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4,5-Dihydro-7,8-dimethoxy-1-phenyl-3*H*-2,3-benzodiazepin-4-one

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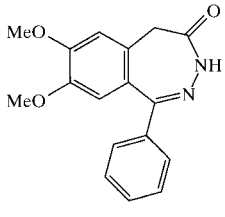
The title compound, $C_{17}H_{16}N_2O_3$, is an antagonist for AMPA/kainate receptors. The molecule has its seven-membered oxadiazole ring in a boat conformation. Asymmetry of the two methoxy bond angles is evident, with (Me)O—C—C angles of 115.45 (12) and 124.78 (13)°, and 114.67 (12) and 125.31 (12)°. A centrosymmetric dimer involving the HN—CO moieties, with an N···O distance of 2.876 (2) Å, graph set $R_2^2(8)$, is further linked into chains through methoxy Csp^3—H···N hydrogen bonds, with a C···N distance of 3.418 (2) Å.

Comment

In previous publications (De Sarro *et al.*, 1995; Chimirri *et al.*, 1997, 1998), we reported chemical and biological studies of some 2,3-benzodiazepine derivatives which have been shown to behave as anticonvulsants, acting as non-competitive antagonists against AMPA/kainate receptors. This paper describes the crystal structure analysis of 4,5-dihydro-7,8-dimethoxy-1-phenyl-3*H*-2,3-benzodiazepin-4-one, (I), one of the most active compounds of the series, with the aim of comparing the molecular geometry with the analogous 2,3-benzodiazepines reported in the literature (Anderson *et al.*, 1996). The results of this investigation will be used for the



(I)

study of structure–activity relationships, in order to understand better the structural characteristics necessary for AMPA/kainate receptor antagonists.

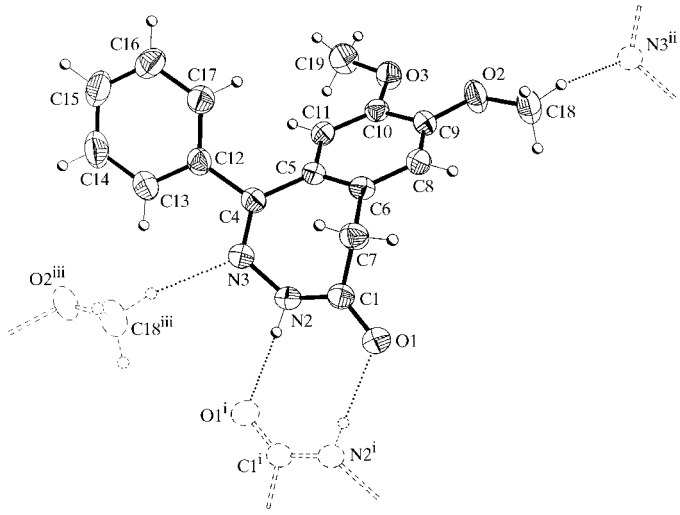


Figure 1
A molecular view of (I) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Dotted lines represent hydrogen bonds to symmetry-related molecules [symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $x, 1+y, z$; (iii) $x, y-1, z$].

Although there are several crystal structure reports of benzodiazepines, 1,2- or 2,3-derivatives are relatively rare. In (I) (Fig. 1), the bond lengths and angles of the seven-membered ring are in good agreement with the corresponding values reported for the parent compound 7,11-dihydro-9,10-dimethoxy-3,11b-diphenyl[1,2,4]oxadiazolo[5,4-*a*][2,3]benzodiazepin-6(5*H*)-one, (II) (Bruno *et al.*, 1999), and for the rare analogous 2,3-benzodiazepine reported in the Cambridge Structural Database (CSD; April 2001 release, Version 5.21; Allen & Kennard, 1993).

In the diazepinone fragment, the bond lengths agree reasonably well with the system of localized single and double bonds (Table 1). Slight deviations from the expected values may be explained by the intra- and intermolecular hydrogen bonds involving this fragment. Atom N3 is involved in an intramolecular contact with the H atom on C13, and this contact is critical for the orientation of the phenyl ring bonded to C4. A strong intermolecular hydrogen bond is seen involving a pair of molecules related by the inversion centre through the HN—CO groups, with graph set $R_2^2(8)$ (Bernstein *et al.*, 1995). This centrosymmetric dimer is connected to adjacent units by intermolecular methoxy C18—H18*A*···N3 hydrogen bonds, graph set $R_4^4(24)$, along the *b* axis. Both intra- and intermolecular contacts and interactions are responsible for the molecular packing observed in the solid state.

The seven-membered ring has a boat conformation [φ_2 = 53.9 (1)°, φ_3 = −102.7 (4)° and θ = 76.6 (1)°, and Q = 0.892 (2) Å; Cremer & Pople, 1975]. As in compound (II) (Bruno *et al.*, 1999), and in the organic structures in the CSD containing the fragment depicted in Fig. 2, a large asymmetry in the dimethoxy ring angles is noticeable in (I): O2—C9—C10 = 115.5 (1), O2—C9—C8 = 124.8 (1), O3—C10—C9 = 114.7 (1) and O3—C10—C11 = 125.3 (1)°. Although the

planarity of the methoxy groups with the phenyl ring was noted in previous work, such an orientation was attributed either to the 'presumable' steric interaction between the methyl and phenyl H atoms (Salem *et al.*, 1988; Sharma *et al.*, 1997; Dijksma *et al.*, 1998; Kumar *et al.*, 1998) or to the correct balance between n^{o} (non-bonding orbital) and the π delocalization of the oxygen lone pairs and the above-mentioned H···H interaction (Bock *et al.*, 1995). The latter explanation was also proposed in a statistical analysis of crystal structure data for monosubstituted methoxy–phenyl compounds (Hummel *et al.*, 1988). The significant asymmetry in the above methoxy–phenyl angles [mean 10.0 (2)°] also causes a close contact of 2.557 (2) Å between the two methoxy O atoms,

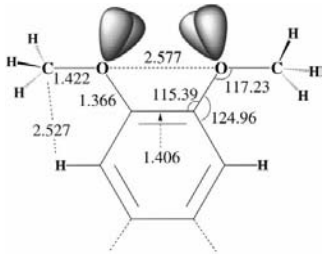


Figure 2
Diagram showing the mean geometric values (Å, °) for the dimethoxy–phenyl fragments reported in the CSD (Allen & Kennard, 1993).

which is smaller than their van der Waals radii sum (2.80 Å; Pauling, 1960).

A search was undertaken of the CSD and 478 organic compounds (with $R < 0.081$) were located containing the fragment shown in Fig. 2, which gives the mean values for the significant structural parameters. We deduce that the planarity of the methoxy group with respect to the phenyl ring is determined by conjugation effects. In order to rationalize this problem still further, we have research in progress into statistical analysis on methoxy–phenyl-substituted compounds, and are carrying out semi-empirical and *ab initio* calculations on this fragment model. This research will be the subject of a forthcoming publication (Bruno & Nicoló, 2001).

Experimental

The title compound was obtained as described previously by De Sarro *et al.* (1995). Suitable single crystals of (I) were obtained by recrystallization from an ethanol solution.

Crystal data

$C_{17}H_{16}N_2O_3$
M_r = 296.32
Monoclinic, $P2_1/n$
a = 8.207 (2) Å
b = 10.312 (2) Å
c = 17.236 (2) Å
β = 95.60 (1)°
V = 1451.7 (5) Å^3
Z = 4
D_x = 1.356 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 30 reflections
θ = 6.4–13.8°
μ = 0.09 mm^{-1}
T = 298 (2) K
Irregular, colourless
0.26 × 0.24 × 0.12 mm

Data collection

Siemens $P4$ diffractometer
$\omega/2\theta$ scans
2903 measured reflections
2567 independent reflections
1734 reflections with $I > 2\sigma(I)$
R_{int} = 0.008
θ_{max} = 25.1°
$h = -1 \rightarrow 9$
$k = -3 \rightarrow 12$
$l = -20 \rightarrow 20$
3 standard reflections
every 197 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.032
$wR(F^2)$ = 0.080
S = 0.84
2567 reflections
204 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0519P)^2]$ 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: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0045 (9)

Table 1
Selected geometric parameters (Å, °).

C1—O1	1.231 (2)	C5—C6	1.388 (2)
C1—N2	1.350 (2)	C6—C7	1.503 (2)
C1—C7	1.501 (2)	O2—C9	1.358 (2)
N2—N3	1.391 (2)	O3—C10	1.367 (2)
N3—C4	1.290 (2)	O2—C18	1.421 (2)
C4—C5	1.479 (2)	O3—C19	1.417 (2)
O1—C1—N2	120.9 (1)	C4—C5—C6	120.6 (1)
O1—C1—C7	123.4 (1)	C5—C6—C7	119.5 (1)
C1—N2—N3	128.5 (1)	C9—O2—C18	118.3 (1)
N2—N3—C4	120.0 (1)	C10—O3—C19	117.5 (1)
N3—C4—C5	126.8 (1)		
N2—C1—C7—C6	−66.28 (17)	C8—C9—O2—C18	−1.6 (2)
C5—C4—C12—C17	−29.7 (2)	C11—C10—O3—C19	4.4 (2)

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···O1^{i}	0.87 (2)	2.01 (2)	2.876 (2)	174 (2)
C18—H18A···N3^{ii}	0.96	2.51	3.418 (2)	158
C13—H13···N3	0.93	2.54	2.793 (2)	96

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

The amine H2 atom was located from a difference map and refined freely. The remaining H atoms were located in idealized positions and allowed to ride on their parent C atoms, with $U_{iso}(H) = 1.2U_{eq}(C)$ and C—H = 0.93–0.97 Å, depending on the C-atom type.

Data collection: *P*3/*V* (Siemens, 1989); cell refinement: *P*3/*V*; data reduction: *SHELXTL-Plus* (Sheldrick, 1990); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XPW* (Siemens, 1996); software used to prepare material for publication: *PARST*97 (Nardelli, 1995) and *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1067). Services for accessing these data are described at the back of the journal.

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