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(9*R*,13*R*,14*R*)-7-(*E*)-Benzylidene-14-hydroxy-3,4-dimethoxy-17-methylmorphinan-6-one

Damon A. Parrish,[a]‡ Linn N. Thatcher,[b] Hui-Fang Wu,[b] Andrew Coop[b] and Jeffrey R. Deschamps[a]*

[a]Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, Washington, DC 20375, USA, and [b]Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, Room 637, 20 Penn Street, Baltimore, MD 21201, USA

‡ ASEE Postdoctoral Fellow

Correspondence e-mail: deschamps@nrl.navy.mil

Key indicators

Single-crystal X-ray study
T = 297 K
Mean σ(Wae) = 0.000 Å
R factor = 0.053
wR factor = 0.147
Data-to-parameter ratio = 8.4

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

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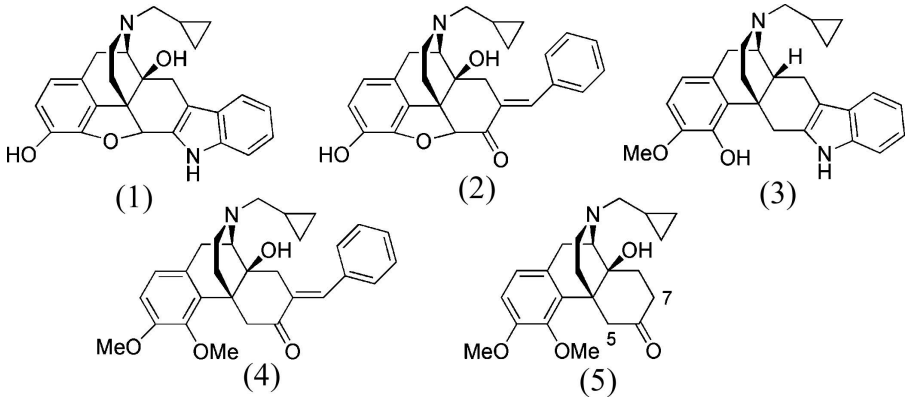
The chiral title compound, $C_{29}H_{33}NO_4$, crystallized from methanol. The absolute configuration was assigned by reference to an unchanging chiral center in the synthetic procedure.

Comment

The indolomorphinans, such as naltrindole, (1), and the opioid benzylidenes, such as benzylidenenaltrexone, (2), are widely used as δ opioid selective antagonists (Portoghese *et al.*, 1992). As part of our studies into developing analogs with improved δ opioid selectivity, we have shown that the corresponding 4,5-ring-opened indolomorphinan analogs, (3), have improved δ opioid selectivity, but the presence of the aromatic 4-hydroxyl group led to compounds which were prone to aerobic oxidation (Coop *et al.*, 1999). Protecting the 4-hydroxyl as a 4-methyl ether would be anticipated to slow aerobic oxidation, and we prepared the title compound, (4), from the 3,4-dimethoxymorphinan, (5) (Wu *et al.*, 2005), through treatment with benzaldehyde and sodium hydroxide. The fact that the ketone of (5) has methylene groups on both sides of the ketone leads to the possibility of addition of the benzylidene group to the undesired 5-position. Results from the present crystallographic study (Fig. 1) confirmed reaction at the desired 7-position to produce (4).



Prior studies have suggested that the pharmacology of the 4-phenolic indolomorphinans cannot be directly compared to the 4,5-oxygen-bridged compounds (indoloepoxymorphinans) due to the fact that opening the bridge changes the conformation of the opioid skeleton (Coop *et al.*, 1999). A comparison of the conformation of the title compound (4) to Naltrexone (Fig. 2) shows that although there is generally good agreement there is a difference in the conformation of the *C* ring (i.e. atoms C5, C6, C7, C8, C13 and C14) as would be expected with the loss of the 4,5-oxygen bridge.

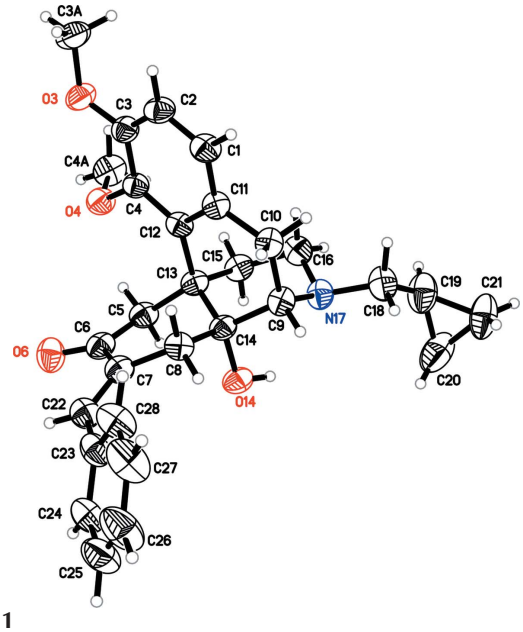


Figure 1
A view of (4), showing the labeling of the non-H atoms. Displacement ellipsoids are drawn at the 30% probability level.

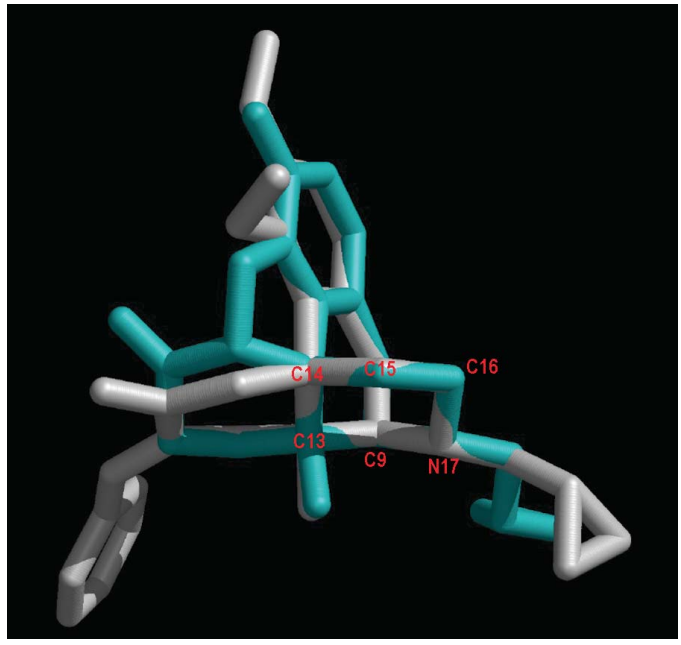


Figure 2
Comparison of (4) with Naltrexone (Le Dain *et al.*, 1992). The labeled atoms were used to align the two molecules.

Experimental

The title compound was prepared from the 3,4-dimethoxymorphinan as described above (Wu *et al.*, 2005) and crystallized by slow evaporation of a solution in methanol.

Crystal data

$C_{29}H_{33}NO_4$
M_r = 459.56
Orthorhombic, $P2_12_12_1$
a = 12.3572 (17) Å
b = 12.6676 (11) Å
c = 15.874 (3) Å
V = 2484.9 (6) Å^3
Z = 4
D_x = 1.228 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 21 reflections
θ = 4.5–22.5°
μ = 0.65 mm^{-1}
T = 297 (2) K
Prism, colorless
0.54 × 0.24 × 0.22 mm

Data collection

Bruker P4 diffractometer
$2\theta/\omega$ scans
Absorption correction: none
6038 measured reflections
2615 independent reflections
2091 reflections with $I > 2\sigma(I)$
R_{int} = 0.053
θ_{max} = 69.0°
$h = -14 \rightarrow 1$
$k = -1 \rightarrow 15$
$l = -19 \rightarrow 19$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.053
$wR(F^2)$ = 0.148
S = 1.04
2615 reflections
310 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0849P)^2 + 0.173P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}

Lacking any suitable heavy atoms, the absolute configuration could not be established by anomalous dispersion and therefore the Friedel pairs were merged during the final refinement. The choice of enantiomer was based on an unchanging chiral center in the synthetic procedure. H atoms were placed in geometric positions and treated as riding, with C—H distances in the range 0.93–0.98 Å and an O—H distance of 0.82 Å, and with $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}(O)$.

Data collection: *XSCANS* (Bruker, 1997); cell refinement: *XSCANS*; data reduction: *XSCANS* 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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