organic compounds

An orthorhombic polymorph of 10,11-dihydrocarbamazepine

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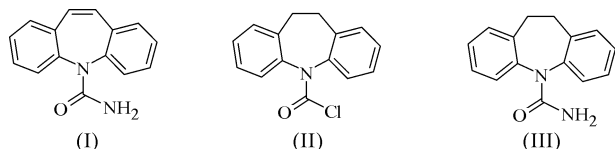The title compound (systematic name: 10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide), $C_{15}H_{14}N_2O$, is shown to crystallize as an orthorhombic polymorph to complement the known monoclinic form. The molecular conformations of both forms are very similar, involving a bent conformation for the seven-membered azepine ring and an overall 'butterfly' shape. The molecules assemble into chains by way of N—H···O bonds and N—H···π interactions in both crystal modifications. The two polymorphs appear to form due to different van der Waals interactions between the layer-like sheets of molecules.

Comment

Carbamazepine, (I), is an anticonvulsant agent with many pharmaceutical and medicinal applications (Birkhimer et al., 1985; Nagaraj et al., 2005). Compound (I) is of considerable structural interest as it serves as a model compound for molecular-crystal polymorphism, with four crystalline forms known (Grzesiak et al., 2003). It has been estimated (Henck et al., 1997) that as many as one third of pharmaceutical solids may display crystal polymorphism which can have a dramatic effect on their physiological properties (Knapman, 2000).

The crystal structures of various derivatives of carbamazepine have been reported (Himes et al., 1981; Lisgarten et al., 1989; Hempel et al., 2005; Nagaraj et al., 2005; Johnston et al., 2005). Recently, the crystal structure of 5-chlorocarbonyl-10,11-dihydro-5H-dibenz[b,f]azepine, (II), was published (Vijay et al., 2005). The structure of the title compound, 10,11-dihydrocarbamazapine, (III), was reported by Bandoli et al. (1992) to be monoclinic, space group $P2_1/c$. We report here a

second, orthorhombic (space group Pbca), modification of (III) (Table 1 and Fig. 1).

The geometric parameters for (III) fall within their expected ranges (Allen et al., 1995). The dihedral angle between the best planes of the two benzene rings (C1–C6 and C9–C14) is 119.03 (4)°, compared with an equivalent value of 118.20 (12)° [calculated with PLATON (Spek, 2003)] in the monoclinic form of (III) (Bandoli et al., 1992). The Bandoli paper cites this dihedral angle as 128°, perhaps as the result of a misprint. The central seven-membered azepine ring (C1/C6–C9/C14/N1) in (I) adopts the so-called bent transition state conformation (Hendrickson, 1967; Bocian & Strauss, 1977), intermediate between the boat and chair forms of a classical cycloheptane ring. In this conformation, five atoms (C1/C6–C8/N1) are almost coplanar [r.m.s. deviation from the best plane = 0.042 Å; maximum deviation = 0.050 (1) Å for atom C7], and atoms C9 and C14 are substantially displaced from the plane by 1.108 (2) and 1.149 (2) Å, respectively. This conformation, commonly seen in 10,11-dihydrocarbamazepines (Vijay et al., 2005), has approximate C_s (mirror) symmetry, with the mirror plane passing through atom C6 and the mid-point of the C9—C14 bond, if atom N1 takes on the identity of a C atom for this analysis. The bond-angle sum of 359.7° about atom N1 in (III) indicates sp^2 hybridization for this atom and the N1/C15/O1/N2 grouping is statistically planar [r.m.s. deviation = 0.0004 Å; maximum deviation = 0.0008 (11) Å for atom C15]. Overall, this azepine conformation results in the molecule of (III) taking on a 'butterfly' shape, as previously described for related carbamazepine derivatives (Vijay et al., 2005).
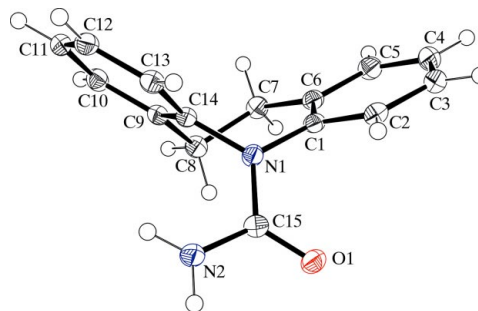

Figure 1
A view of (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitray radii.
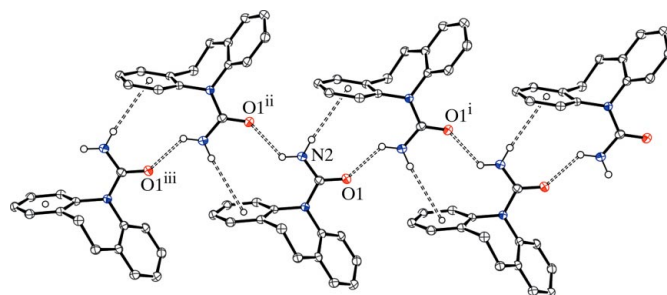

Figure 2
Detail of the structure of (III), showing a chain resulting from N—H···O and N—H···π interactions. All C-bound H atoms have been omitted for clarity. [Symmetry codes are as in Table 2; additionally: (iii) x − 1, y, z.]

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The –NH$_2$ unit in (III) makes only one N—H$\cdots$O hydrogen bond (Table 2). The H$\cdots$O separation of 2.206 (18) Å suggests that it is a relatively weak interaction. This bond links the molecules into one-dimensional strings propagating in the *a* direction. The second H atom points towards the centroid of a nearby C9–C14 benzene ring (Fig. 2) and the resulting almost linear N—H$\cdots\pi$ interaction (Rodham *et al.*, 1993) thus appears to help to stabilize the [100] chains.

Any π–π stacking in (III) must be extremely weak, with the shortest aromatic ring centroid–centroid separation being 4.82 Å (Spek, 2003). A very similar situation occurs for the monoclinic polymorph (the shortest centroid–centroid separation is 4.78 Å). This contrasts strongly with the situation in (II), where no conventional hydrogen bonds are possible and π–π stacking dominates the crystal packing.

The monoclinic form of (III) shows a very similar molecular conformation to the title compound. It possesses the same extended chain structure (propagating in the [010] direction), consolidated by N—H$\cdots$O and N—H$\cdots\pi$ interactions as in the orthorhombic form of (III). It differs in the arrangements of adjacent sheets of chains with respect to the monoclinic [001] and orthorhombic [001] directions. In the monoclinic phase, adjacent pseudo-sheets in the *c* direction all show the same orientation of the carbamoyl groupings (Fig. 3*a*). In the orthorhombic form (Fig. 3*b*), adjacent sheets of carbamoyl groupings alternate in a zigzag pattern. Inversion symmetry

generates the adjacent [001] layer in the monoclinic phase and a glide operation performs the same task in the orthorhombic modification. No unusually short inter-sheet [001] intermolecular contacts were identified in either phase.

The fact that the density of 1.352 Mg m^{-3} of orthorhombic (III) reported here is significantly greater than that of the monoclinic form (1.301 Mg m^{-3}) suggests that the new form of (III) may be a more thermodynamically stable polymorph. Monoclinic (III) was recrystallized from ethanol, resulting in parallelepiped-shaped crystals. Thus, it seems likely (and typical) that the solvent plays an important role in determining the polymorph that results.

Experimental

The sample of (III) was kindly supplied by Jubilant Organosys, Nanjangud, India. The compound was recrystallized from acetonitrile (m.p. 473 K).

Crystal data

C$_{15}$H$_{14}$N$_2$O	Mo $K\alpha$ radiation
$M_r = 238.28$	Cell parameters from 3022
Orthorhombic, $Pbca$	reflections
$a = 9.0592$ (4) Å	$\theta = 2.9$–27.5°
$b = 10.3156$ (5) Å	$\mu = 0.09$ mm^{-1}
$c = 25.0534$ (12) Å	$T = 120$ (2) K
$V = 2341.27$ (19) Å^3	Block, colourless
$Z = 8$	$0.28 \times 0.24 \times 0.18$ mm
$D_x = 1.352$ Mg m^{-3}	

Data collection

Nonius KappaCCD area-detector diffractometer	2680 independent reflections
ω and φ scans	2289 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (*SADABS*; Bruker, 2003)	$R_{int} = 0.042$
$T_{min} = 0.976$, $T_{max} = 0.987$	$\theta_{max} = 27.6°$
16158 measured reflections	$h = -11 \rightarrow 8$
	$k = -13 \rightarrow 12$
	$l = -32 \rightarrow 32$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0384P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.042$	$+ 1.5004P]$
$wR(F^2) = 0.108$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.09$	$(\Delta/\sigma)_{max} < 0.001$
2680 reflections	$\Delta\rho_{max} = 0.24$ e Å^{-3}
169 parameters	$\Delta\rho_{min} = -0.20$ e Å^{-3}
H atoms treated by a mixture of independent and constrained refinement	

Table 1
Selected torsion angles (°).

N1—C1—C6—C7	−4.2 (2)	C8—C9—C14—N1	−2.76 (17)
C1—C6—C7—C8	−4.4 (2)	C6—C1—N1—C14	−52.01 (17)
C6—C7—C8—C9	62.06 (16)	C9—C14—N1—C1	73.18 (16)
C7—C8—C9—C14	−70.51 (15)		

Table 2
Hydrogen-bond geometry (Å, °).

$Cg1$ is the centroid of the C9–C14 ring at (−0.3474, 0.3861, 0.3981).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N2—H1$\cdots Cg1^i$	0.887 (18)	2.86	3.75	173
N2—H2$\cdots$O1^{ii}	0.915 (18)	2.206 (18)	2.8970 (16)	131.7 (14)

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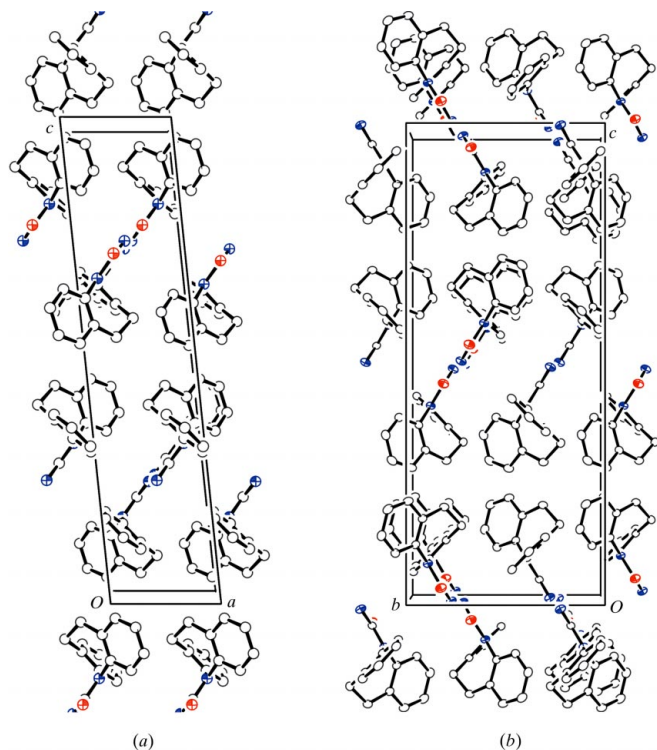

Figure 3
(*a*) Unit-cell packing in the monoclinic form of (III), viewed approximately down [100]. Displacement ellipsoids are drawn at the 50% probability level and all H atoms have been omitted for clarity. (*b*) Unit-cell packing in the orthorhombic form of (III), viewed approximately down [010]. Displacement ellipsoids are drawn at the 30% probability level and all H atoms have been omitted for clarity [redrawn from Bandoli *et al.* (1992)].

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The N-bound H atoms were located in a difference map and their positions were freely refined. The C-bound H atoms were positioned geometrically, with C—H distances in the range 0.95–0.99 Å, and refined as riding. The constraint $U_{iso}(H) = 1.2U_{eq}(carrier)$ was applied in all cases.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997), *SCALEPACK* and *SORTAV* (Blessing, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1995). *International Tables for Crystallography*, Vol. C, edited by A. J. C. Wilson, pp. 685–706. Dordrecht: Kluwer Academic Publishers.

Bandoli, G., Nicolini, M., Onagaro, A., Volpe, G. & Rubello, A. (1992). *J. Chem. Crystallogr.* **22**, 177–183.

Birkhimer, L. J., Curtis, J. L. & Jann, M. W. (1985). *Clin. Pharm.* **4**, 425–434.

Blessing, R. H. (1995). *Acta Cryst.* A**51**, 33–38.

Bocian, D. F. & Strauss, H. L. (1977). *J. Am. Chem. Soc.* **99**, 2876–2882.

Bruker (2003). *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.

Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.

Grzesiak, A. L., Lang, M., Kim, K. & Matzger, A. J. (2003). *J. Pharm. Sci.* **92**, 2260–2271.

Hempel, A., Camerman, N., Camerman, A. & Mastropaolo, D. (2005). *Acta Cryst.* E**61**, o1313–o1315.

Henck, J. O., Griesser, U. J. & Burger, A. (1997). *Pharm. Ind.* **59**, 165–169.

Hendrickson, D. J. (1967). *J. Am. Chem. Soc.* **89**, 7047–7061.

Himes, V. L., Mighell, A. D. & De Camp, W. H. (1981). *Acta Cryst.* B**37**, 2242–2245.

Johnston, A., Florence, A. J. & Kennedy, A. R. (2005). *Acta Cryst.* E**61**, o1777–o1779.

Knapman, K. (2000). *Modern Drug Discov.* **3**, 53–57.

Lisgarten, J. N., Palmer, R. A. & Saldhana, J. W. (1989). *Acta Cryst.* C**45**, 656–658.

Nagaraj, B., Yathirajan, H. S. & Lynch, D. (2005). *Acta Cryst.* E**61**, o1757–o1759.

Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Rodham, D. A., Suzuki, S., Suenram, R. D., Lovas, F. J., Dasgupta, S., Goddard, W. A. III & Blake, G. A. (1993). *Nature (London)*, **362**, 736–737.

Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.

Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Vijay, T., Anilkumar, H. G., Yathirajan, H. S., Narasimhamurthy, T. & Rathore, R. S. (2005). *Acta Cryst.* E**61**, o3718–o3720.