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7β,14β-Epoxyhydrocodone-6,6-dimethoxy ketal: an unusual oxetane-containing opioid

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Key indicators

Single-crystal X-ray study
T = 103 K
Mean σ(C–C) = 0.002 Å
R factor = 0.032
wR factor = 0.083
Data-to-parameter ratio = 8.6

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

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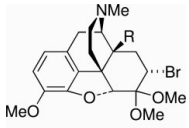
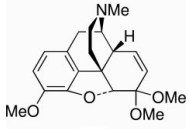
The title compound, $C_{20}H_{25}NO_5$, which was formed by reaction of 7α-bromohydrocodone-6,6-dimethoxy ketal with KO^{t}Bu in tetrahydrofuran, is the first example of a 7,14-bridged oxetane. The geometry of the oxetane ring is consistent with previously reported structures.

Comment

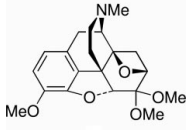
Although oxetanes have previously been described in the C-ring of morphinans and epoxymorphinans (Leland, 1981; Leland & Kotick, 1981; Kotick, 1983), these compounds were either a 6,7-bridged oxetane or an oxetane substituent at position 7. The 6,7-bridged oxetanes are potent agonists. 4,5α-Epoxy-3-methyl-7α,8β,17-trimethyloxetaneo[*b*-6β,7β]morphinan is as potent as hyrocodeinone and morphine in the mouse writhing test (Leland & Kotick, 1981). Changes in the substituent on C8 can alter the potency; the addition of a second carbon to the chain at this position reduces the potency of the above compound by a factor of five, while shortening the chain (from a methyl to an H atom) has no effect (Leland & Kotick, 1981).



(1) *R* = H
(3) *R* = OH



(2)



(4)

In this study, we report the first example of a 7,14-bridged oxetane. The title compound, (4), crystallizes in the triclinic space group *P*1 with a single molecule in the asymmetric unit (Fig. 1). A comparison of the oxetane ring with similar oxetane rings found in the Cambridge Structural Database (CSD, Version 5.25; Allen, 2002) indicated that the observed geometry was consistent with the structures previously reported. An attempt to correlate oxetane-ring parameters with number and placement of substituents did not yield any meaningful pattern.

The conformation of the polycyclic 'backbone' of the morphinan skeleton can be simplified in terms of the angles between the planes of these rings. Ring *A* is defined by atoms C1–C4/C11/C12, ring *B* by atoms C9–C14, ring *C* by atoms C5–C8/C13/C14, and ring *D* by atoms C9/C13–C16/N17. A search of the CSD yields 45 comparable compounds representing 75 independent molecules (see Table 1 for summary). The angle between the planes of ring *B* and *D* has the smallest range of observed values with an average value of 84.1 (16)°. The angle between the rings *B* and *D* of (4) is within this range. In general, the angle between ring *C* and any other ring exhibits a bimodal distribution. This is due to bridging of ring *C* to form another six-membered ring. The *C* ring of (4) is constrained by the oxetane ring. The angle between the planes of ring *C* and either ring *B* or ring *D* is intermediate between the two maxima of the bimodal distribution observed in the earlier structures, while the angle between the planes of the *A* and *C* rings is consistent with the earlier results (Fig. 2).

The presence of an N atom at position 17 is required for pharmacological activity, and its relationship with substituents on C3 and C6 is important to both the potency and the nature of the observed activity. Thus, the relationship between the rings that form the morphinan skeleton is important to the observed activity. The conformational changes noted above between (4) and related structures may offer new opportunities to produce morphinans with altered selectivity.

Room-temperature (*i.e.* 293 K) data had previously been collected using a Bruker *P*4 diffractometer with Cu $K\alpha$ radiation (authors' unpublished results). The unit cell from that experiment was a = 7.573 (1) Å, b = 7.814 (1) Å, c = 8.446 (1) Å, α = 83.67 (1)°, β = 68.58 (1)°, γ = 71.47 (1)°, and V = 441.14 (10) Å^3. These data are in good agreement with the results reported here.

Experimental

Treatment of 7α-bromohydrocodone-6,6-dimethoxy ketal, (1) (see scheme), with base leads to facile elimination of HBr to give the corresponding codeinone-6,6-dimethoxy ketal, (2) (Weller & Rapoport, 1976). The title compound, (4), was prepared from a 14-hydroxyl-substituted analog, *viz*. 7α-bromo-14-hydroxyhydrocodone-6,6-dimethoxy ketal, (3), following similar procedures, but was shown to undergo a different reaction when treated with base. Treatment with excess potassium *t*-butoxide, KO^{t}Bu, in tetrahydrofuran gave rise to a mixture of products, one of which was crystallized from methanol. The crystalline product was shown to be an oxetane, presumably formed from nucleophilic attack of the 14-alkoxide on the 7-bromo group.

Crystal data

$C_{20}H_{25}NO_5$
M_r = 359.41
Triclinic, *P*1
a = 7.509 (2) Å
b = 7.777 (2) Å
c = 8.430 (2) Å
α = 83.776 (6)°
β = 68.993 (5)°
γ = 71.511 (5)°
V = 435.81 (19) Å^3
Z = 1
D_x = 1.369 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3226 reflections
θ = 2.6–28.3°
μ = 0.10 mm^{-1}
T = 103 (1) K
Irregular prism, colorless
0.40 × 0.30 × 0.25 mm

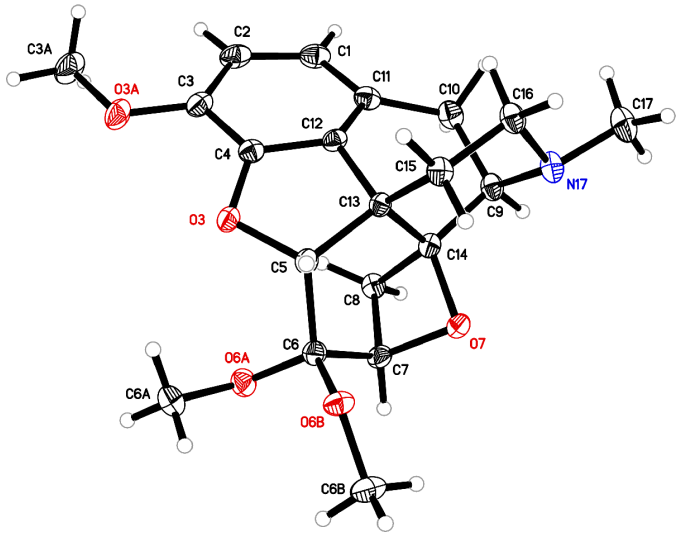


Figure 1
View of the title compound, showing the labeling of the non-H atoms. Displacement ellipsoids are drawn at the 50% probability level.

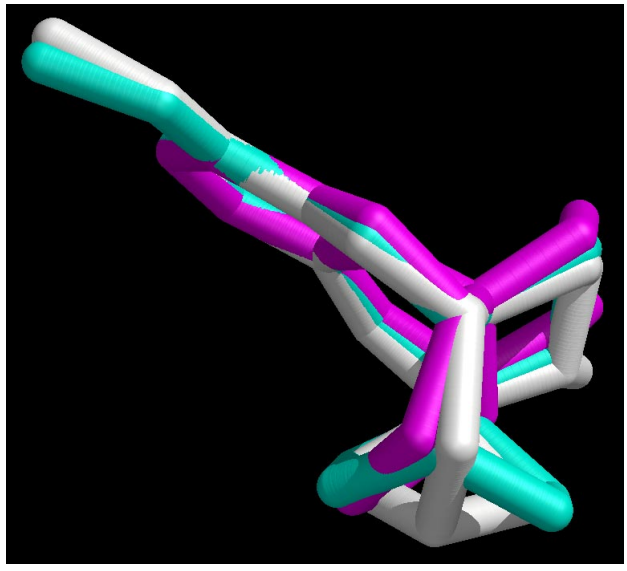


Figure 2
Comparison of the ring conformation of the title compound (white), morphine (magenta) (Gylbert, 1973), and (6*R*,7*R*,14*S*)-6,7,8,14-tetrahydro-6,14-etheno-7-[(1*S*)-1-hydroxyethyl]-17-nor-17-phenylthebaine (cyan) (Bakhanova *et al.*, 1998)

Data collection

Bruker SMART 1000 CCD diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2000)
T_{min} = 0.962, T_{max} = 0.976
3770 measured reflections
2063 independent reflections
2036 reflections with $I > 2\sigma(I)$
R_{int} = 0.010
θ_{max} = 28.4°
$h = -9 \rightarrow 9$
$k = -10 \rightarrow 10$
$l = -11 \rightarrow 11$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.032
$wR(F^2)$ = 0.084
S = 1.03
2063 reflections
239 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0566P)^2 + 0.0944P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 1
Relationship between the four rings of morphinans as determined by the angles (°) between the least-squares planes for the four rings.

Rings	Min	Max	Mean	SD	This study
AB	5.61	25.3	19.5	4.1	25.1
AC[a]	35.0	88.3	68.7	20.9	80.2
AD	74.1	89.7	79.9	3.8	72.5
BC[b]	24.7	83.3	60.7	23.7	55.9
BD	79.4	87.3	84.1	1.6	87.2
CD[c]	2.0	65.0	28.5	24.3	36.2

Notes: (*a*) bimodal with peaks at approximately 41° and 83°; (*b*) bimodal with peaks at approximately 28° and 78°; (*c*) bimodal with peaks at approximately 11° and 64°.

Friedel pairs were merged before the final refinement because the absolute configuration could not be determined from the data. The configuration has been assigned by referencing an unchanging chiral center in the synthetic procedure to the configuration of morphine. H atoms were treated as riding, such that aromatic C—H bond distances were constrained to be 0.95 Å, X_3CH were 1.00 Å, X_2CH_2 were 0.99 Å and XC–H_2 were 0.98 Å, with U_{iso}(H) values equal to $1.5U_{eq}$(C) for methyl H atoms and $1.2U_{eq}$(C) for all other H atoms.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SMART* and *SAINT* (Bruker, 2001); data reduction: *SAINT* and *XPREP* (Bruker, 2001); 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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