8-Chloro-1-methyl-6-phenyl-4*H*-1,2,4-triazolo[4,3-*a*][1,4]benzodiazepine dihydrate

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Abstract

Alprazolam dihydrate ($C_{17}H_{13}ClN_4 \cdot 2H_2O$) crystallizes in space group $P1$ with $Z = 4$. The structure of the triazolobenzodiazepine moiety is quite similar in the four independent molecules and shows only very slight differences from those in related compounds reported in the literature. The diazepine ring displays an almost perfect boat conformation.

Comment

Alprazolam (8-chloro-1-methyl-6-phenyl-4*H*-1,2,4-triazolo[4,3-*a*][1,4]benzodiazepine) is a benzodiazepine used in the treatment of anxiety and depression (Martindale, 1989). Being more effective at lower doses than traditional benzodiazepines (Dawson *et al.*, 1984) has made it a very interesting therapeutic alternative and prompted a search for polymorphs stable at room temperature. Thus, Laihanen *et al.* (1994) reported having found three different forms, obtained through recrystallization of the same raw starting material from different solvents (2-propanol, 1-butanol and distilled water). The resulting products were characterized using X-ray powder diffraction, thermogravimetric analysis and differential scanning calorimetry and labelled as forms I, II (both anhydrates) and III (a monohydrate).

Although structural information is available on several closely related compounds which share the same core [*viz.* the 1*H* derivative, (2) (Kamiya *et al.*, 1973), the 1-(4-pyridyl)-6-(2-chlorophenyl) derivative, (3) (Kemmish & Hamor, 1989), the 6-(2-chlorophenyl) derivative, (4) (Benedetti *et al.*, 1989) and the 8-trifluoromethyl derivative, (5) (Kemmish & Hamor, 1988)], to our knowledge no comprehensive crystallographic study on any of the stable forms of Alprazolam has ever been reported, with only partial data on a hemihydrobromide ethanol solvate (6) having been published (Hester *et al.*, 1971).

With the aim of obtaining single crystals of Alprazolam suitable for X-ray diffraction, we followed the procedure described by Laihanen *et al.* (1994). However, recrystallization under ambient conditions from the

, solvents reported therein to yield phases I, II and III resulted in three quite different habits of a single new dihydrated form, (1), the structure of which is presented here.
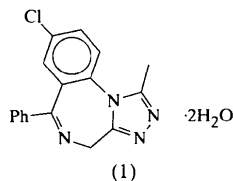

(1)

Fig. 1 shows the unusually complex $P1$ unit cell, with four independent molecules which shall be referred to hereinafter as (1*A*), (1*B*), (1*C*) and (1*D*). Molecules (1*A*) and (1*B*) are related to molecules (1*C*) and (1*D*) by a pseudo centre of symmetry at the origin. The eight hydration water molecules display a roughly similar pseudosymmetric pattern but do so in a much looser sense, thus confirming the non-centrosymmetric character of the structure. The fact of finding $Z \geq 4$ in $P1$ is not uncommon in the literature and a search of the Cambridge Structural Database (CSD; Allen & Kennard, 1993) showed more than 100 such examples, including a few cases with Z values as large as 16, as in some polymorphic forms of cholesterol.

The similarity between the four independent molecules of Alprazolam is apparent from the comparison of equivalent bond distances and angles which show no unusual values. The same conclusion can be obtained from the puckering parameters (Cremer & Pople, 1975) characterizing the diazepine rings: $q_2 = 0.881\,(7),\ 0.870\,(5),\ 0.835\,(5)$ and $0.857\,(3)$ Å, $q_3 = 0.201\,(5),\ 0.189\,(5),\ 0.195\,(5)$ and $0.205\,(4)$ Å, $\theta_2 = 77.2\,(3),\ 77.7\,(3),\ 76.9\,(2)$ and $76.6\,(2)°,\ \varphi_2 = -179.2\,(2),\ -178.4\,(2),\ 0.1\,(3)$ and $0\,(2)°,\ \varphi_3 = -178\,(1),\ 179\,(1),\ 5\,(1)$ and $-1\,(1)°,$ and $Q_T = 0.904\,(7),\ 0.890\,(5),\ 0.857\,(5)$ and $0.882\,(4)$ Å, considering the atomic sequence C21, N22, C8, C9, C14, N15, C20 and where the values cited correspond to molecules (1*A*)–(1*D*), respectively.

The diazepine ring exhibits an almost perfect boat conformation, with the bottom of the boat (C8, C20, N15 and N22) planar and nearly parallel to the plane defined by the prow (C21) and the stern (C19 and C14) of the boat. The maximum deviation from the least-squares plane defined by C8, C20, N15 and C22 is for C20 in all four independent molecules and the deviations range from $0.004\,(4)$ Å for molecule (1*D*) to $0.008\,(4)$ Å for molecule (1*B*). The planes of the boat deviate from being parallel by values that range from $0.1\,(2)$–$1.4\,(2)°$. The high degree of pseudosymmetry of the diazepine ring can be assesed by the very low values of the asymmetry parameters (Nardelli, 1983*a*): $D_S(C21) = 0.007\,(2),\ 0.014\,(2),\ 0.004\,(2)$ and $0.009\,(2)$ for molecules (1*A*)–(1*D*), respectively.

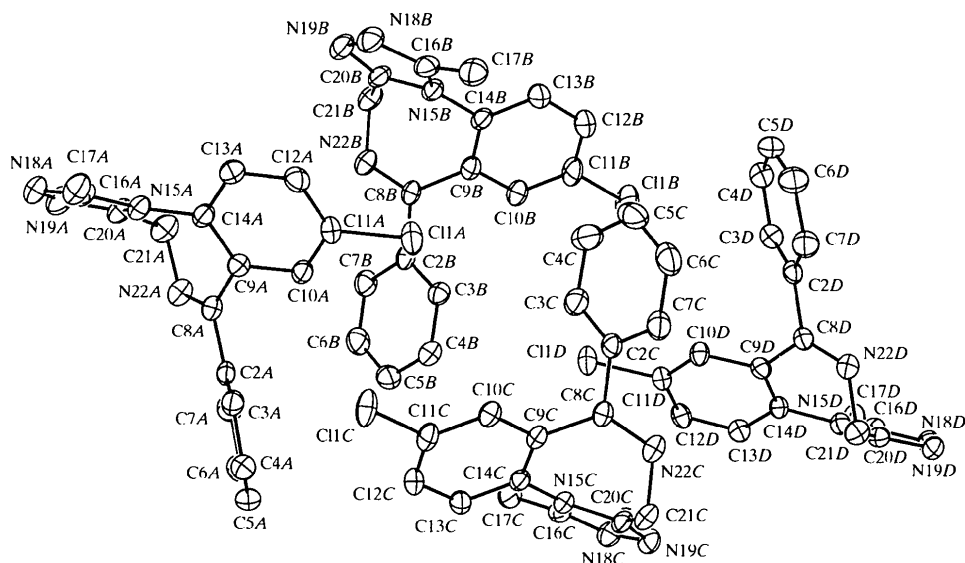The core of three fused rings appears to be particularly rigid, as estimated from the very low r.m.s. devi-

Fig. 1. The molecular diagram showing the four independent molecules in (1) in their pseudocentrosymmetric layout. Displacement ellipsoids are drawn at the 30% probability level and H atoms and hydration water molecules have been omitted for clarity.

ations obtained by the least squares fit of each group with the equivalent values in the remaining molecules: the smallest value corresponds to the fit of (1A) with (1B) [0.021 (3) Å] and the largest one to that of (1C) with (1D) [0.049 (4) Å]. This invariance does not seem to be influenced by the character of the substituents at positions 1, 6 or 8, as very similar values were obtained when the 14-member core of (1A) was fitted to those in the closely related structures (2) to (6) with the following results: (1A)/(2): 0.100 (9), (1A)/(3): 0.103 (8), (1A)/(4): 0.041 (5) and (1A)/(5): 0.033 (5) Å.

The packing is rather complex, with the stabilizing forces being van der Waals interactions and an intricate hydrogen-bonding network involving solvent molecules. Because many of the H atoms bonded to the solvent molecules could not be located in the structure, a thorough description of the hydrogen-bonding network is not possible. Table 1 shows hydrogen bonds involving H atoms which were confidently located. There are, in addition, a number of short $OW \cdots OW$ and $OW \cdots N$ contacts where the possible H atoms involved could not be located and most of these almost certainly participate in the hydrogen-bonding network of the structure (Table 2).

Experimental

The raw material was provided by Laboratorios Gador Argentina and is gratefully acknowledged. Different crystallization batches from distilled water and hydrated 1-butanol and 2-propanol yielded different morphologies of the same dihydrated form, (1). The best crystals were those from 2-propanol, which were accordingly chosen for data collection.

Crystal data

$C_{17}H_{13}ClN_4 \cdot 2H_2O$
$M_r = 344.79$
Triclinic
$P\bar{1}$
$a = 8.5705\,(17)$ Å
$b = 13.657\,(3)$ Å
$c = 14.895\,(3)$ Å
$\alpha = 84.26\,(3)°$
$\beta = 81.95\,(3)°$
$\gamma = 87.11\,(3)°$
$V = 1716.3\,(6)$ Å^3
$Z = 4$
$D_x = 1.334$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 25 reflections
$\theta = 7.5-15°$
$\mu = 0.239$ mm^{-1}
$T = 293\,(2)$ K
Prism
$0.45 \times 0.30 \times 0.20$ mm
Colourless

Data collection

Rigaku AFC-7S diffractometer
$\omega/2\theta$ scans
Absorption correction:
ψ scan (Molecular Structure Corporation, 1988)
$T_{min} = 0.91$, $T_{max} = 0.94$
8670 measured reflections
7898 independent reflections
(plus 328 Friedel-related reflections)

5739 reflections with
$I > 2\sigma(I)$
$R_{int} = 0.036$
$\theta_{max} = 27.52°$
$h = -11 \rightarrow 11$
$k = -17 \rightarrow 0$
$l = -19 \rightarrow 19$
2 standard reflections
every 98 reflections
intensity decay: $<2\%$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.043$
$wR(F^2) = 0.133$
$S = 1.001$

$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.27$ e Å^{-3}
$\Delta\rho_{min} = -0.33$ e Å^{-3}
Extinction correction: none

8226 reflections
914 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.079P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$

Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 0.00 (5)

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

D—H$\cdots$A	D—H	H$\cdots$A	D$\cdots$A	D—H$\cdots$A
O1W—H1WA$\cdots$N22D	0.83 (2)	2.17 (2)	2.985 (5)	168 (2)
O1W—H1WB$\cdots$O8WA	0.84 (4)	1.98 (5)	2.81 (4)	168 (4)
O1W—H1WB$\cdots$O8WB	0.84 (4)	2.05 (5)	2.79 (4)	147 (4)
O2W—H2WA$\cdots$N19D	0.82 (4)	2.12 (4)	2.923 (6)	167 (4)
O2W—H2WB$\cdots$O1W	0.83 (7)	2.02 (6)	2.836 (6)	168 (6)
O3W—H3WA$\cdots$N18B	0.84 (3)	1.98 (2)	2.808 (5)	166 (2)

Table 2. *Contact distances (Å)*

O4W$\cdots$O6W	2.917 (8)	O6W$\cdots$O7WB^{iv}	2.68 (2)
O2W$\cdots$O3W^i	2.781 (6)	O8WA$\cdots$N19B^v	2.90 (3)
O3W$\cdots$O5W^{ii}	2.812 (6)	O8WA$\cdots$N18D^{vi}	2.91 (2)
O4W$\cdots$O5W^{iii}	2.799 (6)	O8WB$\cdots$N19B^v	2.82 (2)
O6W$\cdots$O7WA^{iv}	2.829 (8)	O8WB$\cdots$N18D^{vi}	2.94 (3)

Symmetry codes: (i) $1 + x, 1 + y, z - 1$; (ii) $x - 1, y - 1, z$; (iii) $x - 1, y - 1, 1 + z$; (iv) $1 + x, y, z$; (v) $x, 1 + y, z - 1$; (vi) $x - 1, y, z$.

The conspicuous pseudocentrosymmetry was thoroughly checked by refinement of a model in $P\bar{1}$ but this proved fruitless. Two water molecules (O7W and O8W) out of the eight independent ones in the structure showed disorder and were refined with a split model. The H atoms of these two water molecules could not be located and nor could those for the O6W molecule and three others corresponding to molecules O3W, O4W and O5W, respectively. The remaining H atoms were found in late difference Fourier maps and were refined with geometric constraints and independent isotropic displacement parameters. H atoms attached to C atoms were placed at their calculated sites and allowed to ride on their hosts.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *MSC/AFC Diffractometer Control Software*. Program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997a). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997b). Molecular graphics: *XP* in *SHELXTL/PC* (Sheldrick, 1994). Software used to prepare material for publication: *PARST* (Nardelli, 1983b) and CSD (Allen & Kennard, 1993).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1085). Services for accessing these data are described at the back of the journal.

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5-[(Dimethylamino)methyleneamino]-3-methyl-1-phenylpyrazole

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Abstract

The title substituted pyrazole, $C_{13}H_{16}N_4$, was prepared in order to study some specifics relating to the C—N bond. The dihedral angle between the pyrazole and phenyl planes is 22.75 (8)°. A better coplanarity of the pyrazole and phenyl planes is observed in the title compound in comparison with that of similar systems.

Comment

This work is part of an ongoing study of the synthesis of compounds which are characterized by the presence of a pyrazole ring with different substituents. More than 209 structures of neutral pyrazoles have been analysed (Llamas-Saiz *et al.*, 1994). The structures of these pyrazoles were classified according to the substituent on the N atom at position 1. The structure determination of 5-[(dimethylamino)methyleneamino]-