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Codeinone

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Key indicators

Single-crystal X-ray study
T = 290 K
Mean σ(C–C) = 0.006 Å
R factor = 0.060
wR factor = 0.118
Data-to-parameter ratio = 10.2

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

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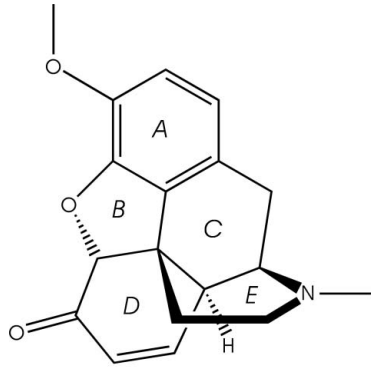
The title compound, 4,5α-epoxy-3-methoxy-17-methylmorphin-7-en-6-one, $C_{18}H_{19}NO_3$, the molecular structure exhibits features typical for morphine derivatives, with a T-shaped configuration. The crystal packing is stabilized by weak intermolecular C—H···O interactions.

Comment

The structure of codeinone, (I), was elucidated as part of our synthetic, spectroscopic and structural investigations of morphine alkaloids, which constitute a major class of pain-alleviating drugs. Codeinone has been found to possess anti-tumour potential, with high cytotoxic activity against human promyelocytic leukaemic cell lines (Hitosugi *et al.*, 2003). The transformation of morphine derivatives into different metabolites is a matter of practical interest for detecting opiates in blood or urine. It is known that codeinone in the living cell is produced from the reaction of codeine with nicotinamide adenine dinucleotide phosphate (NADP+).



(I)

The overall configuration of (I) and the atom-numbering scheme are shown in Fig. 1. The absolute configuration of the chiral centres in the molecule is identical to those of the starting material, codeine. The main structural features of the molecule are very close to those of codeine (Canfield *et al.*, 1987), heroin (Canfield *et al.*, 1979), morphine (Gylbert, 1973) and acetylcodeine (Sonar *et al.*, 2005; Kolev *et al.*, 2005).

The molecule of (I) exhibits the T-shaped configuration characteristic of classical morphine opiates.

The ring fusions and conformations are similar to those previously reported for morphine derivatives (Gelders & de Ranter, 1979; Petrickova *et al.*, 2002; Moody *et al.*, 1997). Aromatic ring *A* is planar, ring *B* is close to an envelope, rings *C* and *D* assume half-chair conformations and ring *E* assumes a chair form (Table 1). The oxidation of codeine to codeinone should mainly affect the shape and properties of ring *D*.

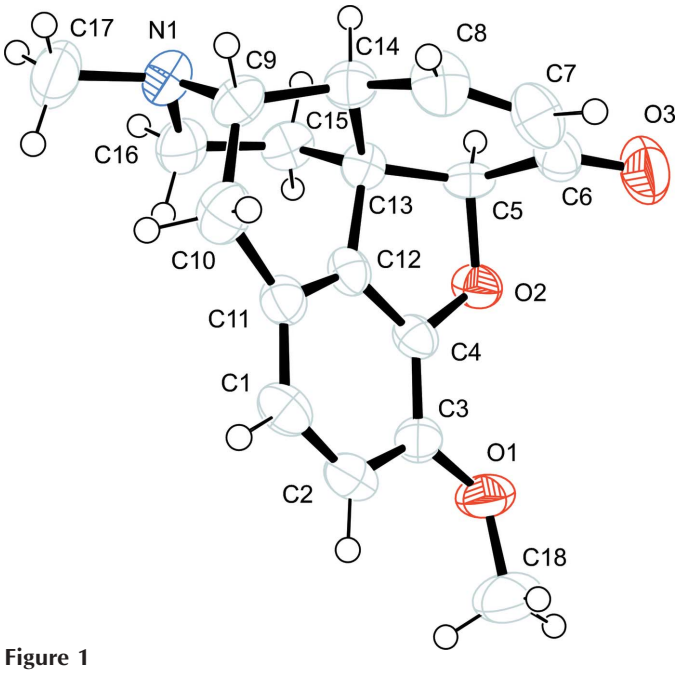


Figure 1
The molecular structure of (I), showing 50% probability displacement ellipsoids.

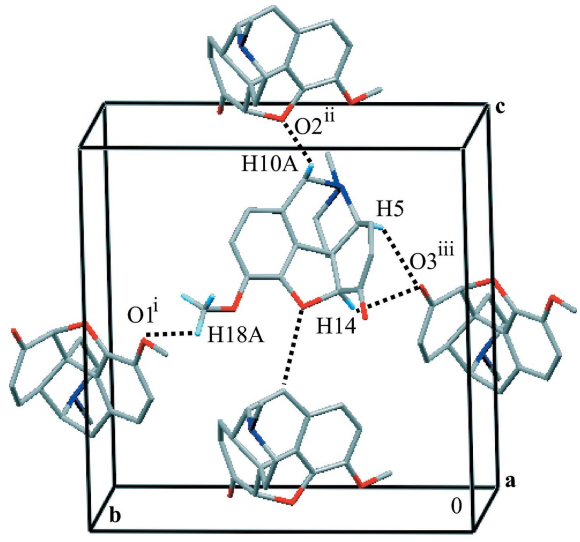


Figure 2
The molecular packing in (I). Intermolecular C—H···O contacts are denoted by dotted lines. H atoms not participating in C—H···O contacts have been omitted for clarity. [Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (ii) $-x+\frac{3}{2}, -y+1, z+\frac{1}{2}$; (iii) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$.]

However, no major differences between the geometric parameters of ring *D* in codeinone, codeine and even 6-*O*-codeine could be established.

The conformation about the single C—C bonds within the rings is staggered, as in codeine; exceptions such as the C5—C6 eclipsed bond in 6-*O*-codeine are not present. This difference between the codeinone and 6-acetylcodeine conformations, along with the absence or presence of a chiral centre at the C6 position, is associated with the different functional groups attached to atom C6.

In the three-dimensional arrangement of the molecules of (I) (Fig. 2), no classical hydrogen bonds could be found. A subsequent examination of intermolecular contacts suggested that molecules of (I) are linked in the crystal structure through weak C—H···O interactions (Desiraju, 1996; Steiner & Desiraju, 1998; Zhu *et al.*, 2005). The interactions involving atoms O1 and O3 (Table 2) connect the molecules to form undulating 'pseudo'-layers perpendicular to the *c* axis. The C10—H10*A*···O2 interaction connects the layers along the *c* axis, extending the structure stabilization in all three directions.

Experimental

Codeinone was prepared according to the method of Bakalska *et al.* (2002). Crystals suitable for X-ray diffraction were obtained by slow evaporation of an ethanol solution at 277 K.

IR spectra were measured on a Bomem–Michelson 100 FT–IR spectrometer in the range 4000–400 cm^{-1}, with 2 cm^{-1} resolution and 150 scans. Solid-state IR spectra were recorded using the KBr pellet technique. Chloroform (Merck) solutions, at a concentration of 0.01 *M*, were measured using 0.05 cm KBr pellets. The bands at 2840 and 2807 cm^{-1} of codeinone were assigned to $\nu^s[CH_3(O)]$ and $\nu^s[CH_3(N)]$ modes, respectively. The most intense peak at 1677 cm^{-1} in the IR spectrum of codeinone belongs to the ν(C═O) mode of the conjugated C═O group. The maxima at 1374 and 1388 cm^{-1} indicate δ^s[CH3(N)] and δ^s[CH3(O)], respectively. Typical for morphine compounds are peaks at about 1633, 1604 and 1506 cm^{-1}, which are assigned as ν(C ═C), 8a and 19a in-plane (A_1) phenyl modes. The series of in-plane peaks of 1,2,3,4-*o*-tetrasubstituted benzene at about 1150 and 1050 cm^{-1} is observed in the 1200–800 cm^{-1} frequency region. Below 1000 cm^{-1}, an intense maximum at 940 cm^{-1} and a pair of maxima at about 936 and 804 cm^{-1} are present, but the exact assignment with conventional IR techniques is ambiguous. A detailed spectroscopic study, combined with *ab initio* UHF calculations of (I), are in progress and will be published at a later date.

Spectroscopic analysis for codeinone: ^{1}H NMR (Bruker 250, 250 MHz, $CDCl_3$, δ, p.p.m.): 6.67 (*d*, 1H, *J* = 8.2 Hz, H-2), 6.62 (*d*, 1H, *J* = 10.2 Hz, H-8), 6.59 (*d*, 1H, *J* = 8.2 Hz, H-1), 6.07 (*dd*, 1H, *J* = 10.2 and 2.9 Hz, H-7), 4.68 (*s*, 1H, H-5), 3.85 (*s*, 3H OCH_3), 3.45–3.35 (*m*, 1H, H-9), 3.25–3.17 (*m*, 1H, H-14), 3.10 (*d*, 1H, *J* = 18.5 Hz, H-10β), 2.61 (*dm*, 1H, *J* = 11.8Hz, H-16$_e$), 2.45 (*s*, 3H, NCH_3), 2.30 (*dd*, 1H, *J* = 18.5 and 5.5 Hz, H-10α), 2.30 (*td*, 1H, *J* = 11.9 and 3.7 Hz, H-16$_a$), 2.06 (*td*, 1H, *J* = 12.0 and 4.8 Hz, H-15$_a$), 1.85 (*dm*, 1H, *J* = 12.5 Hz, H-15$_e$); ^{13}C NMR ($CDCl_3$, δ, p.p.m.): 119.7 (C-1), 114.7 (C-2), 142.3 (C-3), 146.2 (C-4), 88.0 (C-5), 194.1 (C-6), 132.2 (C-7), 149.1 (C-8), 58.9 (C-9), 20.4 (C-10),126.1 (C-11), 129.0 (C-12), 43.1 (C-13), 41.4 (C-14), 33.9 (C-15), 46.7 (C-16), 42.9 (NMe), 56.7 (OMe).

Crystal data

$C_{18}H_{19}NO_3$
M_r = 297.34
Orthorhombic, $P2_12_12_1$
a = 7.2541 (10) Å
b = 14.0943 (14) Å
c = 14.3507 (15) Å
V = 1467.2 (3) Å^3
Z = 4
D_x = 1.346 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 22 reflections
θ = 16.3–17.7°
μ = 0.09 mm^{-1}
T = 290 (2) K
Prism, colourless
0.18 × 0.16 × 0.15 mm

Data collection

Enraf–Nonius CAD-4 diffractometer	$\theta_{max} = 28.0°$
Non–profiled $\omega/2\theta$ scans	$h = 0 \rightarrow 9$
Absorption correction: none	$k = -18 \rightarrow 18$
7258 measured reflections	$l = -18 \rightarrow 18$
2032 independent reflections	3 standard reflections
987 reflections with $I > 2\sigma(I)$	frequency: 120 min
$R_{int} = 0.172$	intensity decay: 2%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0344P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.060$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.118$	$\Delta\rho_{max} = 0.16$ e Å^{-3}
$S = 1.02$	$\Delta\rho_{min} = -0.18$ e Å^{-3}
2032 reflections	Extinction correction: *SHELXL97* (Sheldrick, 1997)
200 parameters	Extinction coefficient: 0.0128 (18)
H-atom parameters constrained	

Table 1
Selected torsion angles (°).

C16—N1—C9—C14	62.5 (5)	C14—C9—C10—C11	−36.2 (6)
O2—C4—C12—C13	4.2 (5)	C10—C11—C12—C13	−5.8 (7)
C13—C5—C6—C7	−1.6 (5)	C4—C12—C13—C5	−21.0 (4)
O2—C5—C13—C14	144.8 (4)	C11—C12—C13—C15	−86.9 (5)
C6—C7—C8—C14	−1.2 (8)	C15—C13—C14—C9	64.1 (5)
C7—C8—C14—C13	26.9 (7)	C13—C15—C16—N1	52.0 (5)

Table 2
Intermolecular C—H···O contacts (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C18—H18*A*···O1^{i}	0.96	2.75	3.285 (6)	116
C10—H10*A*···O2^{ii}	0.97	2.62	3.423 (5)	140
C14—H14···O3^{iii}	0.98	2.66	3.389 (6)	131
C5—H5···O3^{iii}	0.98	2.70	3.260 (5)	117

Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (ii) $-x+\frac{3}{2}, -y+1, z+\frac{1}{2}$; (iii) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$.

All H atoms were placed in idealized positions, with C—H = 0.93–0.98 Å, and constrained to ride on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(Csp^3$ and $C_{aromatic})$, or $1.5U_{eq}(C_{Me})$. In the absence of significant anomalous dispersion effects, Friedel pairs were averaged.

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *MERCURY* (Version 1.3; Bruno *et al.*, 2002); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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