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5-Butylthevinone: stereochemistry of the Diels–Alder reaction of 5-butylthebaine with 3-buten-2-one

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Key indicators

Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.006 Å
R factor = 0.056
wR factor = 0.124
Data-to-parameter ratio = 12.8

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

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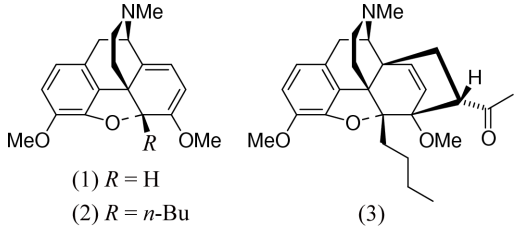
In this paper, we report on the X-ray analysis of 5-butylthevinone (7α-acetyl-4,5α-epoxy-3,6-dimethoxy-5β-butyl-17-methyl-6α,14α-ethenoisomorphinan), $C_{27}H_{35}NO_4$. This compound is the sole product of a Diels–Alder reaction of 5-butylthebaine with 3-buten-2-one, through attack of the dienophile on the β-face of the diene, even though it has been suggested that the introduction of 5β-substituents tends to hinder attack from the β-face, and leads to the production of *exo*-etheno adducts through attack from the α-face.

Comment

The orvinols are an important class of opioids which are of continued interest due to their high potency as analgesics (Casy & Parfitt, 1986; Maat *et al.*, 1999; Coop *et al.*, 2000; Derrick *et al.*, 2000; Meada & Coop, 2001). The preparation of the orvinols involves a Diels–Alder addition of a dienophile to the diene system of thebaine, (1), which occurs from the least hindered β-face (*endo*-adducts). Several reports have shown that the introduction of small substituents into the 5-position of thebaine (Boden *et al.*, 1982) hinders attack on the β-face, giving rise to a small quantity of the adduct arising from attack from the α-face (*exo*-adducts) (Woudenberg *et al.*, 1992, 1994; Baas *et al.*, 1997; Maat *et al.*, 1999). In an attempt to brominate the 5-position of thebaine, we inadvertently obtained the 5β-butylated derivative, (2), and considered that this compound would possess greater steric hindrance than the small substituents already investigated. We hypothesized that a greater quantity of the *exo*-adduct would result.



(1) R = H
(2) R = *n*-Bu
(3)

As expected, a slow reaction was observed, but unexpectedly the only product formed was the *endo*-adduct, (3), resulting from attack from the β-face. Thus, the introduction of a large β-butyl group does not favor attack from the α-face.

The title compound, (3), crystallized in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit (Fig. 1). The absolute configuration could not be determined from the X-ray data and was therefore assigned on the basis of heroin (Deschamps *et al.*, 1996).

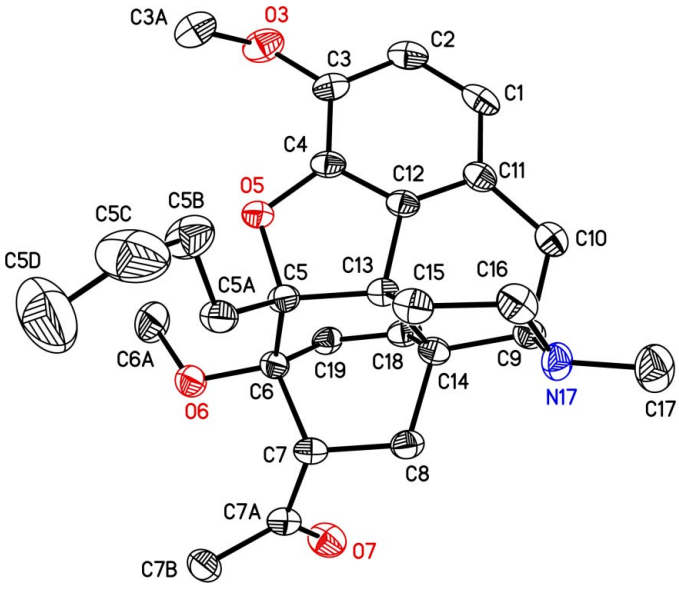


Figure 1
View of 5-butylthevinone, (3). Displacement ellipsoids are shown at the 20% probability level and H atoms have been omitted for clarity.

Experimental

Synthesis of 5-butylthebaine, (2): to a stirred solution of TMEDA (0.78 ml, 5.1 mmol) in dry tetrahydrofuran (THF, 10 ml), cooled to 195 K, was added a solution of BuLi solution (12 ml of a 1.11 *M* solution in hexane, 13.3 mmol). The mixture was stirred for 30 min before the slow addition of a solution of thebaine, (1) (0.93 g, 3.0 mmol) in dry THF (20 ml). The solution was allowed to stir at 195 K for 1 h, followed by the addition of *N*-bromosuccinimide (0.60 g, 3.4 mmol) in THF (10 ml). After stirring for a further 30 min at 195 K, the solution was allowed to come to room temperature over 2 h, and stirred at room temperature overnight. After removal of the solvent, the residue was taken up in $CHCl_3$ (50 ml), washed with $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (gradient from 2% to 10% MeOH in CH_2Cl_2) to afford (2) (0.61 g, 55%), a colorless foam, as the sole product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (*t*, 3H, *J* = 6.6 Hz, CH_3 in butyl group), 2.46 (*s*, NCH_3), 3.29 (*d*, 1H, *J* = 18.3 Hz), 3.56 (*s*, 3H, OMe), 3.65 (*d*, 1H, *J* = 6.1 Hz), 3.83 (*s*, 3H, OMe), 5.07 (*d*, 1H, *J* = 6.4 Hz), 5.55 (*d*, 1H, *J* = 6.4 Hz), 6.57 (*d*, 1H, *J* = 8.3 Hz), 6.63 (*d*, 1H, *J* = 8.3 Hz).

Synthesis of 5-butylthevinone, (3): a mixture of (2) (0.56 g, 1.52 mmol), 3-buten-2-one (4.8 ml, 57.7 mmol) and toluene (10 ml) was heated under reflux for 13 d. The reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (gradient: 1% to 3% MeOH in CH_2Cl_2) to afford (3) (0.28 g, 42%), a colorless solid, as the only product. Evaporative recrystallization from MeOH provided crystals suitable for X-ray analysis; m.p. 456–457 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (*t*, 3H, *J* = 6.6 Hz, CH_3 in butyl group), 2.14 (*s*, 3H, Me in acetyl), 2.34 (*s*, 3H, NMe), 3.11 (*d*, 1H, *J* = 6.4 Hz), 3.24 (*d*, 1H, *J* = 18.3 Hz), 3.58 (*s*, 3H, OMe), 3.82 (*s*, 3H, OMe), 5.48 (*d*, 1H, *J* = 8.8 Hz), 5.97 (*d*, 1H, *J* = 8.8 Hz), 6.47 (*d*, 1H, *J* = 8.0 Hz), 6.61 (*d*, 1H, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.10, 148.64, 141.65, 135.99, 129.29, 125.32, 119.14, 115.09, 100.34, 84.04, 60.88, 57.74, 54.86, 50.53, 49.69, 45.97, 44.83, 43.73, 32.25, 29.24 (2C), 29.11, 28.92, 27.66, 24.16, 23.13, 14.49. EIMS *m*/*z*: 437 (*M*+, 47%), 394 (32%), 206 (100%).

Crystal data

$C_{27}H_{35}NO_4$	D_x = 1.251 Mg m^{-3}
M_r = 437.56	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 1983 reflections
a = 9.706 (5) Å	θ = 2.5–23.7°
b = 7.292 (3) Å	μ = 0.08 mm^{-1}
c = 16.958 (8) Å	T = 298 (2) K
β = 104.519 (6)°	Prism, colorless
V = 1161.8 (9) Å^3	0.64 × 0.18 × 0.06 mm
Z = 2	

Data collection

Bruker SMART 1000 CCD diffractometer	3701 independent reflections
φ and ω scans	2014 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (Bruker, 2000)	R_{int} = 0.056
T_{min} = 0.921, T_{max} = 0.994	θ_{max} = 28.4°
5557 measured reflections	$h = -12 \rightarrow 12$
	$k = -3 \rightarrow 9$
	$l = -20 \rightarrow 22$

Refinement

Refinement on F^2	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)]$ = 0.056	$w = 1/[\sigma^2(F_o^2) + (0.0467P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2)$ = 0.124	$(\Delta/\sigma)_{max} < 0.001$
S = 0.97	$\Delta\rho_{max}$ = 0.29 e Å^{-3}
3701 reflections	$\Delta\rho_{min}$ = −0.25 e Å^{-3}
290 parameters	

The β-butyl side chain, attached at C5, can also be modeled with a disorder of atoms C5*B*, C5*C* and C5*D*. Inclusion of this disorder also requires distance restraints on the C5*C*—C5*D* bond in the major component and the C5*B*′—C5*C*′ and C5*C*′—C5*D*′ distances in the minor component, and restraints on the anisotropic displacement parameters for C5*B*′, C5*C*′ and C5*D*′. The minor component had an occupancy of 30% or less and peaks in the region of this final difference map were still in the area of this disordered side chain, indicating that the disorder may be even more complex (*i.e.* over more than the two positions modeled). Due to problems with modeling of the disorder this was omitted from the final refinement.

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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