SYNTHESIS OF A NOVEL 7,14β-ETHANO-BRIDGED OPIATE

Han Yu, Lijuan Wang, Judith L. Flippen-Anderson,† Xinrong Tian, Andrew Coop,# and Kenner C. Rice*

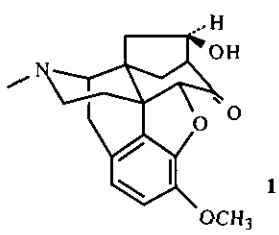
Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, Building 8, Room B1-23, Bethesda, Maryland 20892-0815, USA

† Naval Research Laboratory, 4555 Overlook Avenue, SW, Washington, DC 20375-5000, USA

#Current address: Department of Pharmaceutical Sciences, University of Maryland, Baltimore, Maryland 21201, U.S.A.

Abstract - A novel 7,14β-ethano-bridged opiate (**1**) was prepared from the known 14-alkenylcodeinone (**3**) in two steps. Selective reduction of the enone double bond of **3** followed by ozonolysis led to an aldehyde intermediate, which was cyclized *in situ* through an intramolecular aldol condensation to give the rigid hexacyclic derivative (**1**).

During the course of our research in developing 14-alkyl substituted opioid receptor agonists and antagonists, we synthesized a novel 7,14β-ethano-bridged opiate (**1**). This 7,14β-ethano-bridged opiate (**1**) has a rigid C-ring, and its structure is reminiscent of the 6,14β-ethano-bridged oripavines (**2**), an extremely potent series of compounds derived from thebaine through Diels-Alder addition.[1,2]



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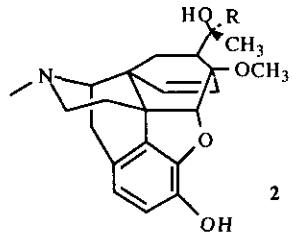

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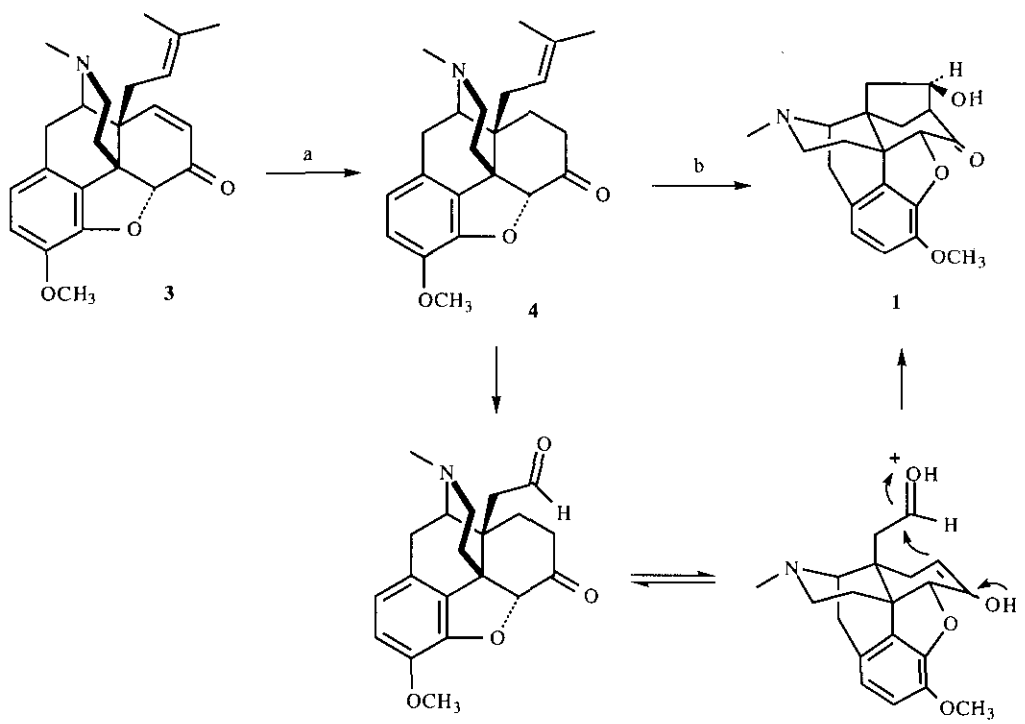
RESULTS AND DISCUSSION

14-Isopentylcodeinone (**3**), the starting material for the synthesis of **4**, was obtained from (-)-thebaine in three steps.[3] 14-Isopentylcodeinone (**3**) was first selectively reduced under transfer hydrogenation conditions[4] to afford the alkene (**4**) as the sole product. Upon ozonolysis, the aldehyde intermediate underwent an acid catalyzed intramolecular aldol condensation reaction, in which the relatively flexible C ring was converted into a rigid cyclohexanone derivative to give the product (**1**) (Scheme 1). The cyclization went to completion, with the aldehyde intermediate not identified in the reaction mixture. It is also noteworthy that although both *R* and *S* alcohols were obtained from the aldol addition, the *R* alcohol (**1**) was crystallized as the major stereoisomer. The relative configuration of the alcohol (**1**) was established by X-Ray analysis (Figure 1). The enantiomer was chosen to agree with the absolute configuration of natural (-)-thebaine that was used as a starting material.



Scheme 1. Reaction conditions and reagents: a) $(C_2H_5)_3N$, formic acid, 10% Pd-C, 90 °C, 2 h, 77% yield; b) O_3, AcOH, 0 °C, then Zn dust, 0 °C, 51% yield.

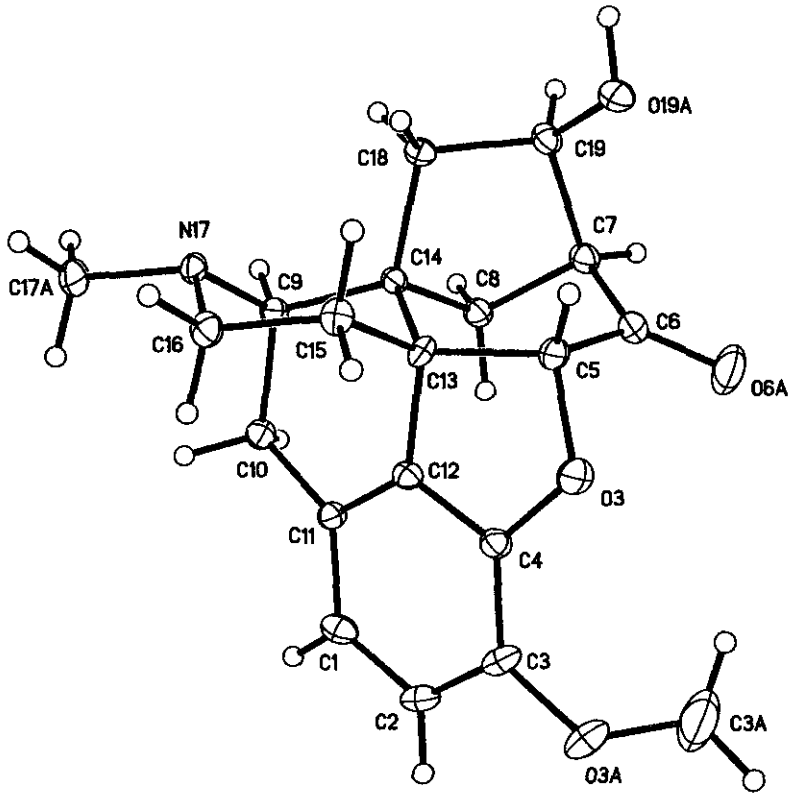


Figure 1. The results of the X-Ray analysis on the R-alcohol (1). The figure is drawn from the experimentally determined coordinates with thermal ellipsoids at the 20% probability level for the C, N and O atoms.

EXPERIMENTAL

General. NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-300 spectrometer. Electron impact (EI) MS spectra were recorded on a VG Micromass 7070F spectrometer. IR spectra were recorded on a Bio-Rad FTS-45 spectrophotometer. Thin layer chromatography (TLC) was performed on Analtech silica gel GHLF 0.25-mm plates. Column chromatography was performed with Fluka silica gel 60 (mesh 220-440). Elemental microanalyses were performed by Atlantic Microlab, Inc. Melting points were recorded on a Mel-Temp II apparatus and are uncorrected. Ozone was generated using a Welsbach Ozone Generator.

7,8-Dihydro-14β-isopentenylcodeinone (4). Neat formic acid (305 mg, 6.6 mmol) was added to a reaction tube containing 14β-isopentenylcodeinone (**3**)[3] (1.5 g, 4.1 mmol), Et_3N (965 mg, 9.5 mmol) and 10 % Pd-C (70 mg). The reaction tube was sealed and the black suspension was heated at 90 °C for 2 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was chromatographed to give the desired alkene (**4**) (1.2 g, 77%) as a clear pale yellow oil: TLC R_f(30% ethyl acetate/hexane) = 0.60; ^{1}H NMR δ 6.68 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 5.18 (t, *J* = 7.6 Hz, 1H), 4.53 (s, 1H), 3.88 (s, 3H), 3.65 (dd, *J* = 8.0 Hz, *J* = 14.2 Hz, 1H), 3.05 (d, *J* = 18.3 Hz, 1H), 2.84 (d, *J* = 5.4 Hz, 1H), 2.50 (m, 2H), 2.32 (s, 3H), 2.26 (m, 4H), 2.11 (m, 2H), 1.76 (s, 3H), 1.74 (s, 3H), 1.41 (m, 2H); ^{13}C NMR δ 209.2, 144.9, 142.7, 134.8, 130.1, 126.8, 119.3, 114.1, 89.7, 59.3, 56.6, 49.1, 45.9, 43.0, 40.1, 36.5, 32.3, 29.1, 28.0, 26.1, 26.0, 19.8, 17.8; IR (cm^{-1}) 2963, 1749, 1711, 1472, 1417, 1156; MS (EI) *m/z* 367 (M^+); HRMS calcd for $C_{23}H_{29}NO_3$ 367.2147, found 367.2157.

7,8-Dihydro-7β,14-(1*R*-hydroxy)ethanocodeinone (1). Alkene (**4**) (304 mg, 0.83 mmol) was dissolved in 4N AcOH (50 mL) and the mixture was cooled in an ice bath. O_3 was passed to the above solution at 0 °C for 30 min, then the reaction mixture was flushed with N_2 for 20 min. Zn dust (200 mg, 3.0 mmol) was added at 0 °C and the mixture was kept stirring for another 20 min. The suspension was filtered and the filtrate was basified with saturated aqueous $NaHCO_3$. The layers were separated, and the mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to provide a mixture of alcohol (**1**) and its stereoisomer in a 2:1 ratio (216 mg, 76% total yield). Further purification by crystallization from CH_2Cl_2 gave alcohol (**1**) (144 mg, 51%) as a white solid: TLC R_f (10% methylene chloride/methanol) = 0.78; mp 235-237 °C; ^{1}H NMR δ 6.68 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 4.80 (s, 1H), 4.71 (dt, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 3.86 (s, 3H), 3.12 (d, *J* = 18.3 Hz, 1H), 3.02 (m, 1H), 2.79 (d, *J* = 6.0 Hz, 1H), 2.60-2.40 (m, 1H), 2.34 (s, 3H), 2.33-2.11 (m, 3H), 1.62-1.39 (m, 3H); IR (cm^{-1}) 2962, 1748, 1416, 1314, 1027; MS (EI) *m/z* 341 (M^+); HRMS calcd for $C_{20}H_{23}NO_4$ 341.1627, found 341.1633. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.15; H, 6.82; N, 4.09.

X-Ray Analysis of 1. A clear flat plate 0.04 x 0.22 x 0.40 mm crystal, $C_{20}H_{23}NO_4$, FW = 341.39, was selected for data collection. Data was collected on a computer controlled Bruker diffractometer equipped with a graphite monochromator on the incident beam (Cu Kα radiation, λ = 1.54178 Å , T = 295 K) to a 2θ max of 115.0°. Three standard reflections measured at 100 reflection intervals showed that the crystal

remained stable during data collection. The crystal is orthorhombic, space group $P2_12_12_1$ with a = 6.966(5), b = 8.664(8), c = 27.873(2) Å, V = 16982.1(2) $Å^3$, Z = 4, and d_{calc} = 1.348 gm/cm^3. A total of 2001 reflections were collected, of which 1748 were unique (Rint = 0.043). The structure was solved by direct methods with the aid of the program SHELXTL[1] and refined on F^2 with a full matrix least-squares[5]. The 230 parameters refined include the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogens were included using a riding model. The final R values were R = 0.052 for the 1349 observed reflections with $F_o > 4\sigma(|F_o|)$, and $wR(F^2)$ = 0.123 for the full set of 1748 data. The goodness of fit parameter was 1.04 and final difference Fourier excursions were 0.22 and -0.19 $eÅ^{-3}$.

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