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

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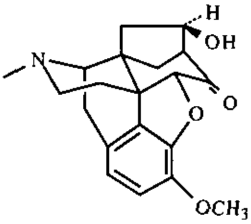
Abstract - A novel 7,14β-ethano-bridged opiate (**1**) was prepared from the known 14-alkenylcodeinone (**3**) in two steps. Selective reduction of the enone double bond of **3** followed by ozonolysis led to an aldehyde intermediate, which was cyclized *in situ* through an intramolecular aldol condensation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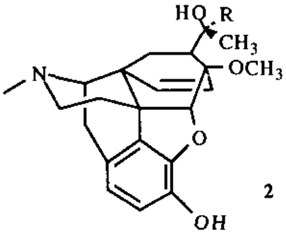

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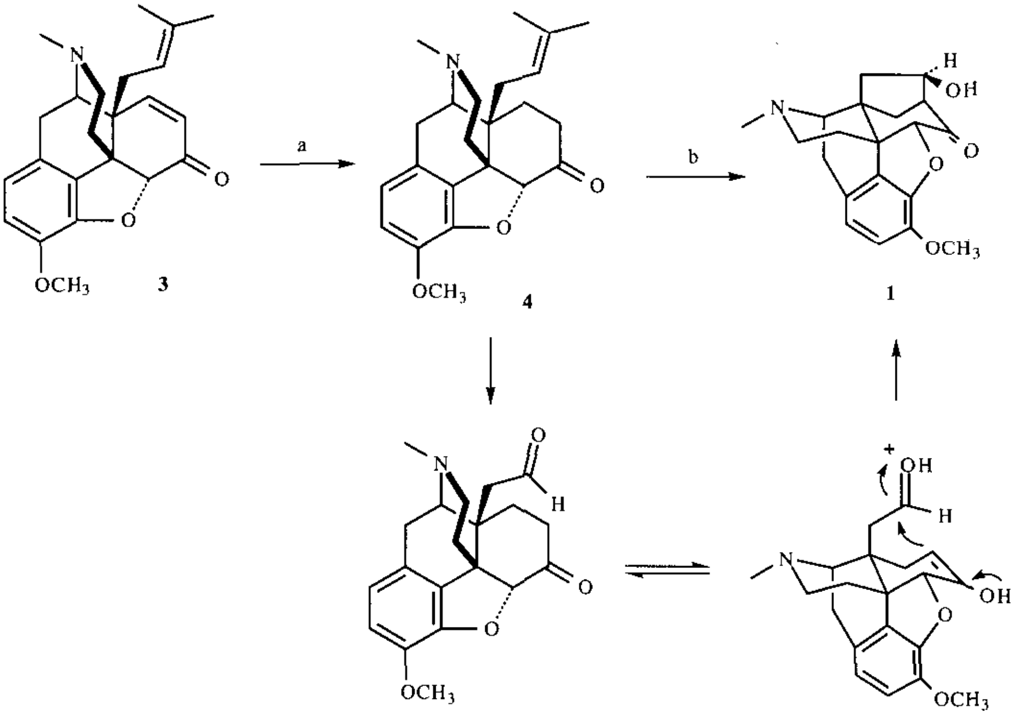
RESULTS AND DISCUSSION

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.

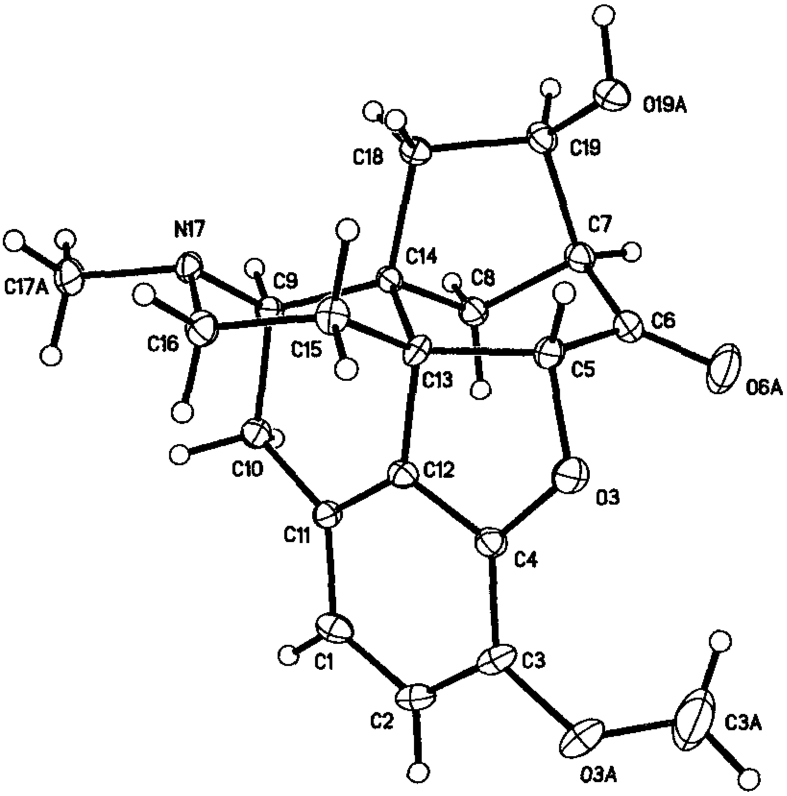


Figure 1. The results of the X-Ray analysis on the R-alcohol (1). The figure is drawn from the experimentally determined coordinates with thermal ellipsoids at the 20% probability level for the C, N and O atoms.

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; ^1H 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; ^1H 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 $F_0 > 4\sigma(|F_0|)$, 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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REFERENCES

1. K. W. Bently and D. G. Hardy, *Proc. Chem. Soc.*, 1963, 220.

2. K. E. MaloneyHuss and P. S. Portoghese, *J. Org. Chem.*, 1990, **55**, 2957.

3. K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, 1967, **89**, 3293.

4. M. Freifelder, 'Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary,' John Wiley and Sons, New York, 1973.

5. G. M. Sheldrick, SHELXTL Release 5.01 for Bruker P4 Crystal Research System, Bruker Analytical X-Ray Instruments, Madison, WI, 1997

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