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7β-Chloro-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine

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Key indicators

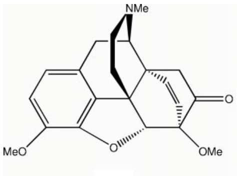
Single-crystal X-ray study
T = 103 K
Mean σ(C–C) = 0.004 Å
R factor = 0.054
wR factor = 0.121
Data-to-parameter ratio = 18.6

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

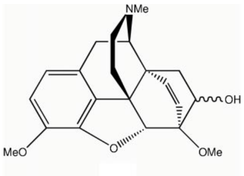
In the crystal structure of the title compound, $C_{21}H_{24}ClNO_3$, there are two independent molecules in the asymmetric unit. The compound is the product of a new procedure for preparing Diels–Alder adducts of thebaine with 7β substituents.

Comment

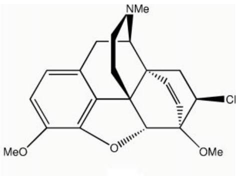
The Diels–Alder adducts of thebaine are key intermediates in the synthesis of the potent opioid analgesic orvinols (Casey & Parfitt, 1986). Diels–Alder reactions between thebaine and dienophiles predominantly give rise to 7α adducts, and the corresponding 7β adducts have received little attention due to their difficulty of preparation (Bentley & Hardy, 1967; Marton *et al.*, 1995; Derrick *et al.*, 2000). We report here a new procedure for preparing adducts of thebaine with 7β substituents, and the structure of 7β-chloro-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine, (3).



(1)



(2)



(3)

The title compound, (3), was prepared from (1) by reduction with lithium aluminium hydride followed by treatment with phosphorus oxychloride. This procedure potentially allows facile access to 7β-substituted adducts of thebaine through the use of the appropriate nucleophiles.

The title compound crystallized in the orthorhombic space group $P2_12_12_1$ with two molecules in the asymmetric unit. The absolute configuration was determined from the X-ray data and is consistent with the known configuration of chiral

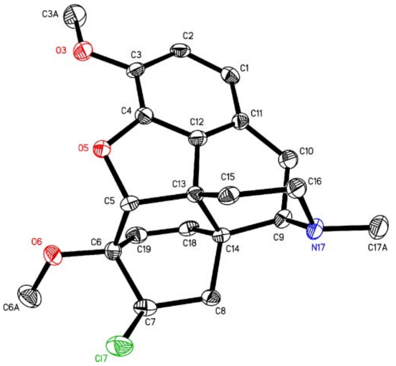


Figure 1
View of (3) showing the labeling of the non-H atoms of one molecule of the asymmetric unit. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

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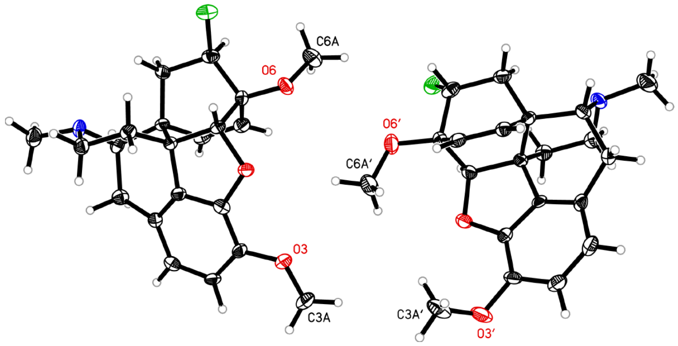

Figure 2
View of (3) showing the relationship of the two independent molecules. The primary difference between these molecules is in the orientations of the methoxy groups (labeled atoms) on C3 and C6.

centers in the starting material. The conformation of a single molecule is shown in Fig. 1.

The two molecules in the asymmetric unit differ primarily in the orientation of the two methoxy groups. In one molecule, the torsion angles for these two groups are 12.4 (5) and −176.9 (3)° (for C2—C3—O3—C3*A* and C5—C6—O6—C6*A*, respectively). In the second molecule, these angles are 112.2 (4) and 70.2 (4)° (for C2′—C3′—O3′—C3*A*′ and C5′—C6′—O6′—C6*A*′, respectively). The different conformations of these groups accomodate the observed packing, as is illustrated in Fig. 2.

Experimental

To a stirred solution of 7-ketone (1) (Maeda & Coop, 2001; Lewis *et al.*, 1973; Lewis & Readhead, 1973) (4.3 g, 12.2 mmol) in tetrahydrofuran (150 ml) at room temperature was added lithium aluminium hydride (0.93 g, 24.2 mmol), and the mixture was stirred under reflux for 1 h. After cooling to room temperature, the excess lithium aluminium hydride was eliminated by careful addition of water. The mixture was then concentrated to dryness and partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, 50% ethyl acetate in hexane) to afford a mixture of alcohols (2) (Hua *et al.*, 1987) (4.2 g, 96%) as a colorless foam (2.6:1 epimeric mixture from ^{1}H NMR). To a stirred solution of (2) (4.0 g, 11.3 mmol) in pyridine (25 ml) was added phosphorus oxychloride (2.12 ml, 22.6 mmol) dropwise. The mixture was heated to reflux for 2 h, cooled to room temperature, poured onto crushed ice (80 g), and dichloromethane extracted. The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 50% ethyl acetate in hexane) to yield only the 7β-chloro derivative (3) (1.89 g, 45%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82 (*d*, 1H, J = 8.8 Hz), 2.07 (*dd*, 1H, J = 14.0, 10.3 Hz), 2.37 (*s*, 3H), 2.40–2.60 (*m*, 4H), 2.98 (*dd*, 1H, J = 14.0, 2.2 Hz), 3.12–3.30 (*m*, 2H), 3.54 (*s*, 3H), 3.83 (*s*, 3H), 4.19 (*dd*, 1H, J = 11.0, 2.6 Hz), 5.13 (*s*, 3H), 5.56 (*d*, 1H, J = 8.4 Hz), 5.91 (*d*, 1H, J = 8.4 Hz), 6.52 (*d*, 1H, J = 8.0 Hz), 6.63 (*d*, 1H, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.99, 142.13, 139.10, 134.58, 127.67, 126.20, 119.25, 113.77, 92.18, 80.77, 59.85, 57.82, 56.69, 52.49, 46.71, 45.49, 43.55, 43.37, 36.11, 31.36, 22.25. It is envisioned that reaction of the 7α-hydroxyl with the phosphorus oxychloride yielded an excellent leaving group, which was displaced by the chloride ion with inversion of configuration. Products arising from the 7β-hydroxyl could not be isolated. Suitable crystals of the title compound, (3), were grown by evaporation of an ethyl acetate solution.

Crystal data

$C_{21}H_{24}ClNO_3$
M_r = 373.86
Orthorhombic, $P2_12_12_1$
a = 7.7262 (4) Å
b = 19.8316 (10) Å
c = 23.6182 (13) Å
V = 3618.8 (3) Å^3
Z = 8
D_x = 1.372 Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 7584 reflections
θ = 2.7–26.7°
μ = 0.23 mm^{-1}
T = 103 (2) K
Plate, colorless
0.35 × 0.23 × 0.02 mm

Data collection

Bruker SMART 1000 CCD diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2000)
$T_{\min}$ = 0.839, $T_{\max}$ = 0.995
29542 measured reflections

8828 independent reflections
5974 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.079
$\theta_{\max}$ = 28.4°
$h = -10 \rightarrow 10$
$k = -26 \rightarrow 26$
$l = -28 \rightarrow 30$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.121
S = 1.23
8828 reflections
475 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0274P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max}$ = 0.29 e Å^{-3}
$\Delta\rho_{\min}$ = −0.28 e Å^{-3}
Absolute structure: Flack (1983), 3864 Friedel pairs
Flack parameter = −0.02 (6)

All H atoms were placed in calculated positions with C—H distances ranging from 0.95 to 1.00 Å and included in the refinement in riding-model approximation with $U_{\rm iso} = 1.2U_{\rm eq}$ ($1.5U_{\rm eq}$ for methyl) of the carrier atom.

Data collection: *SMART* (Bruker, 1999); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2000) and *XPREP* (Bruker, 1997); program(s) used to solve structure: *SHELXTL* (Bruker, 2000); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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