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Ketazolam

Daniel Vega,[a]* Daniel Fernández[b] and Gustavo Echeverría[c]

[a]Departamento de Física, Comisión Nacional de Energía Atómica, Buenos Aires, Argentina, [b]Escuela de Ciencia y Tecnología, Universidad Nacional de General San Martín, Buenos Aires, Argentina, and [c]LANADI, Departamento de Física, Universidad Nacional de La Plata, La Plata, Argentina
Correspondence e-mail: vega@cnea.gov.ar

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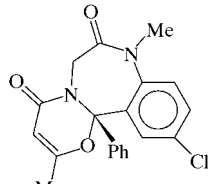
The title compound, 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-*d*][1,4]benzodiazepine-4,7-(6*H*)-dione, $C_{20}H_{17}ClN_2O_3$, is a benzodiazepine with an additional *d*-face-fused heterocyclic ring. In the molecule, a dihedral angle of 86.2 (1)° is formed by the planes of the phenyl and benzo rings and the former is axially oriented from the core, *i.e.* the fused 6,7,6-tricyclic system. Both heterocycles in the core suffer significant deviations from planarity. The central diazepine ring is a twist–boat and the oxazine ring exhibits a conformation intermediate between half-chair and sofa.

Comment

Many benzodiazepines are used in the pharmacotherapy of several neurologic and psychiatric disorders because of their efficacy in the treatment of conditions involving a dysfunction of the GABAergic transmission in the central nervous system (Bradwejn, 1993; Gracies *et al.*, 1997; Mohler, 1998; Nelson & Chouinard, 1999). The title compound, Ketazolam, (I), which is a benzodiazepine of the type possessing an additional fused heterocyclic ring, has proven safe and effective antispastic action (Basmajian *et al.*, 1984), as well as being efffective in the treatment of a variety of manifestations of anxiety (Fabre & Harris, 1976; Fabre *et al.*, 1981).



(I)

The crystal structure has been studied previously and the cell parameters reported (Szmuszkovicz *et al.*, 1971) and deposited without any structural information in the Cambridge Structural Database [CSD (refcode CHMPOA); Allen *et al.*, 1983]; in the final publication, the crystal structure is not actually described. Despite the fact that in the CSD there is information available about 5-phenyl-1,4-benzodiazepines attached to an additional O-containing ring, none of these has an oxazine ring.

This work is part of our ongoing study on benzodiazepines and derived compounds (Vega *et al.*, 1999) and was undertaken to give a detailed description of intra- and intermolecular features of a member of this family of drugs.

In the asymmetric unit of the title compound, the C15—C16 bond makes an angle of 85.3 (4)° with the plane through the oxazine ring so, as is apparent in Fig. 1, the phenyl ring protrudes axially from the tricyclic core of the molecule due to the sp^3 character and tetrahedral angle configuration of the C15 atom (see Table 1). The phenyl ring could be oriented around the C15—C16 bond either (i) to avoid a steric hindrance between H18 and H13 at $\frac{1}{2}-x$, $y-\frac{1}{2}$, $-z-\frac{1}{2}$ (distance H18···H13 2.42 Å) or (ii) to maximize hydrogen-bond interactions involving C20—H20···O4^{i} and C17—H17···N5. The value of the N5—C15—C16—C17 torsion angle [−0.8 (4)°] indicates that the C16—C17 bond of the phenyl ring is coplanar with the C15—N5 bond of the core.

A geometrical descriptor common to benzodiazepines has been the dihedral angle between the phenyl and the benzo rings, ranging from 54 to 75° for 5-(unsubstituted)phenyl-1,4-benzodiazepines (Chananont *et al.*, 1980; Hamor & Martin, 1983; Butcher & Hamor, 1985). In this work, the phenyl ring sustains a dihedral angle of 86.2 (1)° with the benzo ring, which exceeds by more than 10° the value cited in the literature.

The six-membered rings of the core, the oxazine heterocycle and the benzo ring, are fused to the N5—C15 side (*d*-face) and across the C9—C14 bond of the central diazepine ring,

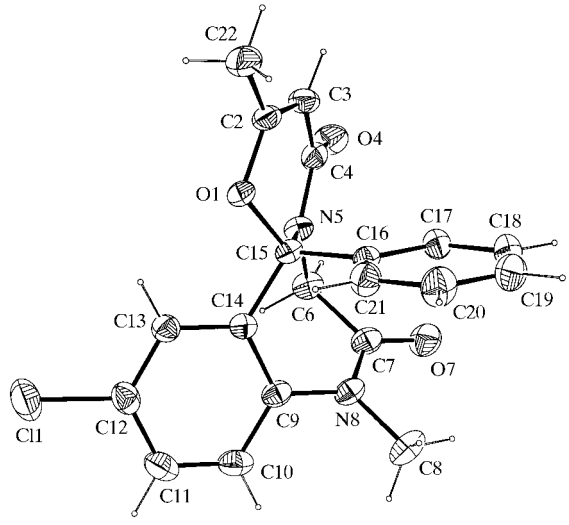


Figure 1
View of the title structure showing the numbering scheme used and displacement ellipsoids drawn at 30% probability.

respectively. The former has a conformation intermediate between half-chair and sofa [the ring puckering parameters (Cremer & Pople, 1975) for C3/C2/O1/C15/N5/C4 are Q_T 0.427 (3) Å, θ_2 63.8 (4)° and φ_2 165.4 (5)°, and the asymmetry parameters (Nardelli, 1983) are Δ_2(C3—C4) 0.061 (1) and Δ_s(C3) 0.069 (1)], whereas the latter deviates slightly from planarity [maximum deviation from least-squares plane defined by C9–C14/Cl1 of 0.038 (4) Å at C11].

The diazepine ring adopts a twist–boat conformation [N5/C15/C14/C9/N8/C7/C6: Q_T 1.066 (3) Å, θ_2 82.4 (2)°, φ_2 92.6 (2)° and φ_3 97 (1)°. The asymmetry parameters are Δ_s(C6) 0.114 (1) and Δ_2(N5) 0.028 (1), *i.e.* with a local pseudo-twofold axis running along N5 and the midpoint of the C9—N8 bond corresponding to a twisted conformation. The asymmetry parameter is representative of the degree of departure from a boat-like conformation of the diazepine ring. By comparison, Δ_s(C6) averages 0.009 (2) (four independent molecules) for such a ring in the benzodiazepine Alprazolam (Vega *et al.*, 1999), hence showing a pseudosymmetry mirror plane passing through the bow atom and the midpoint of the opposite bond, *i.e.* the diazepine ring has an almost perfect boat conformation.

The amide bonds in the vicinity of the C6 atom, N8—C7 and N5—C4, are affected by electron delocalization between the nitrogen lone pair and the carbonyl oxygen. The bond has a length about halfway between the C—N pure single- and double-bond distances and the valency angles at the N atoms are close to 120° (see Table 1). The overall geometry of the C—N bonds resembles that of a normal double bond, and their planar nature is illustrated by the values of the torsion angles of the sequences C15—N5—C4—O4 and C9—N8—C7—O7 [171.1 (3) and −178.7 (3)°, respectively].

The packing for the crystal involves the use of both keto O atoms and the halogen atom as hydrogen-bond acceptors in very weak intermolecular hydrogen bonds, the donors being methyl and aryl C atoms (see Table 2). The C—H···O contacts determine chains of molecules running along the crystallographic *b* direction; meanwhile, parallel chains are held together by C—H···Cl hydrogen bonds, thus forming a layer of molecules, and the packing of a crystal of Ketazolam comprises the stacking of layers.

Experimental

The title compound was obtained from Laboratorios Gador. Crystals suitable for X-ray diffraction were obtained by slow evaporation from a water solution.

Crystal data

$C_{20}H_{17}ClN_2O_3$
M_r = 368.81
Monoclinic, $P2_1/n$
a = 8.6326 (9) Å
b = 13.1190 (10) Å
c = 15.505 (4) Å
β = 96.190 (10)°
V = 1745.7 (5) Å^3
Z = 4
D_x = 1.403 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 10–20°
μ = 0.24 mm^{-1}
T = 293 (2) K
Prism, colourless
0.36 × 0.20 × 0.14 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: numerical integration (Sheldrick, 1976)
T_{min} = 0.91, T_{max} = 0.94
3493 measured reflections
3071 independent reflections
1551 reflections with $I > 2\sigma(I)$
R_{int} = 0.031
θ_{max} = 25°
$h = -10 \rightarrow 10$
$k = -1 \rightarrow 15$
$l = 0 \rightarrow 18$
2 standard reflections every 98 reflections
intensity decay: <2%

Refinement

Refinement on F^2
$R(F)$ = 0.046
$wR(F^2)$ = 0.132
S = 1.07
3071 reflections
235 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0369P)^2 + 0.9696P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—C15	1.438 (4)	N5—C15	1.455 (4)
O4—C4	1.221 (4)	N5—C6	1.462 (4)
O7—C7	1.219 (4)	N8—C7	1.361 (4)
N5—C4	1.377 (4)	N8—C9	1.416 (4)
C4—N5—C15	120.0 (3)	N5—C6—C7	110.9 (3)
C4—N5—C6	119.7 (3)	O1—C15—N5	109.1 (2)
C15—N5—C6	118.9 (3)	O1—C15—C14	105.9 (3)
C7—N8—C9	122.0 (3)	N5—C15—C14	109.0 (3)
C7—N8—C8	119.4 (3)	O1—C15—C16	107.0 (2)
C9—N8—C8	118.7 (3)	N5—C15—C16	113.7 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
C6—H6*B*···O4	0.97	2.33	2.760 (4)	106
C8—H8*C*···O7	0.96	2.31	2.743 (5)	106
C13—H13···O1	0.93	2.28	2.637 (4)	102
C17—H17···N5	0.93	2.54	2.882 (4)	102
C20—H20···O4^{i}	0.93	2.44	3.332 (5)	161
C22—H22*A*···Cl1^{ii}	0.96	2.92	3.721 (4)	142
C22—H22*B*···O7^{i}	0.96	2.63	3.578 (5)	171

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

H atoms were treated as riding (C—H = 0.96 Å for primary, 0.97 Å for secondary, and 0.93 Å for aromatic H atoms) and their isotropic displacement parameters were constrained to be 1.2 times those of their hosts (1.5 for methyl groups).

Data collection and cell refinement: *CAD*-4/*PC* (Enraf–Nonius, 1993); data reduction: *MolEN* (Fair, 1990); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *PARST* (Nardelli, 1995), CSD (Allen *et al.*, 1983) and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1513). Services for accessing these data are described at the back of the journal.

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