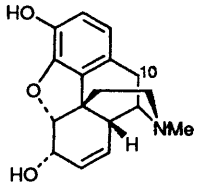
Synthesis from Thebaine of 10-Oxothebaine, Potentially a Precursor for κ-Selective Opiates

Calum F. Henderson, Gordon W. Kirby* and (in part) John Edmiston
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, UK

Thebaine **3** has been converted in an improved yield (72%), with tetranitromethane, oxygen and ammonia, into the 14β-nitro 8α,10α-epidioxide **4**, which reacted with base to give the known 14β-nitro-10-oxo compound **7**. Reduction of this nitro compound with tributyltin hydride gave the 8β-hydroxy-10-oxodihydrothebaine **8**, which was dehydrated with phosphorus oxychloride to give 10-oxothebaine **9**. As expected, this conjugated diene reacted with but-3-en-2-one to form a Diels–Alder cycloadduct **10**, the 10-oxo derivative of thevinone **11**, the precursor of a well known series of opiate analgesics. Unexpectedly, the epidioxide **4** was found to isomerise cleanly on activated alumina to give the 8α,10α-epoxy acetal **5**, in which a peroxide oxygen has been inserted into the 7,8-bond of the bridged peroxide **4**.

Opiate analgesics act at several, well defined sub-populations of receptors in the central nervous system. For example, morphine **1** acts predominantly at μ receptors while ethylketocyclazocine **2** is a prototypical ligand for κ receptors. Several clinically useful opiates have been synthesised from the opium alkaloid



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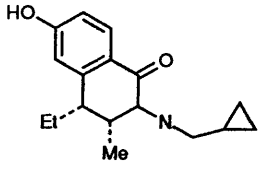

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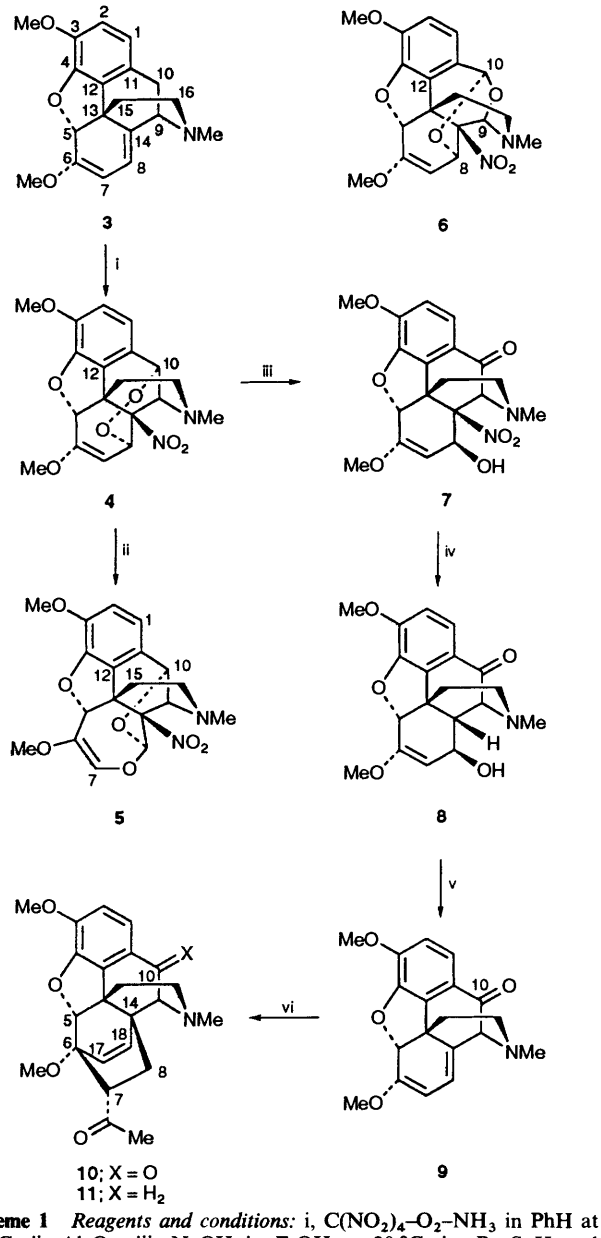
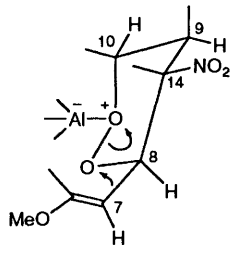
thebaine **3** and, consequently, like morphine, they have C-10 methylene groups. 10-Oxothebaine **9** therefore is an attractive starting material for the synthesis of potentially κ-selective opiates. Direct conversion of the 10-methylene group of several morphinan derivatives into a 10-keto group has been achieved with chromium(VI) reagents, although yields are generally modest.[1] However, the methoxy diene system of thebaine **3** is attacked by powerful oxidants. We report here a 4-step synthesis of 10-oxothebaine **9** from thebaine **3** *via* the known[2] epidioxide **4** and 10-oxo derivative **7** (Scheme 1).

We reported[2] that the thebaine **3** reacts in benzene with tetranitromethane and oxygen to give, unexpectedly, the bridged peroxide **4** as a major product. However, about half the thebaine is concurrently converted into its trinitromethane salt. For the present study, we increased the yield of the epidioxide **4** to *ca.* 70% by conducting the nitration in benzene with slow passage of streams of oxygen and ammonia[2c] through the mixture. Treatment of the epidioxide with sodium hydroxide in ethanol, as before,[2b] gave the keto alcohol **7** in high yield. Removal of the 14β-nitro group was effected with an excess of tributyltin hydride,[3] with heating under reflux in toluene. The radical generator azoisobutyronitrile was added slowly to promote the reduction, which proceeded in *ca.* 70% yield. Finally, the codeine derivative **8** was dehydrated with phosphorus oxychloride in pyridine to afford 10-oxothebaine **9** (73%). The structure **9** was readily discerned by comparison of the product's spectra with those of thebaine **3**, and by the following transformation.

Thevinone **11**, the cycloadduct of thebaine and but-3-en-2-one, is the precursor of an important series of potent analgesics.[4] When 10-oxothebaine **9** was heated with an excess of the



Scheme 1 *Reagents and conditions:* i, $C(NO_2)_4$–O_2–NH_3 in PhH at 20 °C; ii, Al_2O_3; iii, NaOH in EtOH at 20 °C; iv, Bu_3SnH and $[Me_2C(CN)N]_2$ in PhMe at 111 °C; v, $POCl_3$–C_5H_5N in PhMe at 111 °C; vi, $MeCOCH{=}CH_2$ in PhH at 80 °C



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butenone, the corresponding cycloadduct **10** was formed in 86% yield. Again, the structure and stereochemistry of 10-oxothevinone **10** was deduced from the close similarity, *mutatis mutandis*, of its ^{1}H NMR spectrum with that of thevinone **11**. A by-product of the cycloaddition was tentatively identified (^{1}H NMR) as the 7β epimer of 10-oxothevinone **10**.

The epidioxide **4** was routinely purified[2c] by chromatography on neutral, grade III alumina, prior to recrystallisation. When grade I alumina was inadvertently employed, efficient conversion into the isomeric 'isodioxide' **5** took place. The structure **5** was deduced from the following chemical and spectroscopic properties. Unlike the epidioxide **4**,[2b] the isodioxide **5** did not react with triphenylphosphine, or sodium iodide in acetic acid. Also, the mass spectrum showed an intense molecular ion peak, unlike the spectrum of the epidioxide. Clearly then, the isodioxide was not a peroxide. The IR and NMR spectra showed the absence of hydroxy and carbonyl groups and of any newly formed C=C double bond. Therefore, the isodioxide **5** was hexacyclic, like its precursor **4**. The ^{1}H and ^{13}C NMR spectra indicated the presence of a new, acetal, methine group [8-H, δ_C 105.6 and δ_H 5.37 (s)]. Significantly, one other methine group [7-H, δ_C 120.0 and δ_H 5.73 (d, J 1.4 Hz)] had also become attached to oxygen during the isomerisation. Clearly, rearrangement had occurred with cleavage of the peroxide link in the epidioxide **4**, perhaps catalysed by alumina acting as a Lewis acid, and migration of an adjacent methine carbon, C-7 or C-9, on to oxygen. Accordingly, the alternative structures **5** and **6** were considered for the isodioxide. The former better accounted for the ^{1}H and ^{13}C chemical shifts and the vicinal coupling constant $J_{9,10}$ 4.4 Hz. Structure **5** was confirmed when ^{13}C–^{1}H NMR correlations showed (see Experimental section) that the acetal carbon, δ 105.6, was C-8 rather than C-10 (δ 76.6). Migration of C-7, rather than C-9, on to oxygen (O-8) in the epidioxide **4**, concerted with peroxide cleavage, would be favoured by the *anti* arrangement of the 7,8-bond and the peroxide link, as shown in the diagram **12**, based upon the published[2a] X-ray structure. Attack of the other oxygen (O-10) on the cation generated at C-8 would then form the 5-membered, acetal ring. A similar, 8α,10α-epoxy link is present in the epoxide formed[2b] by reduction of the epidioxide **4** with triphenylphosphine.

Experimental

General.—M.p.s. were determined on a Kofler, hot-stage microscope. IR spectra were recorded on either a Perkin–Elmer 580 or 953 spectrometer for chloroform solutions. ^{1}H NMR spectra at 90 MHz were obtained with a Perkin-Elmer R34 spectrometer. ^{13}C NMR spectra at 90.6 and 50.3 MHz, and ^{1}H spectra at 360 and 200 MHz were obtained with Bruker spectrometers. The ^{1}H spectrum at 100 MHz was obtained with a Varian XL 100 spectrometer. All NMR spectra were recorded for deuteriochloroform solutions. J Values are in Hz. Mass spectra were produced by EI at 70 eV with an AEI MS9 instrument. TLC employed Merck GF_{254} silica gel, the flow was assisted by a water pump.[5] Woelm alumina was used for column chromatography. Organic solvents were dried, unless otherwise stated, over magnesium sulphate and evaporated with a Büchi Rotavapor.

Improved Preparation of the Epidioxide **4**.—Tetranitromethane was prepared from fuming nitric acid and acetic anhydride.[6] For best results, the fuming nitric acid was freshly redistilled from a mixture with one third of its volume of concentrated sulphuric acid. The tetranitromethane was steam distilled, washed successively with aq. sodium carbonate and water and then dried (Na_2SO_4); δ_C[50.3 MHz; $CDCl_3$–C_6D_6 (4:1)] 119.8 (nonet, $J_{C,N}$ 9.4). The ^{1}H spectrum likewise showed no signals from any significant impurities. Dry ammonia gas and dry oxygen were passed slowly through a solution of thebaine (18.73 g, 60.2 mmol) in benzene (500 cm^3) at room temperature after which tetranitromethane (18.87 g, 96.3 mmol) in benzene (100 cm^3) was added dropwise during 20 min with continuous passage of both gases. The passage of both gases was continued for a further 2 h during which time a red oil separated from the reaction mixture and collected in the bottom of the flask. The supernatant, benzene solution was decanted off the oil, which was then washed with benzene (2 × 150 cm^3). **CAUTION:** the red oil contains ammonium trinitromethide, which may decompose violently when heated. The combined benzene solutions were washed successively with aq. sodium carbonate and water and then were dried and evaporated. The residual oil was chromatographed on a column of either neutral grade III alumina or TLC grade silica to give the epidioxide **4** (16.76 g, 72%), m.p. 160 °C (from ethyl acetate) (lit.,[2b] 160–161 °C).

The Isodioxide **5**.—The epidioxide (400 mg) **4** was adsorbed onto a column of neutral, grade I alumina (15 g) which after *ca.* 2 h was eluted with chloroform–hexane to give the *isodioxide* **5** (380 mg). Recrystallisation of the product **5** from ethanol gave material (295 mg, 74%), m.p. 270–271 °C (Found: C, 59.0; H, 5.0; N, 7.1%; M$^+$, 388.1276. $C_{19}H_{20}N_2O_7$ requires C, 58.8; H, 5.2; N, 7.2%; M, 388.1270); ν_{max}/cm^{-1} 1549, 1450, 1225 and 1285; δ_H(360 MHz) 6.86 and 6.75 (ABq, J 8.1, 1- and 2-H), 5.73 (d, J 1.4, 7-H), 5.37 (s, 8-H), 5.21 (d, J 1.4, 5-H), 5.12 (d, J 4.4, 10-H), 4.47 (d, J 4.4, 9-H), 3.88 (s, 3-OMe), 3.44 (s, 6-OMe), 2.54 (s, NMe), 2.53 (m, 16-H_2), 2.39 (ddd, J 13.0, 10.3 and 6.9, 15$_{ax}$-H) and 1.78 (dt, J 13.0 and 2.7, 15$_{eq}$-H); δ_C(90.6 MHz) 154.8 (C-6), 146.1 (C-3), 145.1 (C-4), 130.3 (C-12), 125.9 (C-11), 120.0 (C-7), 119.3 (C-1), 113.9 (C-2), 105.6 (C-8), 95.5 (C-14), 92.7 (C-5), 76.6 (C-10), 71.3 (C-9), 56.3 (OMe), 56.1 (OMe), 46.6 (C-13), 45.8 (C-16), 43.1 (NMe) and 31.3 (C-15). ^{13}C-^{1}H Correlations (50.3 and 200 MHz) showed, *inter alia*, that C-8 in structure **5** rather than C-10 in structure **6** was the acetal carbon (δ_C 105.6). Thus, the following 1- and 3-bond ^{13}C-^{1}H couplings allowed signals for 10-H, C-10, 8-H and C-8 to be successively identified: C-12 (δ 130.3) coupled with 1-H (6.87), 15$_{ax}$-H (2.38) and 10-H (5.12); C-10 (76.6) with 10-H and 8-H (5.37); and C-8 (105.6) with 8-H and 10-H.

8,14-*Dihydro*-8β-*hydroxy*-14β-*nitro*-10-*oxothebaine* **7**.—The epidioxide **4** (600 mg) was suspended in ethanol (75 cm^3) at room temperature and treated with aq. sodium hydroxide (4 mol dm^{-3}; *ca.* 0.2 cm^3). The mixture was stirred for 18 h, by which time a clear solution had formed. Work-up[2b] gave the nitro ketone **7** (560 mg, 93%), m.p. 220 °C (from methanol) (lit.,[2b] 219 °C) (Found: C, 58.8; H, 5.3; N, 7.1. Calc. for $C_{19}H_{20}N_2O_7$: C, 58.8; H, 5.2; N, 7.2%). The UV and ^{1}H NMR spectra agreed well with those reported.[2b]

8,14-*Dihydro*-8β-*hydroxy*-10-*oxothebaine* **8**.—The nitro ketone **7** (2.00 g, 5.15 mmol) and tributyltin hydride[3] (9.00 g, 31 mmol) were heated under reflux in dry toluene (250 cm^3) under

nitrogen and azoisobutyronitrile was added slowly in toluene to the mixture, the course of reaction being monitored by TLC. Addition was continued until reduction of the nitro compound was almost complete. The time (*ca.* 2 h) and the quantity of azo compound (a large excess) required depended upon the rate of addition. The mixture was heated for a further 2 h and then was evaporated to give an oily residue. The residue was shaken with acetonitrile (100 cm^3) and hexane (100 cm^3). The acetonitrile layer was washed with hexane (4 × 100 cm^3) and then evaporated to give a yellow–green solid. Chromatography on a silica gel (TLC grade) column eluted with ethyl acetate gave successively the nitro compound **7** (0.27 g) and the *hydroxy ketone* **8** (1.28 g, 72%), m.p. 158–160 °C (from methanol) for the first batch prepared; later batches had m.p. *ca.* 260 °C (decomp.) with sintering from 235 °C (from ethanol) (Found: C, 66.3; H, 6.15; N, 4.0%; M^+, 343.1413. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%; *M*, 343.1419); ν_{max}/cm^{-1} 3600, 3400, 1672, 1620 and 1600; ν_{max}(KBr)/cm^{-1} 3528, 1665, 1624 and 1605; δ_H(200 MHz) 7.38 and 6.80 (ABq, *J* 8.4, 1- and 2-H), 4.95 (d, *J* 1.3, 5-H), 4.82 (d, *J* 1.8, 7-H), 3.92 (s, 3-OMe), 3.78 (dt, *J* 9.3 and *ca.* 1.5, 8-H), *ca.* 3.56 (signal partly obscured, 9-H), 3.55 (s, 6-OMe), 2.72 (ddd, *J* 12.1, 5.0 and 1.8, 16_{eq}-H), 2.44 (s, NMe), 2.37 (td, partly obscured, *J* 12.1 and 4.5, 16_{ax}-H), 2.27 (dd, *J* 9.3 and 2.6, 14-H), 2.10 (td, *J* 12.3 and 5.0, 15_{ax}-H), 1.95 (ddd, *J* 12.5, 4.3 and 1.8, 15_{eq}-H) and 1.72 (br s, OH, exch. with D_2O); δ_C(50.3 MHz) 34.8 (C-15), 42.3 (C-13), 43.5 (NMe), 47.3 (C-16), 51.5 (C-14), 54.9 (OMe), 56.3 (OMe), 65.9 (C-8 or -9), 66.0 (C-9 or -8), 87.5 (C-5), 104.7 (C-7), 113.5 (C-2), 118.7 (C-1), 125.2 (C-11), 136.7 (C-12), 143.8 (C-4), 150.2 (C-3), 151.6 (C-6) and 192.4 (C-10).

10-*Oxothebaine* **9**.—The hydroxy ketone **8** (1.00 g), dry pyridine (4 cm^3) and freshly distilled phosphorus oxychloride (1 cm^3) were heated under reflux in dry toluene (150 cm^3) under nitrogen for 3 h, by which time a black oil had separated out. The mixture was evaporated to low volume and the residue was treated with sufficient aq. sodium hydrogen carbonate to render the mixture distinctly alkaline. The toluene and aq. layers were separated and the aq. layer was extracted with toluene (4 × 40 cm^3). The combined toluene solutions were washed with aq. sodium hydrogen carbonate, dried and evaporated. Pyridine was removed from the residue by repeated addition and evaporation of toluene. The resulting yellow–green solid was chromatographed on a column of silica gel (TLC grade). Elution with chloroform then chloroform–methanol (10:1) gave a green oil (0.77 g), which crystallised slowly. Recrystallisation from ethanol gave 10-*oxothebaine* **9** (0.69 g, 73%), m.p. 195–198 °C (Found: C, 70.3; H, 5.8; N, 4.3%; M^+ 325.1305. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%; *M*, 325.1314); ν_{max}/cm^{-1} 1680, 1666 and 1607; λ_{max}(MeOH)/nm 263 (ε 12 900 dm^3 mol^{-1} cm^{-1}), 285 (10 450) and 330 (8470); δ_H(200 MHz) 7.35 and 6.76 (ABq, *J* 8.4, 1- and 2-H), 5.64 (d, *J* 6.5, 8-H), 5.38 (s, 5-H), 5.09 (d, *J* 6.5, 7-H), 3.92 (s, 3-OMe), 3.62 (s, 6-OMe and 9-H), 2.77 (ddd, *J* 12.6, 6.5 and 2, 16_{eq}-H), 2.69 (td, *J* 12.4 and 3.5, 16_{ax}-H), 2.52 (s, NMe), 2.28 (td, *J* 12 and 6.4, 15_{ax}-H) and 1.87 (ddd, *J* 12.6, 3 and 2, 15_{eq}-H); δ_C(50.3 MHz) 36.8 (C-15), 43.4 (NMe), 47.4 (C-16), 47.7 (C-13), 55.1 (OMe), 56.3 (OMe), 70.5 (C-9), 88.5 (C-5), 96.4 (C-7), 112.3 (C-8), 113.0 (C-2), 119.7 (C-1) 125.4 (C-11), 130.7 (C-12), 138.7 (C-14), 143.9 (C-4), 149.6 (C-3), 152.4 (C-6) and 193.8 (C-10).

10-*Oxothevinone* **10**.—10-Oxothebaine **9** (120 mg) and freshly distilled but-3-en-2-one (1.2 cm^3) were heated under reflux with benzene (1.2 cm^3) for 5 h. The solution was evaporated and the residue was chromatographed first in diethyl ether on a short column of silica gel (TLC grade) and then on silica plates developed with diethyl ether. The band having R_f *ca.* 0.4 was extracted with ethyl acetate to give 7α-*acetyl*-6,7,8,14-*tetrahydro*-10-*oxo*-6α,14α-*ethenothebaine* (10-*oxothevinone*) **10** (126 mg, 86%), m.p. 129 to 131 °C (from methanol) (Found: C, 69.8; H, 6.4; N, 3.5. $C_{23}H_{25}NO_5$ requires C, 69.9; H, 6.3; N, 3.5%); ν_{max}/cm^{-1} 1719 and 1675; δ_H(200 MHz) 7.28 and 6.76 (ABq, *J* 8.4, 1- and 2-H), 5.98 (dd, *J* 8.8 and 1.2, 18-H), 5.55 (d, *J* 8.8, 17-H), 4.68 (d, *J* 1.2, 5-H), 3.92 (s, 3-OMe), 3.61 (s, 6-OMe), 3.18 (s, 9-H), 2.48 (s, NMe), 2.16 (s, Ac) and 1.39 (m, 8α-H); *m/z* 395 (M^+), 352 and 325. The product **10** before TLC showed weak ^1H NMR signals at δ 6.13 (dd, *J ca.* 9 and 1, 18-H), 5.44 (d, *J* 8.8, 17-H) and 5.05 (d, *J ca.* 1, 5-H) possibly arising from the protons indicated in the corresponding 7β-acetyl derivative.

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