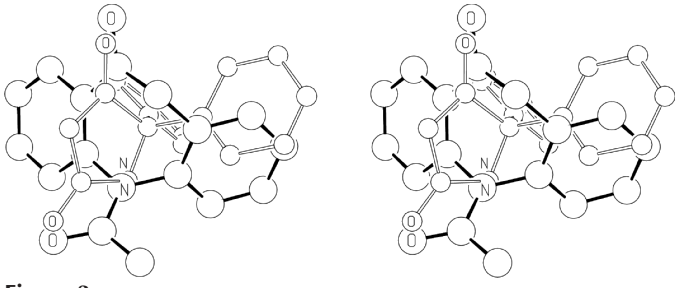


Figure 3
The superposition of oxcarbazepine (large circles, filled bonds) with phenytoin.

interactions. Interestingly, the second H182 atom at N18 of the carboxamide group has no acceptor available within a reasonable distance, and therefore does not contribute to the hydrogen-bonding scheme.

We have compared (Fig. 3) the structure of oxcarbazepine with that of the well known anticonvulsant phenytoin (II) (Camerman & Camerman, 1971) in order to correlate anti-epileptic activity with stereochemical features. The structures were superposed by optimizing the fit of the two O atoms and one N atom in each. No bond rotations or other molecular alterations were performed. The two O atoms in each molecule superpose well, and when they do, a phenyl ring in each molecule occupies a similar area. Since these are the determinants of anticonvulsant activity in phenytoin (Camerman & Camerman, 1981), oxcarbazepine (and its metabolite hydroxycarbazepine) may also utilize a similar mechanism of action.

Experimental

The compound was dissolved in a 1:1 mixture of boiling distilled water and methanol and the solution allowed to stand for slow evaporation. Crystals grew in about 14 d as colorless needles.

Crystal data

$C_{15}H_{12}N_2O_2$
$M_r = 252.27$
Monoclinic, $P2_1/c$
$a = 5.276$ (2) Å
$b = 9.307$ (4) Å
$c = 24.841$ (7) Å
$\beta = 95.64$ (2)°
$V = 1213.9$ (8) Å^3
$Z = 4$
$D_x = 1.380$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
$\theta = 30$–54°
$\mu = 0.76$ mm^{-1}
$T = 294$ (2) K
Needle, colorless
0.49 × 0.15 × 0.11 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.867$, $T_{max} = 0.917$
2072 measured reflections
2072 independent reflections
1761 reflections with $I > 2\sigma(I)$
$\theta_{max} = 65.0°$
$h = 0 \rightarrow 6$
$k = -10 \rightarrow 0$
$l = -29 \rightarrow 28$
3 standard reflections
every 100 reflections
intensity decay: 0.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.124$
$S = 0.81$
2072 reflections
221 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.1065P)^2 + 0.235P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.16$ e Å^{-3}
$\Delta\rho_{min} = -0.15$ e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0115 (12)

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

D—H···A	D—H	H···A	D···A	D—H···A
N18—H181···O17^{i}	0.86 (2)	2.10 (2)	2.800 (2)	137.7 (18)
C1—H1···O19^{ii}	0.96 (2)	2.56 (2)	3.475 (2)	158.4 (18)
C4—H4···O17^{iii}	0.974 (19)	2.587 (18)	3.346 (2)	134.9 (13)

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

All H atoms were located in a difference map and refined independently with isotropic displacement parameters. The range of C—H and N—H distances are 0.94 (2)–1.00 (2) and 0.86 (2)–0.92 (2) Å, respectively.

Data collection: *Picker Software* (Picker, 1967); cell refinement: *Picker Software*; data reduction: *Picker Software*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics:

ORTEP-3 for Windows (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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