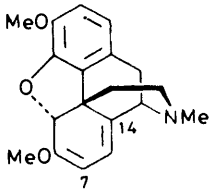
The Nitration of Thebaine with Tetranitromethane

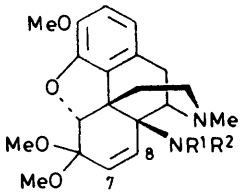
By **Robert M. Allen, Gordon W. Kirby,* and David J. McDougall,** Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

Thebaine (1) reacts in methanol with tetranitromethane to give, as the major product, 14β-nitrocodeinone dimethyl acetal (2a), which has been converted into, *inter alia*, 14β-nitrocodeinone (3a), 14β-aminocodeinone dimethyl acetal (2b), 14β-aminocodeinone (3b), and 14β-aminocodeine. The nitration of thebaine with tetranitromethane in benzene in the presence of oxygen takes a different course. The major product has been identified as the cyclic peroxide 8α,10α-epidioxy-8,14-dihydro-14β-nitrothebaine (5) by a series of degradations leading to new 10α-hydroxy- and 10-oxo-thebaine derivatives.

NITROSATION of the alkaloid thebaine (1) gave products arising from electrophilic attack at C-7 of the methoxydiene system.[1] However, it was reasoned [1,2] that nitrosation might have occurred reversibly at C-14, the more usual site for electrophilic attack, and that the formation of the observed products was dictated by subsequent, irreversible reactions. Since codeine derivatives [as (2) and (3)] were required, for pharmacological

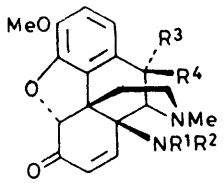


(1)



(2)

a; $R^1 = R^2 = O$
b; $R^1 = R^2 = H$



(3)

a; $R^1 = R^2 = O$, $R^3 = R^4 = H$
b; $R^1 = R^2 = R^3 = R^4 = H$
c; $R^1 = CN$, $R^2 = R^3 = R^4 = H$
d; $R^1 = Ac$, $R^2 = R^3 = R^4 = H$
e; $R^1 = (E)$-PhCH=CHCO, $R^2 = R^3 = R^4 = H$
f; $R^1 = PhCH_2OCO$, $R^2 = R^3 = R^4 = H$
g; $R^1 = R^2 = O$, $R^3R^4 = O$
h; $R^1 = R^2 = O$, $R^3 = OH$, $R^4 = H$

evaluation, with substituents attached *via* nitrogen at C-14, we elected next to study the nitration of thebaine. Tetranitromethane [3] was selected as an appropriate, mild reagent. We considered that competitive nitration of the aromatic ring was unlikely to occur and that the skeletal rearrangements characteristically induced by acylating agents and strong acids would be avoided.

RESULTS AND DISCUSSION

Equimolar amounts of thebaine (1) and tetranitromethane reacted smoothly in methanol at room temperature with slow separation of the trinitromethane salt of thebaine. After 6 h, this salt, which accounted for *ca.* 50% of the original thebaine, was filtered off and the products of nitration were isolated from the filtrate by chromatography. The major product (48% yield, based upon the amount of thebaine consumed †) was assigned the structure (2a) on the basis of its spectroscopic properties and chemical reactions. Thus, the ^1H n.m.r. spectrum showed 3 singlets (τ 6.16, 6.55, and 6.95), attributable to methoxy-groups, and a broad 2-proton singlet (τ 4.12) arising from 7-H and 8-H. The presence of a nitro-group was indicated by a strong i.r. absorption band at 1 546 cm^{-1}. Hydrolysis of this acetal with dilute hydrochloric acid gave the corresponding enone (3a) which had the expected spectroscopic properties.

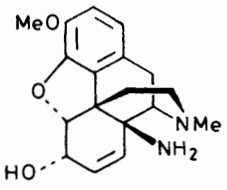
Reduction of (2a) with zinc and ammonium chloride gave the amino-acetal (2b) which was hydrolysed by hydrochloric acid to afford 14β-aminocodeinone (3b). The structure of the latter amine was confirmed by its conversion, with cyanogen bromide in chloroform, into 14β-cyanoaminocodeinone (3c), which was identical with material prepared [5] from the cycloadduct of nitrosyl cyanide and thebaine. Acylation of 14β-aminocodeinone was readily achieved by standard methods; the *N*-acetyl, *N*-cinnamoyl, and *N*-benzyloxycarbonyl derivatives were fully characterised. Reduction of 14β-aminocodeionone with sodium borohydride in methanol gave 14β-aminocodeine (4) in good yield.

When the nitration of thebaine (1) with tetranitromethane was conducted in benzene rather than methanol, in the presence of air or, preferably, oxygen, the reaction took a different and unexpected course. The major product was shown, as described in the sequel, to be the unusual epidioxide (5), which was also detected as a minor product from the nitration of thebaine in methanol. The yield of (5) was greatly reduced when nitration was carried out in benzene under nitrogen.

In a typical experiment, dry oxygen was passed slowly through an equimolar solution of thebaine and tetranitromethane for 3 h at room temperature to yield the trinitromethane salt of thebaine (*ca.* 50%), 14β-nitrocodeinone (3a) (8%), and the epidioxide (5) (31%).

† More recent work [4] has shown that higher conversions of thebaine into (2a) may be achieved with tetranitromethane in the presence of methanolic ammonia.

The presence of an oxygen atom at C-10 in (5) was revealed by isomerisation in ethanolic sodium hydroxide to give a hydroxy-ketone (6a), which had a u.v. spectrum characteristic [6] of 10-oxomorphinan derivatives. The location of the new carbonyl group at C-10 was confirmed by n.m.r. spectroscopy which showed the expected deshielding of the adjacent aromatic proton



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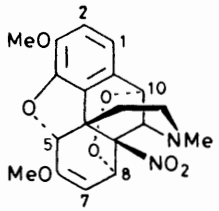
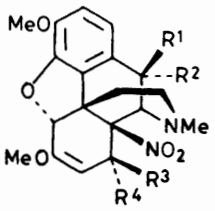


(5)



(6)

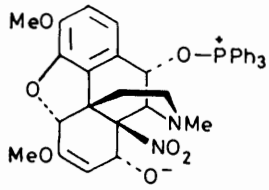
a; R^1R^2 = O, R^3 = OH, R^4 = H
b; R^1R^2 = O, R^3 = OAc, R^4 = H
c; R^1 = R^3 = H, R^2 = R^4 = OH
d; R^1 = R^4 = H, R^2 = R^3 = OH
e; R^1R^2 = R^3R^4 = O
f; R^1R^2 = O, R^3 = H, R^4 = OH

(1-H). The presence of a secondary, allylic hydroxy-group in (6a) was established by oxidation with manganese dioxide to form the diketone (6e). Moreoever, acetylation of the hydroxy-ketone caused a down-field shift, of appropriate magnitude (1.14 p.p.m.), of the n.m.r. signal assigned to the proton at C-8. Finally, hydrolysis of (6a) with hot, dilute hydrochloric acid gave 14β-nitro-10-oxocodeinone (3g), thus indicating the relative positions of the enol-ether and hydroxy-groups in ring C.

The nitration product (5) showed no i.r. bands attributable to hydroxy- or carbonyl groups, yet was isomerised by base to give the hydroxy-ketone (6a). This implied linkage of C-8 and C-10 in (5) by a peroxy-bridge. However, the proton at C-8 in (5) was judged to be pseudo-equatorial (β) from the observed vicinal coupling constant, $J_{7,8}$ 6.4 Hz, whereas in (6a) the corresponding proton was clearly pseudo-axial (α), $J_{7,8}$ *ca.* 1 Hz. Nevertheless, an initially formed, pseudo-axial alcohol (6f) might be expected to isomerise under basic conditions to give the more stable epimer providing that the hydroxy- and nitro-groups were vicinal. This process is illustrated in the Scheme. Direct evidence for a peroxy-bridge in (5) and for the proposed epimerisation at C-8 was obtained as follows.

The epidioxide (5), treated with sodium iodide in acetic acid at room temperature yielded iodine (37% by titration) and the diol (6c) (45%), which clearly had an α-hydroxy-group at C-8 ($J_{7,8}$ 6 Hz). Tretament of this 8α,10α-diol with ethanolic sodium hydroxide caused epimerisation, as predicted, to give the 8β,10α-diol (6d) ($J_{7,8} < 1$ Hz). The relative stereochemistry of the two diols was confirmed by spectroscopic evidence (see Experimental section) of intramolecular hydrogen-bonding in the 8α,10α-diol, but not in the 8β,10α-diol. Both diols were oxidised by manganese dioxide to give, in high yield, the same diketone (6e) previously obtained from the hydroxy-ketone (6a).

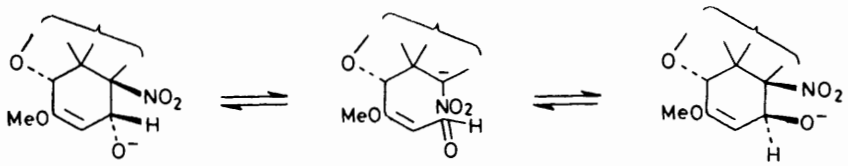
Further evidence for a peroxy-group in (5) was readily obtained. Treatment of (5) with triphenylphosphine (1 mol equiv.) in benzene under reflux gave triphenylphosphine oxide (98%) and the 8α,10α-epoxide (5; ---O--- in place of ---O_2---) (84%). The removal of one oxygen atom from (5) with retention of configuration at C-8 and C-10 is thought to involve an intermediate (7), which



(7)

may lose triphenylphosphine oxide to form a stabilised, benzylic carbonium ion. This would cyclise rapidly to give the 8α,10α-epoxide. The proposed structure for the epoxide was supported by its hydrolysis with hydrochloric acid to form 10α-hydroxy-14β-nitrocodeinone (3h), which was oxidised by manganese dioxide to give 14β-nitro-10-oxocodeinone (3g).

Consideration of the above degradations led us to the structure (5) for the nitration product of thebaine. However, it was not possible to convert (5) or any of its degradation products into compounds of unequivocally known structure. Also, the formation of the peroxide bridge in (5) lacked any clear mechanistic precedent.



Accordingly, a single-crystal, *X*-ray study of (5) was undertaken. The outcome [7] confirmed the structure (5) and established a relatively strain-free, chair conformation for the peroxide bridge with an antiperiplanar arrangement of the O–O and C(10)–H bonds. This latter feature would account for the ready cleavage of (5)

by ethoxide to give the hydroxy-ketone (6a). It is likely that the 8α,10α-diol (6c) adopts a conformation similar to that of (5) with a hydrogen bond [C(10)–O–H · · · O–C(8)] bridging the two oxygen atoms.

Archer and Osei-Gyimah [8] have recently described an alternative method for preparing 14β-nitrocodeinone (3a). Thebaine was treated with dinitrogen tetroxide at low temperature in ethyl acetate to give 14β-nitrocodeinone (23%) and 8-nitrothebaine (7%). The physical constants for the ketone agree well with those reported earlier [2] and in this paper.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. ^{1}H N.m.r. spectra were measured, unless otherwise stated, in deuteriochloroform. I.r. spectra were measured, unless otherwise stated, in chloroform. Column chromatography was carried out on neutral, grade III, Woelm alumina and thin-layer chromatography on Merck GF_{254} alumina plates.

14β-*Nitrocodeinone Dimethyl Acetal* (2a).—Tetranitromethane (3.68 g) was added dropwise to thebaine (5.84 g) in methanol (200 ml) and the resulting brown mixture was stirred at room temperature for 6 h; a yellow precipitate of the trinitromethane salt of thebaine began to appear after *ca.* 0.5 h. The precipitate (4.7 g) was filtered off and the filtrate was evaporated to dryness under reduced pressure. CAUTION: Overheating of residues containing tetranitromethane or trinitromethane may lead to violent decomposition. The residue was extracted with benzene–chloroform (1 : 1) and the extract was chromatographed on alumina (200 g). Elution with benzene–chloroform (1 : 1) gave 14β-*nitrocodeinone dimethyl acetal* (2a) (1.67 g), m.p. 227—227.5 °C (from EtOH), $[\alpha]_D$ −91° (*c* 0.55 in $CHCl_3$) (Found: C, 62.0; H, 6.5; N, 7.3. $C_{20}H_{24}N_2O_6$ requires C, 61.8; H, 6.2; N, 7.2%); $\nu_{max.}$ 1 546 cm^{-1}; τ 3.37 and 3.47 (ABq, *J* 8 Hz, 2-H and 1-H), 4.12 (br s, 7-H and 8-H), 4.96 (s, 5-H), 6.16 (s, 3-OMe), 6.55 (s, 6-OMe), 6.95 (s, 6-OMe), and 7.58 (s, NMe); *m/e* 388, 342, 310, and 278. The mother liquors from the crystallisation of (2a) contained a small amount of the epidioxide (5). Further elution with benzene–chloroform (1 : 1) yielded some 14β-nitrocodeinone (3a).

Later experiments [4] showed that higher conversions of thebaine into the acetal (2a) may be achieved using tetranitromethane in methanolic ammonia.

14β-*Nitrocodeinone* (3a).—The acetal (2a) was suspended in water and dissolved by dropwise addition of 2N-hydrochloric acid with warming. Hydrolysis was complete within 1 h and gave 14β-*nitrocodeinone* (3a), m.p. 172.5—173 °C (lemon yellow plates from EtOH), $[\alpha]_D$ +196° (*c* 0.61 in $CHCl_3$) (Found: C, 63.1; H, 5.3; N, 7.9. $C_{18}H_{18}N_2O_5$ requires C, 63.15; H, 5.3; N, 8.2%); $\nu_{max.}$ 1 690 and 1 548 cm^{-1}; τ 3.32 (s, 1-H and 2-H), 3.38 and 3.82 (ABq, *J* 10 Hz, 8-H and 7-H), 4.86 (s, 5-H), 5.92 (d, *J* 6 Hz, 9-H), 6.18 (s, 3-OMe), 6.60 (d, *J* 18 Hz, 10β-H), 7.40 (q, *J* 18 and 6 Hz, 10α-H), and 7.60 (s, NMe); *m/e* 342, 295, and 253.

14β-*Aminocodeinone Dimethyl Acetal* (2b).—Zinc powder (2.5 g) was added to 14β-nitrocodeinone dimethyl acetal (1.61 g) in hot methanol (200 ml) containing ammonium chloride (2.5 g). The mixture was heated under reflux for 1 h then filtered while still hot. The filtrate was evaporated and the residue partitioned between water and chloroform. The chloroform layer was percolated through alumina and evaporated to give 14β-*aminocodeinone dimethyl acetal* (2b) as an oil (1.17 g) which crystallised, with some difficulty, from methanol as needles, m.p. 133—134 °C, $[\alpha]_D$ −173° (*c* 0.55 in $CHCl_3$); $\nu_{max.}$ 3 470 and 3 370 cm^{-1}; τ 3.36 and 3.44 (ABq, *J* 8 Hz, 2-H and 1-H), 4.02 (d, *J* 10 Hz, 8-H), 4.34 (dd, *J* 10 and 1 Hz, 7-H), 5.28 (d, *J* 1 Hz, 5-H), 6.15 (s, 3-OMe), 6.55 (s, 6-OMe), 6.70 (br s, NH_2, exchangeable with D_2O), 6.79 (s, 6-OMe), and 7.60 (s, NMe); *m/e* 358.1897 ($C_{20}H_{26}N_2O_4$ requires *M* 358.1893).

14β-*Aminocodeinone* (3b).—The acetal (2b) was hydrolysed with dilute hydrochloric acid to give 14β-*aminocodeinone*, m.p. 192—194 °C, $[\alpha]_D$ −192° (*c* 0.34 in $CHCl_3$) (Found: C, 69.0; H, 6.45; N, 9.0. $C_{18}H_{20}N_2O_3$ requires C, 69.2; H, 6.45; N, 9.0%); $\nu_{max.}$ 3 360, 3 290, and 1 682 cm^{-1}; τ 3.26 and 3.95 (ABq, *J* 10 Hz, 8-H and 7-H), 3.34 (s, 1-H and 2-H), 5.28 (s, 5-H), 6.19 (s, 3-OMe), 6.74 (d, *J* 19 Hz, 10β-H), 7.25 (dd, *J* 19 and 6 Hz, 10α-H), 7.60 (s, NMe), and 7.61 (br s, NH_2, exchangeable with D_2O); *m/e* 312.

14β-*Cyanoaminocodeinone* (3c).—Cyanogen bromide (150 mg) and 14β-aminocodeinone (90 mg) were heated in ethanol-free chloroform (20 ml) under reflux for 15 min. The resulting precipitate was collected, dissolved in water, and treated with an excess of aqueous sodium hydrogencarbonate. Extraction with chloroform gave 14β-cyanoaminocodeinone (3c) (51 mg), m.p. 201—202 °C (from MeOH), which was identical (mixed m.p., n.m.r. spectrum) with a sample prepared [5] from the cycloadduct of thebaine and nitrosyl cyanide.

14β-*Acetylaminocodeinone* (3d).—Acetylation of 14β-aminocodeinone with acetic anhydride in pyridine in the usual way gave 14β-*acetylaminocodeinone*, m.p. 257.5—258 °C (from MeOH), $[\alpha]_D$ +99° (*c* 0.35 in $CHCl_3$) (Found: C, 67.7; H, 6.6; N, 8.0. $C_{20}H_{22}N_2O_4$ requires C, 67.8; H, 6.3; N, 7.9%); $\nu_{max.}$ 3 370 and 1 695 cm^{-1}; τ 2.96 (s, NH, exchangeable with D_2O–CD_3CO_2D), 3.34 (s, 1-H and 2-H), 3.78 and 3.83 (ABq, *J* 10 Hz, 8-H and 7-H), 5.09 (s, 5-H), 6.20 (s, OMe), 6.75 (d, *J* 18 Hz, 10β-H), 6.88 (d, *J* 6 Hz, 9-H), 7.56 (dd, *J* 18 and 6 Hz, 10α-H), 7.59 (s, NMe), and 8.18 (s, Ac); *m/e* 354.

14β-*Cinnamoylaminocodeinone* (3e).—14β-Aminocodeinone was treated in pyridine at 0 °C with an excess of cinnamoyl chloride in tetrachloromethane and gave 14β-*cinnamoylaminocodeinone*, m.p. 229—230 °C (from MeOH), $[\alpha]_D$ +188° (*c* 0.39 in $CHCl_3$) (Found: C, 72.3; H, 6.0; N, 6.2. $C_{27}H_{26}N_2O_4$·0.5MeOH requires C, 72.0; H, 6.2; N, 6.1%); $\nu_{max.}$ 3 350, 1 695, and 1 670 cm^{-1}; $\lambda_{max.}$ (EtOH) 280 nm (ε 35 700); τ 2.39 and 3.45 (ABq, *J* 18 Hz, *trans*-CH=CH), 2.66 (m, Ph), 3.36 (s, 1-H and 2-H), 3.75 (s, 7-H and 8-H), 4.96 (s, 5-H), 6.22 (s, OMe), and 7.56 (s, NMe); *m/e* 442.

14β-*Benzyloxycarbonylaminocodeinone* (3f).—14β-Aminocodeinone was heated with benzyl chloroformate in chloroform under reflux and gave 14β-*benzyloxycarbonylaminocodeinone*, m.p. 219—222 °C (from MeOH) (Found: C, 68.8; H, 5.9; N, 5.9. $C_{26}H_{26}N_2O_5$·0.5MeOH requires C, 68.8; H, 6.1; N, 6.1%); $\nu_{max.}$ 3 350, 1 720, and 1 693 cm^{-1}; τ 2.64 (br s, Ph), 3.35 (s, 1-H and 2-H), 3.52 (s, NH), 3.81 (s, 7-H and 8-H), 4.96 (s, $PhCH_2O$), 5.11 (s, 5-H), 6.22 (s, OMe), 6.78 (d, *J* 18 Hz, 10β-H), 7.02 (d, *J* 6 Hz, 9-H), 7.62 (dd, *J* 18 and 6 Hz, 10α-H), and 7.65 (s, NMe); *m/e* 446.

14β-*Aminocodeine* (4).—Sodium borohydride (150 mg) was added to 14β-aminocodeinone (89 mg) in methanol (50 ml) at room temperature. After 4 h, the mixture was worked up in the usual way to give 14β-*aminocodeine* (4) (66 mg), m.p. 185—186 °C (from MeOH) (Found: C, 68.8; H, 7.2; N, 8.9. $C_{18}H_{22}N_2O_3$ requires C, 68.8; H, 7.05; N, 8.9%); τ

3.40 (s, 1-H and 2-H), 4.20 (d, *J* 10 Hz, with fine splitting, 7-H), 4.58 (dd, *J* 2 and 10 Hz, 8-H), 5.09 (d, *J* 6 Hz, with fine splitting, 5-H), 5.33 (m, 6-H), 6.20 (s, OMe), 6.83 (d, *J* 19 Hz, 10β-H), 7.38 (dd, *J* 19 and 6 Hz, 10α-H), 7.54 (s, NH_2, exchangeable with D_2O), and 7.64 (s, NMe); *m/e* 314.

8α,10α-*Epidioxy*-8,14-*dihydro*-14β-*nitrothebaine* (5).—Dry oxygen was passed slowly through a solution of thebaine (1.56 g) in benzene (70 ml) at room temperature. Tetranitromethane (1.6 ml) in benzene (12 ml) was added, in portions, during 12 min and the mixture was kept for 3 h at room temperature with continuing passage of oxygen. The resulting precipitate of the trinitromethane salt of thebaine was filtered off and the filtrate was evaporated (at <30 °C; see foregoing note of CAUTION) to near dryness. Separation of the residue by preparative t.l.c. on alumina plates developed with chloroform–benzene (1 : 1) afforded thebaine (18 mg), 14β-nitrocodeinone (154 mg), and 8α,10α-*epidioxy*-8,14-*dihydro*-14β-*nitrothebaine* (5) (600 mg), m.p. 160—161 °C (from EtOAc; dried at 65 °C and 1 mmHg) (Found: 58.7; H, 5.3; N, 7.2. $C_{19}H_{20}N_2O_7$ requires C, 58.8; H, C, 5.3; N, 7.2%); $\nu_{max.}$ 1 644 and 1 551 cm^{-1}; $\lambda_{max.}$ (EtOH) 283 (ε 2 100) and 289 (2 130); τ 3.02 and 3.16 (ABq, *J* 8 Hz, 2-H and 1-H), 4.58 (d, *J* 3.5 Hz, 10-H), 4.73 (s, 5-H), 5.05 (d, *J* 6.4 Hz, 7-H), 5.41 (d, *J* 6.4 Hz, 8-H), 5.78 (d, *J* 3.5 Hz, 9-H), 6.13 (s, 3-OMe), 6.45 (s, 6-OMe), and 7.46 (s, NMe); *m/e* 390, 389, 388, and 342.1340 ($C_{19}H_{20}NO_5$ requires *M* 342.1341). When freshly crystallised from ethyl acetate, this product (5) formed the non-stoicheiometric solvate used for *X*-ray diffraction analysis.[7] The solvate lost ethyl acetate at *ca.* 80 °C (ambient pressure) or at 65 °C (1 mmHg).

When the above nitration was carried out under oxygen-free nitrogen, only a trace of the peroxide (5) was formed; the major products were 14β-nitrocodeinone (23%) and 14β-nitrocodeinone dimethyl acetal (28%).

8,14-*Dihydro*-8β-*hydroxy*-14β-*nitro*-10-*oxothebaine* (6a).—The epidioxide (5) (220 mg), dissolved in the minimum amount of ethanol, was treated with 4N-sodium hydroxide (4 drops). After 1.5 h at room temperature the mixture was neutralised with hydrochloric acid and extraction into chloroform gave the *hydroxy-ketone* (6a) (158 mg), m.p. 219 °C (Found: C, 58.8; H, 5.35; N, 7.3. $C_{19}H_{20}N_2O_7$ requires C, 58.8; H, 5.2; N, 7.2%); $\nu_{max.}$ 3 585, 1 680, 1 619, and 1 547 cm^{-1}; $\lambda_{max.}$ (EtOH) 241 (ε 12 400), 288 (11 000), and 320 nm (6 900); τ 2.58 and 3.16 (ABq, *J* 9 Hz, 1-H and 2-H), 4.70 (s, 5-H), 5.47 (d, *J ca.* 1 Hz, 7-H), 5.67 (dd, *J* 7.5 Hz and *ca.* 1 Hz, 8-H), 5.84 (s, 9-H), 6.05 (s, 3-OMe), 6.44 (s, 6-OMe), 6.87 (d, *J* 7.5 Hz, 8-OH, exchangeable with D_2O), and 7.56 (s, NMe); *m/e* 388.1265 ($C_{19}H_{20}N_2O_7$ requires *M* 388.1270).

Acetylation of the hydroxy-ketone (6a) with acetic anhydride in pyridine at room temperature gave the corresponding O-*acetyl derivative* (6b), m.p. 241.5 °C (from EtOH) (Found: C, 58.7; H, 5.2; N, 6.2. $C_{21}H_{22}N_2O_8$ requires C, 58.6; H, 5.15; N, 6.5%); $\nu_{max.}$ (KBr) 1 755, 1 683, 1 603, and 1 552 cm^{-1}; $\lambda_{max.}$ (EtOH) 243 (ε 13 900), 289 (11 600), and 321 nm (7 050); τ 2.47 and 3.08 (ABq, *J* 9 Hz, 1-H and 2-H), 4.53 (m, 8-H), 4.68 (d, *J* 1.25 Hz, 5-H), 5.62 (d, *J ca.* 1 Hz, 7-H), 6.02 (s, 3-OMe), 6.10 (s, 9-H), 6.73 (s, 6-OMe), 7.53 (s, NMe), and 7.87 (s, Ac); *m/e* 430.

14β-*Nitro*-10-*oxocodeinone* (3g).—The hydroxy-ketone (6a) (167 mg) was heated in 5N-hydrochloric acid (15 ml) under reflux for 10 min. The solution was cooled, adjusted to pH 8 with saturated aqueous sodium hydrogencarbonate, and then extracted with chloroform. Separation of the chloroform-soluble products on alumina t.l.c. plates developed in chloroform–benzene (1 : 1) gave 14β-*nitro*-10-*oxocodeinone* (43 mg), R_F 0.85, m.p. 205—207 °C (from EtOH) (Found: C, 60.6; H, 4.6; N, 8.35. $C_{18}H_{16}N_2O_6$ requires C, 60.7; H, 4.5; N, 7.9%); $\nu_{max.}$ 1 690, 1 686, 1 608, 1 586, and 1 549 cm^{-1}; $\lambda_{max.}$ (EtOH) 242 (ε 11 700), 293 (8 470), and 324 nm (4 720); τ 2.57 and 3.14 (ABq, *J* 8.4 Hz, 1-H and 2-H), 3.46 and 3.74 (ABq, *J* 10 Hz, 8-H and 7-H), 4.78 (s, 5-H), 5.92 (s, 9-H), 6.08 (s, 3-OMe), and 7.51 (s, NMe); *m/e* 356. A second product, tentatively identified as 7,8-dihydro-8β-hydroxy-14β-nitro-10-oxocodeinone was obtained as an oil (34 mg), R_F 0.15; $\nu_{max.}$ 3 610, 3 450, 1 744, 1 683, 1 622, and 1 554 cm^{-1}; τ 2.56 and 3.10 (ABq, *J* 9 Hz, 1-H and 2-H), 4.92 (s, 5-H), 5.76 (s, 9-H), 5.98 (s, 3-OMe), 6.42 (br d, *J* 8 Hz, 8-OH), and 7.53 (s, NMe); *m/e* 374.1112 ($C_{18}H_{18}N_2O_7$ requires *M* 374.1114).

8,14-*Dihydro*-8α,10α-*dihydroxy*-14β-*nitrothebaine* (6c).—The epidioxide (5) (50 mg) in acetic acid (10 ml) was treated with sodium iodide (115 mg) in acetic acid (3 ml) at room temperature under nitrogen for 16 h. The mixture was poured into ice–water (25 ml) and the resulting solution was adjusted to pH 8 with aqueous sodium hydrogencarbonate. The mixture was extracted with chloroform and the extracts were washed successively with aqueous sodium thiosulphate, aqueous sodium hydrogencarbonate, and brine. Evaporation of the chloroform gave the 8α,10α-*diol* (6c) (23 mg), m.p. 175—177 °C (from ethanol) (Found: C, 57.8; H, 6.5; N, 6.6. $C_{19}H_{22}N_2O_7 \cdot C_2H_6O$ requires C, 57.8; H, 6.5; N, 6.4%); $\nu_{max.}$ (10^{-3}M in CCl_4) 3 570, 3 500, and 1 545 cm^{-1}; $\lambda_{max.}$ (EtOH) 279 (ε 2 130) and 284 nm (2 190); τ 2.96 and 3.13 (ABq, *J* 8 Hz, 1-H and 2-H), 4.82 (s, 5-H), 4.97 (d, *J* 12 Hz, 10-H, collapsed to singlet after treatment with D_2O), 5.11 (d, *J* 6 Hz, 7-H), 5.30 (dd, *J* 9 and 6 Hz, 8-H, collapsed to d, *J* 6 Hz, after treatment with D_2O), 5.54 (d, *J* 12 Hz, 10-OH, exchangeable with D_2O), 6.04 (s, 9-H), 6.09 (s, 3-OMe), 6.44 (s, 6-OMe), 7.49 (s, NMe), and signals for ethanol; *m/e* 390.

In a separate experiment under the same conditions, the amount of iodine liberated (0.37 mol equiv.) after reduction of the epidioxide by iodide was determined by titration with aqueous sodium thiosulphate.

8,14-*Dihydro*-8β,10α,-*dihydroxy*-14β-*nitrothebaine* (6d).—The 8α,10α-diol (6c) (70 mg) in ethanol (10 ml) was treated with 4N-sodium hydroxide (4 drops). After 0.5 h at room temperature the mixture was poured into brine and extraction with chloroform gave the 8β,10α-*diol* (6d) (41 mg), m.p. 210—211 °C (decomp.) (from EtOH) (Found: C, 58.7; H, 5.7; N, 7.4. $C_{19}H_{22}N_2O_7$ requires C, 58.45; H, 5.7; N, 7.2%); $\nu_{max.}$ 3 610, 3 500br, 1 651, 1 623, 1 539, and 1 441 cm^{-1}; τ 3.05 and 3.18 (ABq, *J* 8 Hz, 1-H and 2-H), 4.74 (s, 5-H), 4.82 (s, 10-H), 5.32 (s, 7-H), 5.78 (s, 8-H), 5.94 (s, 9-H), 6.16 (s, 3-OMe), 6.53 (s, 6-OMe), 7.0 (br s, 8-OH and 10-OH, exchangeable with D_2O), and 7.45 (s, NMe).

8,14-*Dihydro*-8,10-*dioxo*-14β-*nitrothebaine* (6e).—The hydroxy-ketone (6a) (25 mg) was shaken in benzene (30 ml) with activated manganese dioxide[9] (*ca.* 250 mg) for 4 h. The mixture was filtered through Celite. Evaporation of the filtrate gave the *diketone* (6e) (20 mg), m.p. 232—233 °C (from Et_2O) (Found: C, 59.1; H, 4.7; N, 7.25. $C_{19}H_{18}N_2O_7$ requires C, 59.05; H, 4.7; N, 7.3%); $\nu_{max.}$ (KBr) 1 691, 1 623, 1 602, and 1 554 cm^{-1}; $\lambda_{max.}$ (EtOH) 220 (ε 15 200), 238 (16 200), 280 (11 100), and 318 nm (5 110); τ 2.55 and 3.06 (ABq, *J* 8.5 Hz, 1-H and 2-H), 4.39 (s, 7-H), 4.64 (s, 5-H), 5.56 (s, 9-H), 6.02 (s, 3-OMe), 6.23 (s, 6-OMe), and 7.48 (s, NMe); *m/e* 386.

Oxidation of the 8α, 10α-diol (6e) and the 8β,10α-diol (6d) as above also gave the same diketone (6e).

8,14-*Dihydro*-8α,10α-*epoxy*-14β-*nitrothebaine* (5; ---O--- in place of ---O_2---).—The epidioxide (5) (97 mg) was heated overnight under reflux in benzene containing triphenylphosphine (65.6 mg). The solution was evaporated and the mixture of products was separated by t.l.c. on alumina plates, developed in benzene–chloroform (1 : 1), to afford the epidioxide (5) (6.5 mg), R_F 0.8—0.9; triphenylphosphine oxide (68.5 mg), R_F 0.2—0.4; and the 8α,10α-*epoxide* (5; ---O--- in place of ---O_2---) (78 mg), R_F 0.4—0.6, m.p. 131—132 °C (from MeOH) (Found: C, 61.5; H, 5.4; N, 7.8. $C_{19}H_{20}N_2O_6$ requires C, 61.3; H, 5.4; N, 7.5%); $\nu_{max.}$ 1 640 and 1 549 cm^{-1}; τ 3.22 (s, 1-H and 2-H), 4.66 (s, 5-H), 4.95 and 5.30 (ABq, *J* 5 Hz, 10-H and 9-H), 5.20 (s, 7-H and 8-H), 6.11 (s, 3-OMe), 6.51 (s, 6-OMe), and 7.41 (s, NMe); *m/e* 372.

10α-*Hydroxy*-14β-*nitrocodeinone* (3h).—The above epoxide (5; ---O--- in place of ---O_2---) (74 mg) was kept at room temperature in 5M-hydrochloric acid (20 ml) for 2 h. The mixture was made alkaline with sodium hydrogencarbonate and the product was extracted into chloroform in the usual way. Chromatography on alumina plates developed with chloroform gave 10α-*hydroxy*-14β-*nitrocodeinone* (43 mg), m.p. 206—027 °C (from EtOH) (Found: C, 60.4; H, 5.1; N, 7.5. $C_{18}H_{18}N_2O_6$ requires C, 60.3; H, 5.1; N, 7.8%); $\nu_{max.}$ 3 610, 1 698, and 1 555 cm^{-1}; τ 3.03 and 3.16 (ABq, *J* 8 Hz, 1-H and 2-H), 3.06 and 3.83 (ABq, *J* 10 Hz, 8-H and 7-H), 4.78 (br s, 10-H, sharpened after treatment with D_2O), 4.84 (s, 5-H), 5.87 (br s, 9-H), 6.10 (s, 3-OMe), and 7.42 (s, NMe); *m/e* 358.

Oxidation of the hydroxy-enone (3h) with manganese dioxide in benzene, as before, gave 14β-nitro-10-oxocodeinone, which was identical with material prepared by hydrolysis of the hydroxy-ketone (6a).

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