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cis-6-Phenyl-4b*H*,6*H*,11*H*,13*H*-isoindolo[1,2-*c*]benz[2,4]oxazepin-13-one

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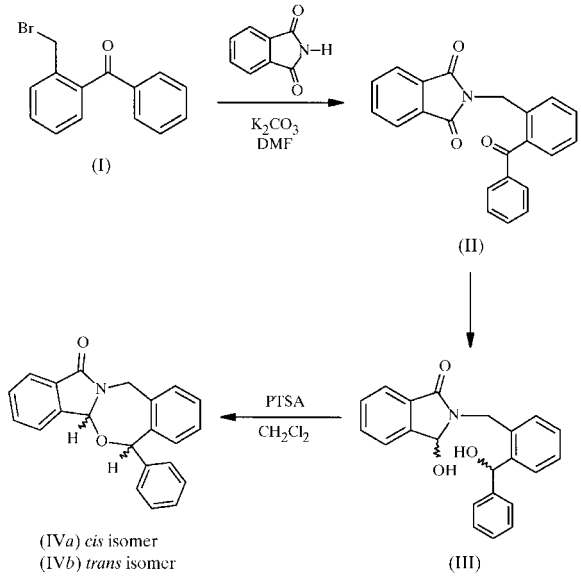
The title compound, $C_{22}H_{17}NO_2$, contains an isoindolinone moiety joined to a phenyl-substituted benzoxazepine ring. The isoindolinone moiety is essentially planar and the oxazepine ring adopts a distorted chair conformation, with the phenyl substituent equatorial. Owing to the severe puckering of the central oxazepine ring, the molecule as a whole is non-planar; the benzene ring of the benzoxazepine fragment makes an angle of 67.7 (1)° with respect to the isoindoline ring.

Comment

The work presented here is part of a continuing study aimed at designing modulators of hormonal/neurotransmitter systems as potential drugs to treat neuronal and cardiovascular disorders. Based on the recent pharmacophore/receptor model of the benzodiazepine (BDZ) receptor subtype located in the central nervous system (CNS; Huang *et al.*, 2000), we designed the title compound, (IV), as a potential anxiolytic agent. Synthesis of (IV) was achieved by a sequential reaction (see Scheme below) and led to a 5:1 diastereomeric (racemic) mixture of *cis* and *trans* isomers, (IV*a*) and (IV*b*), respectively. In order to establish the detailed stereochemistry of the two diastereomers, *viz*. the spatial relationship between the putative pharmacophoric elements (the phenyl rings and the two O atoms), which is indispensable for future molecular-modelling studies, the crystal structure determination of (IV*a*) and (IV*b*) has been undertaken. In this communication, we report on the structure of the *cis* isomer, (IV*a*).

The molecular structure of (IV*a*) is shown in Fig. 1. As expected, the isoindolinone ring is nearly planar, with an average deviation of the ring atoms from the least-squares plane of 0.016 (3) Å. As shown in Table 1, the N1—C2 bond is much shorter than the N1—C9 and N1—C18 bonds. Moreover, the N1 atom is sp^2 hybridized, as evidenced by the sum of the valence angles at this atom [360.0 (2)°]. These data are consistent with conjugation of the lone-pair electrons on N1 with the adjacent carbonyl function, similar to what is observed for amides. Indeed, the N—C bond lengths at N1 are in good agreement with the comparable bond lengths found in cyclic amino acids (Benedetti *et al.*, 1983). A similar pattern of bond distances and angles within the isoindolinone moiety has



been found in other compounds incorporating this molecular fragment (Barrett *et al.*, 1995; McNab *et al.*, 1997; Khan *et al.*, 1998), as revealed by a search of the Cambridge Structural Database (Allen & Kennard, 1993).

As mentioned above, the main purpose of the present structure determination was to establish the relative three-dimensional disposition of the phenyl rings and the two O atoms (and the orientation of the lone pairs on them), which are assumed to constitute the interaction pharmacophore responsible for the binding of the compound to the CNS-subtype of the BDZ receptor. Obviously, the disposition of these structural elements depends primarily on the conformation of the seven-membered oxazepine ring, which is the most flexible part of the molecule. A comparison of the endocyclic torsion angles for the oxazepine ring (Table 1) reveals that it adopts a distorted chair conformation, with an

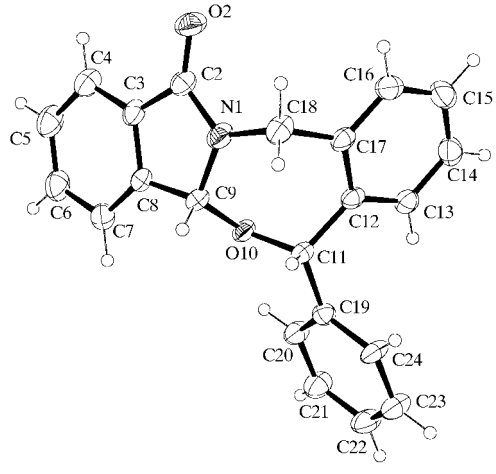


Figure 1
The molecular structure of (IV*a*), showing the atom-labelling scheme. Displacement ellipsoids are shown at the 30% probability level and H atoms are drawn as small circles of arbitrary radii.

approximate mirror plane passing through C9 and the midpoint of the C12—C17 bond; N1, C18, O10 and C11 lie in the plane and C9, C12 and C17 are, respectively, 0.640 (2), −1.115 (2) and −1.146 (2) Å out of it. The puckering parameters according to Cremer & Pople (1975) are q_2 = 0.465 (2) Å, φ_2 = −111.5 (3)°, q_3 = 0.624 (3) Å and φ_3 = 29.6 (2)° for the sequence N1/C9/O10/C11/C12/C17/C18. The deviation from ideal C_s symmetry described by the asymmetry parameter ΔC_s(C9) is 0.046 (1) (Nardelli, 1983).

As a result of the relatively severe puckering of the central oxazepine ring, the molecule as a whole is non-planar; the two (planar) terminal segments of the molecule (the isoindoline ring and the benzene ring fused to the oxazepine moiety) are inclined at an angle of 67.7 (1)° to each other. The phenyl group at C11 is in a pseudo-equatorial orientation and is rotated around the C11—C19 bond in such a manner that the O10—C11—C19—C20 torsion angle is 10.5 (2)°.

Experimental

As noted above, the diastereomers (IV*a*) and (IV*b*) were synthesized by a three-step reaction (see Scheme). In the first step, to bromomethylbenzophenone, (I), freshly prepared from 2-methylbenzophenone (1.96 g, 0.01 mol) and *N*-bromosuccinimide (1.76 g, 0.01 mol), were added phthalimide (1.5 g, 0.01 mol), potassium carbonate (1.1. g, 8 mmol) and *N*,*N*-dimethylformamide (25 ml). The mixture was stirred overnight, diluted with water, extracted with diethyl ether (3 × 20 ml) and dried (magnesium sulfate). The solvent was evaporated under reduced pressure and the solid recrystallized from ethanol to give 2-(*N*-phthalimidomethyl)benzophenone, (II) (77% yield, m.p. 388 K). In the second step, to a mixture of (II) (0.5 g, 15 mmol) in dry methanol (20 ml) at 273–283 K was added sodium borohydride (0.69 g, 30 mmol) in portions. The mixture was stirred for 2 h and monitored by thin-layer chromatography (dichloromethane/acetone 5:1). After 2 h, the starting material disappeared and the excess of sodium borohydride was decomposed by addition of cold water (10 ml) and 10% hydrochloric acid to neutral pH. The precipitate was separated by filtration, washed with water, dried, concentrated under reduced pressure and recrystallized from ethanol to afford a 5:1 ratio of the diastereomers of (III) (79% yield). Finally, compound (IV) was prepared when the diols (III) (0.5 g, 1.5 mmol) were stirred in dry dichloromethane (20 ml) with a catalytic amount of *p*-toluenesulfonic acid for 30 min at room temperature. The solution was washed with saturated sodium hydrogen carbonate and then with water, then dried and concentrated under reduced pressure. Separation by flash chromatography, followed by recrystallization from ethanol, gave a 5:1 ratio of the oxazepines (IV*a*) and (IV*b*) [70% yield; m.p. 496 K for (IV*a*) and 482 K for (IV*b*)].

Crystal data

$C_{22}H_{17}NO_2$
M_r = 327.37
Triclinic, $P\overline{1}$
a = 7.153 (3) Å
b = 8.961 (4) Å
c = 13.156 (7) Å
α = 92.69 (5)°
β = 106.83 (5)°
γ = 96.79 (4)°
V = 798.6 (6) Å^3
Z = 2
D_x = 1.361 Mg m^{-3}
D_m = 1.36 (1) Mg m^{-3}
D_m measured by flotation in bromoform/*c*-hexane
Mo $K\alpha$ radiation
Cell parameters from 15 reflections
θ = 10–26°
μ = 0.09 mm^{-1}
T = 293 (2) K
Prism, colourless
0.50 × 0.35 × 0.30 mm

Data collection

Syntex $P2_1$ diffractometer
$\theta/2\theta$ scans
3271 measured reflections
3271 independent reflections
2513 reflections with $I > 2\sigma(I)$
θ_{max} = 26.6°
$h = 0 \rightarrow 8$
$k = -11 \rightarrow 11$
$l = -15 \rightarrow 15$
2 standard reflections
every 98 reflections
intensity decay: 2%

Refinement

Refinement on F^2
$R(F)$ = 0.047
$wR(F^2)$ = 0.133
S = 1.10
3271 reflections
226 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0478P)^2 + 0.3839P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.350 (3)	C2—O2	1.217 (2)
N1—C9	1.439 (3)	C9—O10	1.399 (2)
N1—C18	1.443 (3)	O10—C11	1.439 (2)
C2—N1—C9	113.90 (16)	N1—C2—C3	106.04 (17)
C2—N1—C18	124.57 (17)	O10—C9—N1	113.94 (16)
C9—N1—C18	121.53 (16)	O10—C9—C8	109.38 (16)
O2—C2—N1	126.21 (19)	N1—C9—C8	102.13 (16)
O2—C2—C3	127.74 (19)	C9—O10—C11	114.19 (14)
C18—N1—C9—O10	−60.7 (2)	C11—C12—C17—C18	−1.1 (3)
N1—C9—O10—C11	66.4 (2)	C9—N1—C18—C17	74.4 (2)
C9—O10—C11—C12	−88.91 (18)	C12—C17—C18—N1	−59.1 (2)
O10—C11—C12—C17	68.1 (2)	O10—C11—C19—C20	10.5 (2)

All H atoms were treated as riding, with C—H = 0.93 Å (aromatic) or 0.97 Å, and with U_{iso} set to 1.2 (1.5 for the methyl-H atoms) times U_{eq} of the parent atom.

Data collection and cell refinement: $P2_1$ *Software* (Syntex, 1973); data reduction: *XP*21 (Pavelčík, 1987); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1142). Services for accessing these data are described at the back of the journal.

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