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6α-Acetoxy-4,5α-epoxy-3-methoxy-17-methylmorphin-7-ene

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Key indicators

Single-crystal X-ray study
T = 90 K
Mean σ(C–C) = 0.006 Å
R factor = 0.047
wR factor = 0.112
Data-to-parameter ratio = 7.3

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

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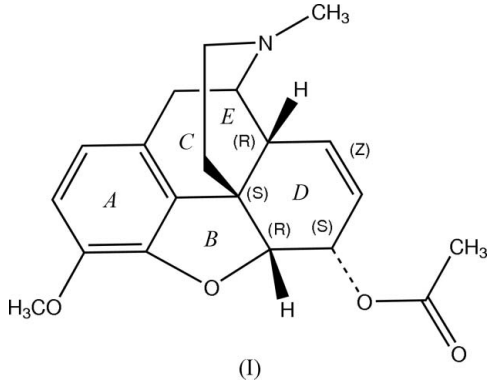
Crystals of the title compound, which is also commonly known as 6-*O*-acetylcodeine, $C_{20}H_{23}NO_4$, were obtained by acetylation of codeine and subsequent crystallization of the product from ethyl acetate. The atoms of the benzene ring are nearly coplanar, whereas the five-memberedring is distorted. The ethanamine ring has a typical chair form conformation, while the cyclohexene ring is in a twisted boat form.

Comment

Morphine is the most important component of *Papaver somniferum* extracts and its semisynthetic analogs, which have been used as pain-alleviating medicines (Brock *et al.*, 1996; Brown *et al.*, 1985). 6-*O*-Acetylcodeine is a useful intermediate for the synthesis of a variety of pharmacologically active morphine and codeine analogs, and is a useful synthon for reactions in which the 6-hydroxy group needs to be protected. Such compounds that are of considerable pharmacological interest are 10-hydroxymorphine, and 10-hydroxycodeine. The title compound, (I), was prepared by the reaction of codeine phosphate with acetic anhydride in the presence of pyridine and dimethylaminopyridine. To obtain more detailed structural information on the conformation of the molecule in the solid state, the X-ray crystal structure determination of (I) has been carried out.



(I)

The numbering system of the non-H atoms and the overall configuration of the title compound is shown in Fig. 1, which shows the absolute configuration of the chiral centers in the molecule as identical to that of the starting material, codeine. Selected geometric parameters are presented in Table 1. The atoms of the benzene ring (*A*) are nearly coplanar, whereas the five membered ring (*B*) is distorted. The ethanamine ring (*E*) has a typical chair conformation, while the conformation of ring *D* is a twist boat. This is caused by the 4,5-ether bridge,

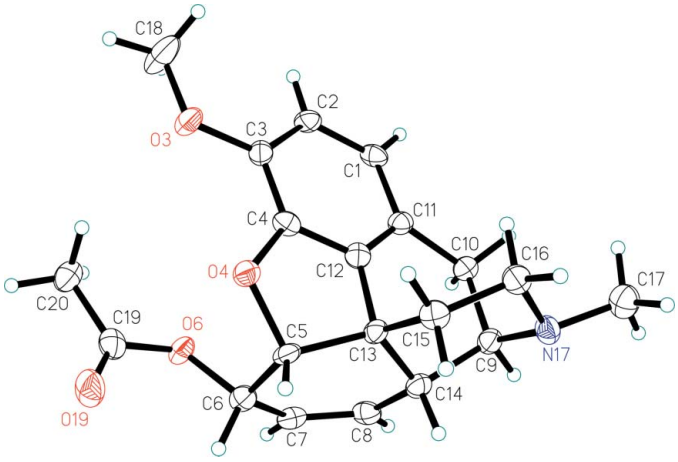


Figure 1
The molecular structure of (I), with displacement ellipsoids drawn at the 50% probability level.

which is also responsible for the overall rigidity of the molecule. The bond lengths and bond angles for the non-H atoms are in agreement with the literature values for codeine hydrobromide (Kartha *et al.*, 1962).

Another structure determination of 6-*O*-acetylcodeine is reported in the following paper (Kolev *et al.*, 2005).

Experimental

To a stirred mixture of codeine phosphate (1.74 g, 4.29 mmol), DMAP (0.183 g, 1.5 mmol) and pyridine (8 ml) was added acetic anhydride (1.02 g, 10 mmol) at 273 K dropwise. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, then water (10 ml) was added to the residue followed by potassium carbonate solution (20 ml, 2.5%). The resulting solution was extracted with diethyl ether (3 × 80 ml), and the ether layers were combined and washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a pale-yellow solid which on crystallization from ethyl acetate afforded (I) as colorless flakes suitable for X-ray analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86 (*d*, 1H), 2.05 (*td*, 1H), 2.16 (*s*, 3H), 2.33 (*td*, 2H), 2.44 (*s*, 3H), 2.59 (*dd*, 1H), 2.74 (*s*, 1H), 3.04 (*d*, 1H), 3.36 (*q*, 1H), 3.85 (s, 3H), 5.07 (*d*, 1H), 5.19 (*q*, 1H), 5.53 (*dd*, 2H), 6.60 (*dd*, 2H).

Crystal data

$C_{20}H_{23}NO_4$
M_r = 341.39
Orthorhombic, $P2_12_12_1$
a = 8.6588 (4) Å
b = 12.3368 (7) Å
c = 15.4441 (9) Å
V = 1649.77 (15) Å^3
Z = 4
D_x = 1.374 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2134 reflections
θ = 1.0–27.5°
μ = 0.10 mm^{-1}
T = 90.0 (2) K
Irregular fragment, colorless
0.25 × 0.15 × 0.10 mm

Data collection

Nonius KappaCCD diffractometer
ω scans at fixed χ = 55°
Absorption correction: none
2902 measured reflections
1683 independent reflections
1116 reflections with $I > 2\sigma(I)$
R_{int} = 0.074
θ_{max} = 25.0°
$h = -10 \rightarrow 10$
$k = -14 \rightarrow 14$
$l = -18 \rightarrow 18$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.113
S = 0.98
1683 reflections
229 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0595P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O3—C3	1.385 (5)	O6—C19	1.353 (5)
O3—C18	1.413 (5)	C7—C8	1.331 (6)
O4—C4	1.387 (4)	C12—C13	1.505 (6)
O4—C5	1.471 (4)	O19—C19	1.203 (5)
C4—C12	1.374 (6)	C19—C20	1.492 (6)
C5—C13	1.541 (6)		
C3—O3—C18	116.8 (3)	C7—C8—C14	122.7 (4)
C2—C3—O3	125.9 (4)	C11—C12—C13	127.9 (4)
C4—O4—C5	105.0 (3)	C14—C13—C5	118.5 (3)
C12—C4—O4	111.1 (3)	C14—C13—C15	108.0 (3)
O4—C5—C13	104.1 (3)	C8—C14—C13	112.3 (4)
C19—O6—C6	116.3 (3)	C16—N17—C9	114.2 (3)
C7—C6—C5	116.2 (3)	O19—C19—O6	124.4 (4)
C8—C7—C6	125.1 (4)	O19—C19—C20	126.5 (4)
C18—O3—C3—C2	5.8 (6)	C6—C7—C8—C14	−0.3 (7)
C19—O6—C6—C5	−74.6 (4)		

H atoms were found in difference Fourier maps and subsequently placed using riding models in which the H atom coordinates were determined geometrically from their attached parent atom. Bond distances for these H atoms were fixed as follows: aromatic C—H = 0.95 Å, CH C—H = 1.00 Å, CH_2 C—H = 0.99 Å and methyl C—H = 0.9 Å. Isotropic displacement parameters for the H atoms were defined as $1.2U_{eq}$(C) for aromatic, CH and CH_2, and $1.5U_{eq}$(C) for the methyl H atoms. The absolute configuration of this compound is known; it was not determined from the X-ray data. Nonetheless, the bulk of the refinement was carried out against data in which the Friedel pairs were kept unmerged. This enabled the Flack (1983) parameter to be determined so as to confirm the expected result that the data do not contain the information required to define $x(u)$. Later, the model was rerefined to convergence with merged data, and it is this model that is contained within this CIF.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL/PC* (Sheldrick, 1995); software used to prepare material for publication: *SHELXL97* (Sheldrick, 1997) and local procedures.

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