Data collection

Enraf–Nonius CAD-4 diffractometer
ω scans
Absorption correction: ψ scan (North, Phillips & Mathews, 1968)
T_{min} = 0.922, T_{max} = 0.958
5858 measured reflections
5664 independent reflections
3326 reflections with $I > 2\sigma(I)$
R_{int} = 0.0181
θ_{max} = 24.97°
$h = -12 \rightarrow 12$
$k = 0 \rightarrow 21$
$l = 0 \rightarrow 20$
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.067
$wR(F^2)$ = 0.195
S = 1.107
5664 reflections
370 parameters
H atoms: riding model with $U(H) = 1.5U_{eq}(C,N)$; water H atoms were calculated, U = 0.10 Å^2
$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.370 e Å^{-3}
$\Delta\rho_{min}$ = −0.267 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

O1—C25	1.246 (4)	N1···O1	2.871 (3)
O2—C25	1.217 (4)	N1···O4^{i}	2.908 (3)
O3—C31	1.235 (3)	N2···O1	2.846 (3)
O4—C31	1.245 (3)	N2···O3	2.717 (3)
N1—C1	1.499 (3)	O5···O2^{ii}	2.602 (6)
N1—C7	1.496 (3)	O5···O4	2.778 (6)
N2—C13	1.493 (3)	O5···O6	2.674 (7)
N2—C19	1.499 (3)	O5′···O2^{ii}	2.656 (6)
N3—C26	1.337 (3)	O5′···O4	2.710 (5)
N3—C30	1.339 (3)	O6···O5^{iii}	2.825 (9)
C1—N1—C7	116.8 (2)	O1—C25—O2	124.0 (3)
C13—N2—C19	119.6 (2)	O1—C25—C26	118.6 (3)
C26—N3—C30	118.7 (2)	O2—C25—C26	117.5 (3)
N1—C1—C2	108.2 (2)	N3—C26—C25	117.2 (2)
N1—C1—C6	112.2 (2)	N3—C26—C27	122.0 (2)
N1—C7—C8	109.1 (2)	N3—C30—C29	122.2 (2)
N1—C7—C12	112.3 (2)	N3—C30—C31	115.5 (2)
N2—C13—C14	108.5 (2)	O3—C31—O4	124.6 (2)
N2—C13—C18	112.7 (3)	O3—C31—C30	117.8 (2)
N2—C19—C20	108.1 (2)	O4—C31—C30	117.7 (2)
N2—C19—C24	110.8 (2)		

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

Data collection: *CAD-4-VAX/PC* (Enraf–Nonius, 1988). Cell refinement: *CAD-4-VAX/PC*. Data reduction: *NRCVAX* (Gabe, Le Page, Charland, Lee & White, 1989). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *PLUTON* (Spek, 1994), *ZORTEP* (Zsolnai & Pritzkow, 1996). Software used to prepare material for publication: *SHELXL93*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: KH1129). Services for accessing these data are described at the back of the journal.

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Characterization of Quinoline Derivatives. I. 6,7-Dihydro-8-(4-methyl-1-piperazinyl)[1]-benzoxepino[4,5-*c*]quinoline 0.13-Hydrate

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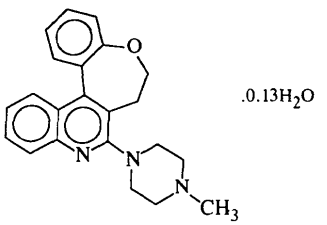
Abstract

The title compound, $C_{22}H_{23}N_3O.0.13H_2O$, is a novel potent and selective serotonin 5-HT_3 receptor antagonist. Three independent molecules constitute the asymmetric unit. While two of these molecules show only small differences in their metric and conformational parameters, the third differs from the other two, mainly as a result of the conformation of the oxepine ring. The conformations of the seven-membered ring determine quite different orientations of the oxepine-fused benzene ring, whose role is important in the exploitation of biological activity.

Comment

Serotonin (5-hydroxytriptamine, 5-HT) exerts a wide range of actions in the human body mediated by at least seven classes of receptors. One of these is represented by the 5-HT_3 receptors (Fozard, 1992). In view of their numerous potential applications in therapy, a lot of effort has been devoted to finding new active compounds. As part of a research program devoted to synthesizing and characterizing new serotonin receptor antagonists, we wish to report here the crystal and molecular structure of a novel benzoxepinoquinoline derivative, (I), which is a potent and selective serotonin 5-HT_3 receptor antagonist (Anzini *et al.*, 1995). It is of particular interest to evaluate the influence exerted by the conformation of the oxepine ring on the orientation of the fused benzene ring, the latter playing an important role in determining the biological properties of the molecule and its selectivity for serotonin receptors.



(I)

The crystal structure of the title compound shows three independent molecules in the asymmetric unit (Fig 1). In the three molecules, the quinoline moiety shows quite similar and regular bond lengths. The N1—C1 and N1—C5 distances are not equal and average 1.321 (5) and 1.371 (5) Å, respectively. The quinoline ring system is planar with the largest deviations from the least-squares plane due to atoms C31 [0.045 (4) Å], C62 [0.083 (5) Å] and C13 [0.112 (4) Å] in molecules 1, 2 and 3, respectively.

In the oxepine ring, the O1—C11 and O1—C12 distances average 1.444 (5) and 1.386 (5) Å, respectively, for the three molecules. In the last case, a partial π bond with the fused benzene ring is observed. The C10—C11 and C2—C10 bond lengths average 1.511 (5) and 1.507 (5) Å, respectively. The C3—C17 distance averages 1.489 (5) Å for the three molecules, ranging from 1.485 (5) (C33—C173) to 1.494 (5) Å (C31—C171). These values are close to those found in analogous heterocyclic systems.

While two independent molecules (1 and 2) show only small differences in their metric and conformational parameters, the third molecule differs from the other two, mainly in the conformation of the benzoxepine ring. For example, the torsion angle defined by C17—C12—O1—C11 has values of 73.0 (5) and 76.7 (4)° in molecules 1 and 2, respectively, but −74.8 (5)° in molecule 3. A mutual influence occurs between the conformation of the seven-membered ring and the orientation of the fused benzene, the last being of interest in relation to the biological activity of the molecule (Anzini *et al.*, 1995). The torsion angle C2—C3—C17—C12 has values of −49.1 (5), −45.6 (4) and 46.8 (5)° in molecules 1, 2 and 3, respectively.

In the three molecules, atoms C10, C11, C12 and C17 lie on one side of the least-squares plane through the oxepine ring, while atoms C2, C3 and O1 lie on

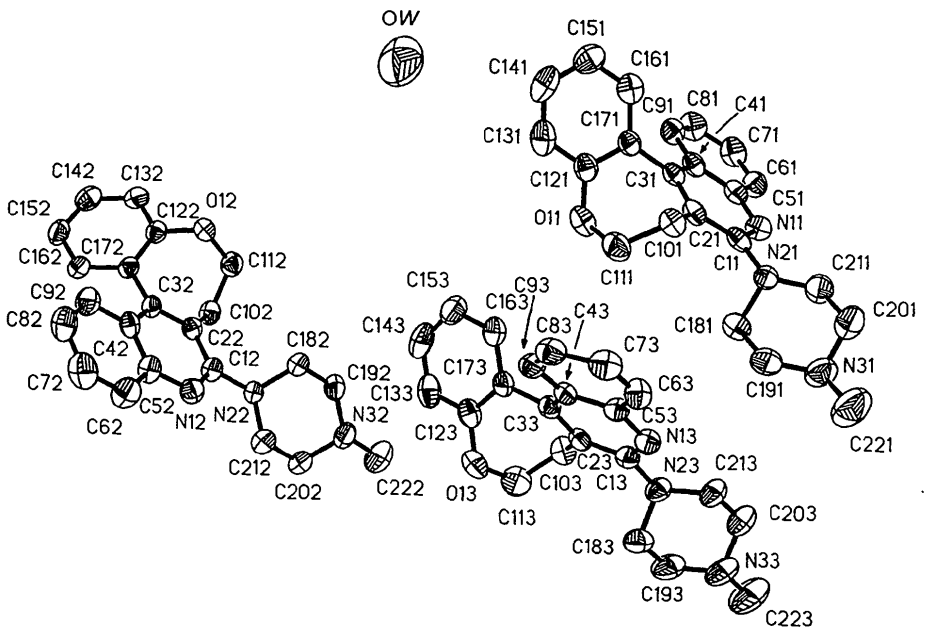


Fig. 1. The molecular structure of (I) showing 50% probability displacement ellipsoids. H atoms have been omitted for clarity.

the other side; atom C10 shows the largest deviation, ranging from 0.565 (3) Å in molecule 2 to 0.701 (4) Å in molecule 3. The least-squares plane through the oxepine ring forms dihedral angles with the fused benzene ring of 38.7 (1), 41.5 (1) and 39.0 (1)° in molecules 1, 2 and 3, respectively. The dihedral angles between the quinoline and oxepine-fused benzene rings are 52.1 (1), 46.0 (1) and 49.4 (1)° in molecules 1, 2 and 3, respectively. In addition, the Cremer & Pople (1975) total puckering amplitudes (Q_T) of the oxepine rings are equal to 1.022 (3) and 1.010 (3) Å for molecules 1 and 2, respectively, while a reduction [Q_T = 0.997 (3) Å] is found for molecule 3. This further validates the observation that molecule 3 has a different conformation to the other two.

A comprehensive search for the 4-phenylquinoline fragment in the Cambridge Structural Database (Version 5.11; Allen *et al.*, 1991) yielded 44 entries. Most of these are acridine and phenanthroline derivatives, either free or complexed by metal ions. The orientation of the phenyl group with respect to the quinoline nucleus shows large variations, ranging from about 40° [dihedral angle 39.3 (2)°; Klemens, Fanwick, Bibler & McMillin, 1989] to being nearly perpendicular (dihedral angle 88°; Goubitz, Reiss & Heijdenrijk, 1990). It has been proposed that the dihedral angle is more likely a function of the crystal packing than the effects exerted by the substituents of the phenyl ring (Stowell, Toma & Byrn, 1991).

Only three 4-phenylquinolines were found in the search of the Cambridge Structural Database, namely, 7-(4-methoxyphenyl)-2*H*-benzo[*f*][1]benzopyrano[4,3-*b*]quinolin-6-one (Martinez, Cortes, Toscano & Alfaro, 1990), 2,4-diphenylquinoline (Ahmet, Miller, Osborne & Warmsley, 1995) and 3-methyl-2,4-diphenylquinoline (Ahmet, Miller, Osborne & Warmsley, 1995). The dihedral angles between the pendant phenyl and the quinoline ring are 64, 64.9 and 88.9°, respectively. Owing to the driving role exerted by the seven-membered ring on the orientation of the fused benzene, the values found in the title compound are considerably lower than those reported above.

In each molecule of the title compound, the piperazine ring shows a chair conformation with typical puckering parameters (Cremer & Pople, 1975). The Q_T values are equal to 0.587 (4), 0.586 (4) and 0.591 (4) Å for molecules 1, 2 and 3, respectively, indicating that the entity of puckering in the piperazine moiety is unchanged in the three molecules. The dihedral angles between its least-squares plane and that of the quinoline are 43.7 (1), 42.0 (1) and 45.4 (1)° in molecules 1, 2 and 3, respectively. It is interesting to compare the orientation of the piperazine ring with those of other substituents in position 2 of the quinoline system. As an example, in 2,4-diphenylquinoline, the dihedral angle between the phenyl ring in position 2 and the aromatic base is 21.1 (2)°, while in its sterically hindered 3-methyl derivative, this angle is 52.6 (1)° (Ahmet, Miller, Osborne & Warmsley, 1995).

The crystal packing is stabilized both by stacking interactions between the quinoline systems [molecule 2 with molecule 1 (at $1-x, -y, -z$) and molecule 3 with molecule 1 (at $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$)], with mean interplanar distances equal to 3.5 Å, and by hydrogen bonds. The water molecule interacts *via* hydrogen bonds with the N31($x+1, y, z$) atom [O*W*···N31 2.62 (1) Å].

Experimental

The title compound was synthesized and purified as previously reported (Anzini *et al.*, 1995). Single crystals suitable for X-ray data collection were obtained by dissolving 100 mg of powder in 50 ml of *n*-hexane and allowing the solution to concentrate at room temperature.

Crystal data

$C_{22}H_{23}N_3O.0.13H_2O$
M_r = 347.8
Monoclinic
$P2_1/n$
a = 15.0089 (14) Å
b = 16.952 (2) Å
c = 22.124 (2) Å
β = 96.172 (6)°
V = 5596.3 (9) Å^3
Z = 12
D_x = 1.249 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 40 reflections
θ = 5–15°
μ = 0.079 mm^{-1}
T = 293 (2) K
Prism
0.2 × 0.2 × 0.1 mm
Pale yellow

Data collection

Siemens *P*4 diffractometer
Profile data from ω scans
Absorption correction: none
11 874 measured reflections
9838 independent reflections
4167 reflections with $I > 2\sigma(I)$
R_{int} = 0.0306
θ_{max} = 24.99°
$h = -1 \rightarrow 17$
$k = -1 \rightarrow 20$
$l = -26 \rightarrow 26$
3 standard reflections every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.0694
$wR(F^2)$ = 0.1143
S = 1.212
9834 reflections
715 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0451P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.041
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

	Molecule 1	Molecule 2	Molecule 3
O1—C11	1.446 (5)	1.443 (4)	1.443 (5)
O1—C12	1.383 (5)	1.389 (4)	1.387 (5)
C2—C3	1.377 (5)	1.379 (4)	1.379 (4)

C2—C10	1.510 (5)	1.503 (3)	1.510 (5)
C3—C17	1.494 (5)	1.489 (4)	1.485 (5)
C10—C11	1.511 (5)	1.508 (5)	1.516 (5)
C12—C17	1.388 (5)	1.400 (5)	1.383 (5)
C11—O1—C12	114.1 (3)	114.4 (3)	115.5 (3)
C2—C3—C17	119.0 (3)	119.9 (3)	119.9 (3)
C2—C10—C11	113.2 (3)	114.1 (3)	114.1 (3)
O1—C11—C10	114.4 (3)	112.9 (3)	113.5 (3)
O1—C12—C17	120.6 (3)	119.9 (3)	120.3 (3)
C3—C17—C12	120.7 (4)	120.0 (3)	121.0 (3)
C11—O1—C12—C17	73.0 (5)	76.7 (4)	−74.8 (5)
C2—C3—C17—C12	−49.1 (5)	−45.6 (4)	46.8 (5)
C2—C10—C11—O1	−44.7 (4)	−43.3 (4)	46.5 (4)

At an initial stage, the cell parameters were determined from Weissenberg films. In order to ascertain the correctness of the metric parameters, accurate cell determination and refinement were carried out on different crystals both from the same crystallization batch and from different crystallization procedures. In all cases, the same cell parameters were obtained. Structure solution was performed by direct methods and Fourier syntheses (*SHELXTL*; Sheldrick, 1990). Refinement was carried out by full-matrix anisotropic least squares on F^2 for all non-H atoms (*SHELXL*93; Sheldrick, 1993). H atoms were located in Fourier difference maps and included in the refinement using a riding model. The isotropic displacement parameters for H atoms belonging to CH or CH_2 groups were refined to a common value equal to 0.063 (2) $Å^2$, while those of the methyl groups were fixed at 0.09 $Å^2$. The water H atoms were not located. Geometric calculations were carried out using *PARST*95 (Nardelli, 1995). The molecular graphics were produced with the *SHELXTL* package. Siemens *P*4 software was used for data collection, cell refinement and data reduction.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1266). Services for accessing these data are described at the back of the journal.

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