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trans-5,6a-Dihydro-5-phenylisoindolo[1,2-*b*]-benz[1,3]oxazepin-11-one

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.074
wR factor = 0.194
Data-to-parameter ratio = 12.9

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The title compound, $C_{22}H_{17}NO_2$, is composed of an oxoisoindoline moiety fused to a phenyl-substituted benzoxazepine ring and was designed and synthesized as a potential anxiolytic drug. The isoindolinone moiety is essentially planar and the central oxazepine ring adopts a twist-boat conformation with the phenyl group equatorial. In the two independent molecules, the benzene ring of the benzoxazepine fragment makes an angle of 74.4 (1) or 86.1 (1)° with the plane of the isoindoline ring.

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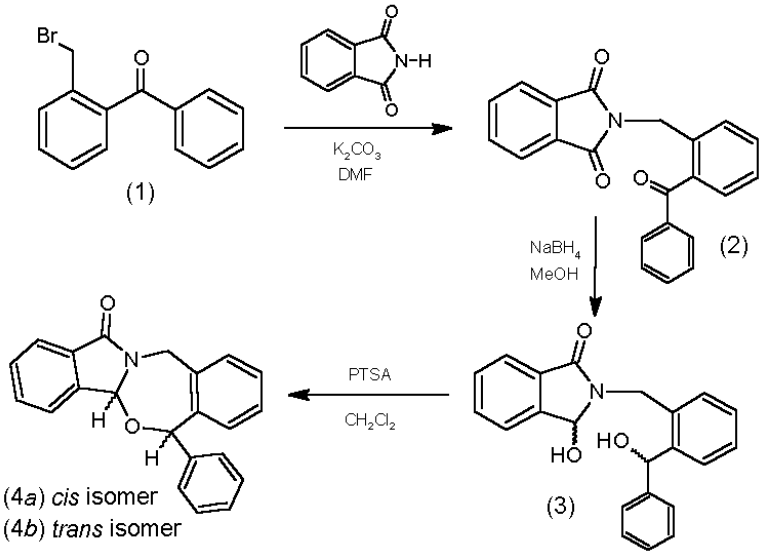
Comment

This work is part of our 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 (Huang *et al.*, 2000), we designed the compound (4), as potential anxiolytic agent. Synthesis of the molecule (4) was achieved by a sequential reaction and led to a 5:1 diastereomeric (racemic) mixture of *cis*-(4*a*) and *trans*-(4*b*) isomers. In order to establish the detailed stereochemistry of the two diastereomers, *viz*. spatial relationship between the putative pharmacophoric elements (phenyl rings and the two O atoms) which is indispensable for future molecular-modelling studies, the crystal structure determination of (4*a*) and (4*b*) has been undertaken. We report here on the structure of the *trans*-(4*b*) isomer.



In *trans*-(4*b*), two independent molecules (*A* and *B*) are identical to within 4σ as far as bond distances and angles are concerned. Thus, only one molecule (*A*) along with the atom-numbering scheme is shown in Fig. 1. As expected, the isoindolinone ring is essentially planar. The N1—C2 bond is much shorter than the N1—C9 and N1—C18 bonds (Table 1); such N—C bond lengths resemble those typically found in cyclic amino acids (Benedetti *et al.*, 1983), indicating that the lone-pair electrons on N1 are involved in conjugation with the adjacent carbonyl group. A similar pattern of bond distances and angles within the isoindolinone moiety has been found in the *cis* isomer (Lokaj *et al.*, 2001) as well as other compounds incorporating this molecular fragment (Barrett *et al.*, 1995; McNab *et al.*, 1997; Khan *et al.*, 1998).

As mentioned above, the main purpose of this structure determination was to establish the relative three-dimensional disposition of the phenyl rings and the two O atoms which are assumed to constitute the interaction pharmacophore responsible for 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 the ring adopts a twist-boat conformation with an approximate twofold axis passing through C9 and the midpoint of the C12—C17 bond.

The puckering parameters according to Cremer & Pople (1975) are q_2 = 0.817 (4) Å, φ_2 = 175.7 (3)° and q_3 = 0.370 (4) Å, φ_3 = 106.8 (5)° for the sequence N1*A*/C9*A*/O10*A*/C11*A*/C12*A*/C17*A*/C18*A*. The corresponding parameters in molecule *B* are q_2 = 0.814 (4) Å, φ_2 = 169.2 (3)° and q_3 = 0.378 (4) Å, φ_3 = 108.8 (6)°. The deviation from ideal C_2 symmetry described by the asymmetry parameter ΔC_2(C9) is 0.062 (1) (molecule *A*) and 0.026 (1) (molecule *B*) (Nardelli, 1983). Although the puckering mode of the oxazepine ring in molecules *A* and *B* is the same, the endocyclic torsion angles in the two molecules differ by up to 23σ. Another difference between molecules *A* and *B* concerns the orientation of the phenyl group (at C11) as shown by the torsion angle O10—C11—C19—C24 which is 46.3 (3)° in *A* and 64.0 (3)° in *B*. This points to the flexibility of the oxazepine ring and the shallow shape of the potential well corresponding to rotation of the phenyl group about the exocyclic C11—C19 bond. In both molecules, of course, the phenyl substituent occupies a pseudo-equatorial position. The equatorial arrangement of the phenyl group has also been observed for the *cis* isomer (Lokaj *et al.*, 2001) but in the latter compound the oxazepine ring exists in a distorted C9-chair conformation. This is in line with the known fact that the equatorial orientation of bulky substituents attached to a saturated (or partially unsaturated) seven-membered ring is more important than the actual conformation of the ring, obviously due to low barriers along the pseudorotation pathway. Due to the relatively severe puckering of the central seven-membered ring, the molecules as a whole are non-planar: the two planar 'ends' (*viz*. the isoindoline and the benzene ring of the benzoxazepine moiety) are inclined at an angle of 74.4 (1) and 86.1 (1)° in molecules *A* and *B*, respectively. A similar molecular shape has been found for the *cis*-isomer [bent angle 67.7 (1)°]. This implies an equivalent spatial relationship between the pharmacophoric elements in the two diastereomers and hence, based on the crystal structure data, a similar pharmacological behaviour for the two isomers is predicted.

Experimental

The diastereomers (4*a*) and (4*b*) were synthesized by a three-step reaction. As the first step, to bromomethylbenzophenone (1), prepared freshly from 2-methylbenzophenone (1.96 g, 0.01 mol) and *N*-bromosuccinimide (1.76 g, 0.01 mol), was 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, (2) (77% yield, m.p. 388 K). In the second step, to a solution of (2) (0.5 g, 15 mmol) in dry methanol (20 ml) at 273–283 K was added sodium borohydride (0.69 g, 30 mmol) by portions. The mixture was stirred for 2 h and monitored by TLC (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 diastereomers (3) (79% yield). Finally, compound (4) was prepared when the diols (3) (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, with water, then dried and concentrated under reduced pressure. Separation of the product by flash chromatography and recrystallization from ethanol gave the corresponding 5:1 ratio of oxazepines (4*a*) and (4*b*) (70% yield); m.p. (4*a*) 496 K and (4*b*) 482 K. The isomers were initially characterized by IR, ^{1}H and ^{13}C NMR spectral analyses.

Crystal data

$C_{22}H_{17}NO_2$
M_r = 327.37
Triclinic, $P\overline{1}$
a = 10.799 (3) Å
b = 12.113 (4) Å
c = 13.775 (4) Å
α = 104.47 (4)°
β = 99.40 (3)°
γ = 101.26 (5)°
V = 1667.9 (9) Å^3
Z = 4
D_x = 1.304 Mg m^{-3}
D_m = 1.30 (1) Mg m^{-3}
D_m measured by flotation in bromoform/cyclohexane
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 7–18°
μ = 0.08 mm^{-1}
T = 293 (2) K
Prism, colourless
0.40 × 0.30 × 0.25 mm

Data collection

Siemens *P*4 diffractometer
$\omega/2\theta$ scans
6826 measured reflections
5812 independent reflections
3954 reflections with $I > 2\sigma(I)$
R_{int} = 0.050
θ_{max} = 25.0°
$h = -1 \rightarrow 12$
$k = -13 \rightarrow 13$
$l = -16 \rightarrow 16$
3 standard reflections
every 97 reflections
intensity decay: 2%

Refinement

Refinement on F^2	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.074$	$w = 1/[\sigma^2(F_o^2) + (0.1139P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.194$	$(\Delta/\sigma)_{max} = 0.001$
$S = 1.04$	$\Delta\rho_{max} = 0.35$ e Å^{-3}
5812 reflections	$\Delta\rho_{min} = -0.52$ e Å^{-3}
451 parameters	

Table 1
Selected geometric parameters (Å, °).

N1*A*—C2*A*	1.368 (4)	N1*B*—C2*B*	1.370 (4)
N1*A*—C9*A*	1.447 (3)	N1*B*—C9*B*	1.449 (3)
N1*A*—C18*A*	1.449 (3)	N1*B*—C18*B*	1.456 (3)
C2*A*—O2*A*	1.227 (3)	C2*B*—O2*B*	1.224 (3)
C2*A*—C3*A*	1.490 (4)	C2*B*—C3*B*	1.486 (4)
C3*A*—C8*A*	1.373 (4)	C3*B*—C8*B*	1.382 (4)
C8*A*—C9*A*	1.510 (4)	C8*B*—C9*B*	1.506 (4)
C9*A*—O10*A*	1.421 (3)	C9*B*—O10*B*	1.427 (3)
O10*A*—C11*A*	1.455 (3)	O10*B*—C11*B*	1.454 (3)
C11*A*—C19*A*	1.510 (3)	C11*B*—C19*B*	1.512 (3)
C11*A*—C12*A*	1.537 (3)	C11*B*—C12*B*	1.533 (3)
C12*A*—C17*A*	1.403 (3)	C12*B*—C17*B*	1.407 (3)
C17*A*—C18*A*	1.520 (4)	C17*B*—C18*B*	1.522 (4)
C2*A*—N1*A*—C9*A*	114.1 (2)	C2*B*—N1*B*—C9*B*	113.4 (2)
C2*A*—N1*A*—C18*A*	125.8 (2)	C2*B*—N1*B*—C18*B*	125.0 (2)
C9*A*—N1*A*—C18*A*	119.9 (2)	C9*B*—N1*B*—C18*B*	119.2 (2)
O2*A*—C2*A*—N1*A*	125.9 (3)	O2*B*—C2*B*—N1*B*	125.9 (3)
O2A—C2A—C3A	128.7 (3)	O2*B*—C2*B*—C3*B*	128.0 (3)
N1A—C2A—C3A	105.5 (2)	N1*B*—C2*B*—C3*B*	106.1 (2)
O10*A*—C9*A*—N1*A*	111.18 (19)	O10*B*—C9*B*—N1*B*	110.8 (2)
O10*A*—C9*A*—C8*A*	116.6 (2)	O10*B*—C9*B*—C8*B*	115.0 (2)
N1*A*—C9*A*—C8*A*	101.9 (2)	N1*B*—C9*B*—C8*B*	102.3 (2)
C9*A*—O10*A*—C11*A*	112.93 (18)	C9*B*—O10*B*—C11*B*	112.97 (18)
C18*A*—N1*A*—C9*A*—O10*A*	46.6 (3)	C18*B*—N1*B*—C9*B*—O10*B*	43.7 (3)
N1*A*—C9*A*—O10*A*—C11*A*	47.9 (3)	N1*B*—C9*B*—O10*B*—C11*B*	51.1 (3)
C9*A*—O10*A*—C11*A*—C12*A*	−93.7 (2)	C9*B*—O10*B*—C11*B*—C12*B*	−91.7 (2)
O10*A*—C11*A*—C12*A*—C17*A*	44.1 (3)	O10*B*—C11*B*—C12*B*—C17*B*	39.8 (3)
C11*A*—C12*A*—C17*A*—C18*A*	−1.2 (4)	C11*B*—C12*B*—C17*B*—C18*B*	−2.6 (4)
C9*A*—N1*A*—C18*A*—C17*A*	−77.2 (3)	C9*B*—N1*B*—C18*B*—C17*B*	−81.5 (3)
C12*A*—C17*A*—C18*A*—N1*A*	23.5 (4)	C12*B*—C17*B*—C18*B*—N1*B*	30.5 (4)

Although most of the H atoms were observed in a difference Fourier map, all were refined with fixed geometry, riding on their carrier atoms, with U_{iso} set to $1.2U_{eq}$ of the parent atom.

Data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; 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); software used to prepare material for publication: *SHELXL*97.

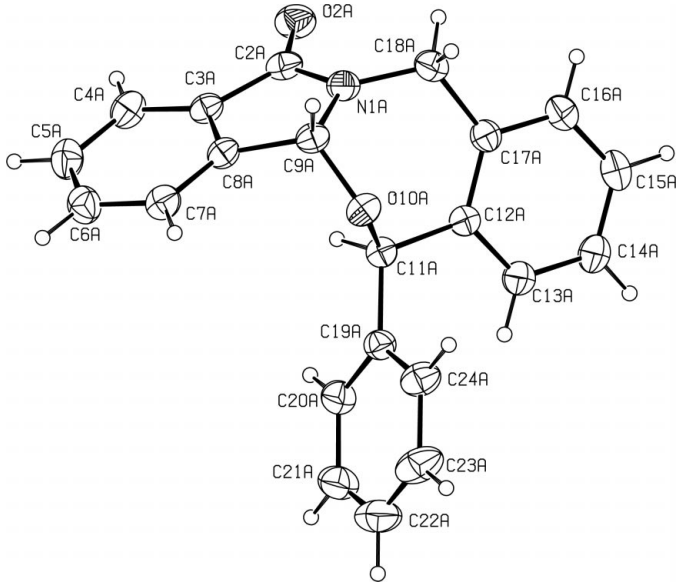


Figure 1
A view of the title molecule, showing the labelling of the non-H atoms. Displacement ellipsoids are shown at the 30% probability level. For clarity, only molecule *A* is shown.

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