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(*Z*)-2-(3-Hydroxy-4-methoxybenzylidene)-1-azabicyclo[2.2.2]octan-3-one

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Crystals of the title compound, $C_{15}H_{17}NO_3$, were obtained from a condensation reaction of 3-hydroxy-4-methoxybenzaldehyde with 1-azabicyclo[2.2.2]octan-3-one and subsequent crystallization of the product from methanol. The title compound, containing a double bond that connects the azabicyclic ring system to the 3-hydroxy-4-methoxybenzylidene group, was obtained with *Z* geometry.

Comment

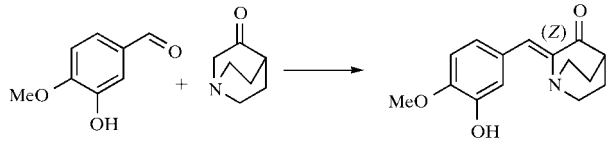
Dopamine is a biogenic amine biosynthesized in the hypothalamus, the arcuate nucleus, the caudad, and various areas of the central and peripheral nervous system. It has been widely established that dopamine and dopamine analogues play an important role in cardiovascular, renal, hormonal and central nervous system regulation through stimulation of α and β adrenergic and dopaminergic receptors.

Dopamine receptor agonists and antagonists have been evaluated and extensively reviewed as medications for cocaine abuse (Witkin, 1994; Mello & Negus, 1996). Although the behavioural effects of cocaine are not consistently altered by selective dopamine receptor antagonists (Spealman, 1990; Witkin *et al.*, 1991), many studies have reported their mediation of the reinforcing effects of cocaine (Corrigall & Coen, 1991; Britton *et al.*, 1991).

The dopamine D_3 receptor has been of particular interest, because of its relatively restricted localization within the limbic system compared with the dopamine D_2 receptor, and due to its role as a possible target for the treatment of schizophrenia and drug abuse (Shafer & Levant, 1998). A recent report of selective inhibition of cocaine-seeking behaviour by a partial dopamine D_3 receptor agonist suggested that this receptor is an important target for the development of medications for cocaine abuse (Pilla *et al.*, 1999).

The nicotinic modulation of [^{3}H]dopamine release from striatal preparations has been exploited as a model system for examining native nicotine acetylcholine receptor (nAChR) responses (Soliakov & Wonnacott, 1996; Grady *et al.*, 1997) and evaluating novel ligands (Holladay *et al.*, 1997; Bencherif *et al.*, 1998; Xu *et al.*, 2002). 1-Azabicyclo[2.2.2]octane is a very important biological moiety, and its analogues are agonists at the α7 nAChR subtype, with selective affinity for the α7 *versus* $\alpha4\beta2$ nAChR subtype (Mullen *et al.*, 2000).

In view of these findings, we planned to synthesize rigid analogues of dopamine. The title compound, (I), is a synthetic precursor of a drug candidate designed as a conformationally restrained dopamine analogue with defined double-bond geometry, and was prepared by condensation of 3-hydroxy-4-methoxybenzaldehyde with 1-azabicyclo[2.2.2]octan-3-one under base catalysis to afford a single geometrical isomer. The product, (*Z*)-2-(3-hydroxy-4-methoxybenzylidene)-1-azabicyclo[2.2.2]octan-3-one, (I), was identified by NMR spectroscopy. In order to confirm the geometry of this compound, and to obtain more detailed information on the structural conformation of the molecule and on synthetic products derived from this intermediate that may be of value in subsequent structure–activity studies, an X-ray structure determination was carried out and the results are presented here.



(I)

The present X-ray data confirm the *Z* geometry of the molecule and show that, in the crystal structure of (I), the H atom attached to atom O1 is involved in an intermolecular hydrogen bond [2.774 (2) Å] with atom O16($x, \frac{1}{2}-y, z+\frac{1}{2}$) of a *c*-glide related molecule. An ellipsoid plot of (I) is shown in Fig. 1 and selected geometric parameters are presented in Table 1.

The molecule of (I) contains a double bond (C8═C9) that connects a 1-azabicyclo[2.2.2] ring system to a 3-hydroxy-4-methoxybenzylidene group; geometric isomerism about this double bond affords the possibility of *E* and *Z* isomers. In the *Z* isomer, the C9—C16 bond is in a *trans* position with respect to the C3—C8 bond. The double bond has a nearly planar atomic arrangement, since the r.m.s. deviation from the best plane passing through atoms N10, C9, C16, C8 and C3 is 0.018 (1) Å. Deviations from ideal geometry are observed in the bond angles around atoms C3 and C9. While the C8—C9—C16 angle of 121.82 (19)° is close to the ideal value of 120°, the N10—C9—C16, C8—C9—N10 and C9—C8—C3 angles are more distorted, at 113.33 (17), 124.84 (19) and 130.2 (2)°, respectively, as a consequence of the strain induced by the double-bond linkage at C8═C9.

The azabicyclic system of (I) presents small distortions in its geometry with respect to literature data on the 1-azabicyclo[2.2.2]octane moiety, which is caused by the effect of the

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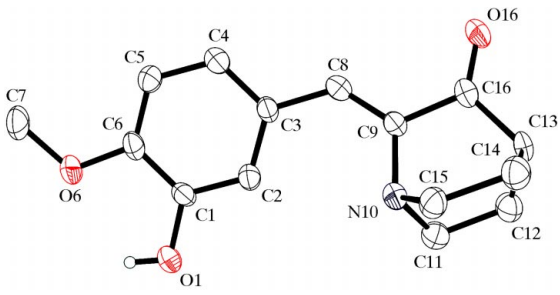

Figure 1
A view of the molecule of (I). Displacement ellipsoids are drawn at the 50% probability level. Only the H atom involved in hydrogen bonding is shown, as a small sphere of arbitrary radius.

double bonds connecting C8═C9 and C16═O16 on the bicyclic system. In both cases, Csp^2 atoms replace Csp^3 atoms and, as a result, atoms N10, C9, C16 and C13 assume a planar arrangement [N10—C9—C16—C13 = 3.1 (2)°], with partial conjugation between the double bond and the carbonyl bond, as indicated by the significant shortening of the C9—C16 single bond [1.484 (3) Å]. The bond angles for atoms C12, C13, C14 and N10 are, on average, smaller than the ideal tetrahedral value of 109.5°, while those for atoms C11 and C15 are, on average, slightly larger than the tetrahedral value. The bond angles about the sp^2 atoms C9 and C16 are larger than the ideal value.

The value of the C2—C3—C8—C9 torsion angle [−21.8 (3)°] indicates a deviation of the phenyl ring from the plane of the double bond connected to the azabicyclic ring. However, the C3—C8 bond length [1.465 (3) Å], when compared with the standard value for a single bond connecting a C_{ar} atom to a Csp^2 atom (1.470±0.015 Å), suggests extensive conjugation, beginning at the O16 carbonyl and extending through to the aromatic ring. The observed C6—O6 [1.372 (2) Å], O6—C7 [1.424 (2) Å] and C1—O1 [1.366 (2) Å] bond lengths are comparable with values found for aromatic methoxy and hydroxy groups in the literature, and there is an intramolecular O1—H1···O6 hydrogen bond [2.676 Å], because of the close proximity of these atoms on the phenyl ring.

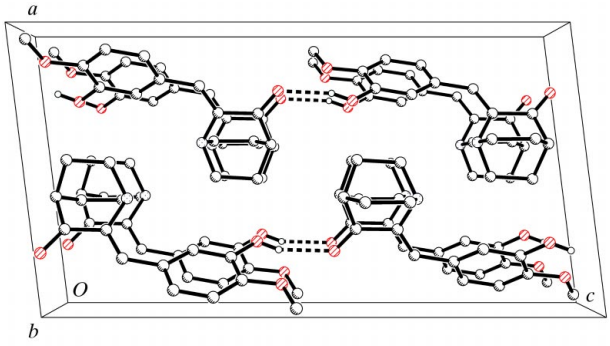

Figure 2
The packing of (I) in a projection along the *b* direction.

The mode of packing of compound (I) along the *b* direction is illustrated in Fig. 2. It is important to note that in the structurally related compound 2-(1-benzyl-1*H*-indol-3-yl-methylene)-1-azabicyclo[2.2.2]octan-3-one (Sonar *et al.*, 2003), the C2—C3—C10—C11 torsion angle, which corresponds to the C2—C3—C8—C9 torsion angle in (I), is −4.4 (3)°, suggesting that, in addition to van der Waals forces and in the absence of steric factors, intermolecular hydrogen bonding contributes significantly to the stabilization of the crystal structure conformation of (I).

Experimental

A mixture of 3-hydroxy-4-methoxybenzaldehyde (0.456 g, 3 mmol) and 1-azabicyclo[2.2.2]octan-3-one hydrochloride (0.483 g, 3 mmol) was dissolved in 10% methanolic KOH (10 ml) and the solution refluxed for 5 h. The cooled reaction mixture was poured on to crushed ice (100 g) and the solution was carefully neutralized by dropwise addition of dilute hydrochloric acid. The yellow crystalline solid that separated was collected by filtration and dried. Recrystallization from methanol afforded a yellow crystalline product, (I), which was suitable for X-ray analysis. Spectroscopic analysis: ^{1}H NMR ($CDCl_3$, p.p.m.): 2.01 (*td*, *J* = 7.8 and 3 Hz, 4H), 2.61 (*p*, *J* = 3 Hz, 1H), 2.95–3.02 (*m*, 2H), 3.09–3.19 (*m*, 2H), 3.92 (*s*, 3H), 5.62 (*s*, 1H), 6.84 (*d*, *J* = 8.1 Hz, 1H), 6.93 (*s*, 1H), 7.37 (*dd*, *J* = 8.25 and 1.8 Hz, 1H), 8.03 (*d*, *J* = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, p.p.m.): 26.3, 40.6, 47.8, 56.1, 110.2, 117.6, 125.1, 126.0, 127.8, 143.4, 145.3, 148.0, 206.5; high-resolution MS, calculated: 259.1208; found: 259.1204.

Crystal data

$C_{15}H_{17}NO_3$
M_r = 259.30
Monoclinic, $P2_1/c$
a = 10.7480 (4) Å
b = 5.8950 (2) Å
c = 20.4650 (8) Å
β = 97.030 (2)°
V = 1286.90 (8) Å^3
Z = 4
D_x = 1.338 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 9554 reflections
θ = 1.0–25.4°
μ = 0.09 mm^{-1}
T = 173 (2) K
Hemi-wedge slab, pale yellow
0.17 × 0.15 × 0.04 mm

Table 1
Selected geometric parameters (Å, °).

C1—O1	1.366 (2)	C9—N10	1.442 (2)
C1—C6	1.393 (3)	C9—C16	1.484 (3)
C2—C3	1.404 (3)	N10—C11	1.482 (2)
C3—C8	1.465 (3)	N10—C15	1.482 (2)
C6—O6	1.372 (2)	C13—C16	1.497 (3)
O6—C7	1.424 (2)	C16—O16	1.228 (2)
C8—C9	1.339 (3)		
O1—C1—C2	118.40 (19)	C8—C9—C16	121.82 (19)
O1—C1—C6	121.45 (18)	N10—C9—C16	113.33 (17)
C2—C3—C8	122.25 (18)	C9—N10—C11	108.61 (16)
O6—C6—C1	114.48 (18)	C9—N10—C15	107.98 (16)
C6—O6—C7	117.43 (16)	C11—N10—C15	108.43 (16)
C9—C8—C3	130.2 (2)	O16—C16—C9	124.66 (19)
C8—C9—N10	124.84 (19)	O16—C16—C13	124.60 (19)
O1—C1—C2—C3	−179.69 (17)	C1—C6—O6—C7	179.93 (17)
O1—C1—C6—O6	0.9 (3)	C4—C3—C8—C9	159.1 (2)
C2—C1—C6—O6	−178.11 (17)	C2—C3—C8—C9	−21.8 (3)
O1—C1—C6—C5	−179.33 (18)	C3—C8—C9—N10	−4.5 (3)

Data collection

Nonius KappaCCD area-detector diffractometer
ω scans at fixed $\chi = 55^\circ$
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)
$T_{min} = 0.984$, $T_{max} = 0.996$
8509 measured reflections
2251 independent reflections

1493 reflections with $I > 2\sigma(I)$
$R_{int} = 0.083$
$\theta_{max} = 25.0^\circ$
$h = -12 \rightarrow 12$
$k = -7 \rightarrow 7$
$l = -24 \rightarrow 24$
Intensity decay: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.054$
$wR(F^2) = 0.119$
$S = 1.03$
2251 reflections
174 parameters

H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0543P)^2$
$(\Delta/\sigma)_{max} = 0.003$
$\Delta\rho_{max} = 0.20$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}

H atoms were located in difference electron-density maps and allowed for as riding atoms during the refinement, with C—H = 0.95–0.99 Å and O—H = 0.84 Å.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL*/*PC* (Sheldrick, 1995); software used to prepare material for publication: *SHELXL*97 and local procedures.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1126). Services for accessing these data are described at the back of the journal.

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