Formation of a Bridged Peroxide from Thebaine and Tetranitromethane; *X*-Ray Crystal Structure of 8α,10α-Epidioxy-8,14-dihydro-14β-nitrothebaine

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Summary Thebaine (**1**) reacts with tetranitromethane in benzene in the presence of oxygen to give, as the major product, the bridged peroxide, 8α,10α-epidioxy-8,14-dihydro-14β-nitrothebaine (**3**), the structure of which has been determined by *X*-ray crystallography.

THEBAINE (**1**) reacts with the mild nitrating agent, tetranitromethane,[1] in methanol to yield mainly 14β-nitrocodeinone dimethyl acetal (**2**).[2] However, in benzene, in the presence of air or preferably oxygen, the unusual epidioxide (**3**) is formed as the major product. The structure (**3**) was deduced tentatively by chemical degradation† and confirmed by *X*-ray diffraction analysis.

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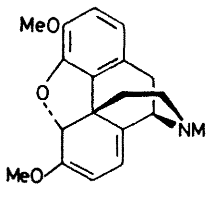
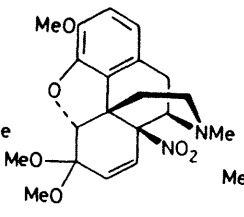
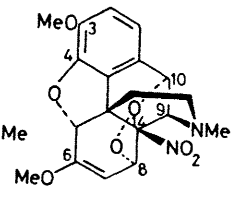
† I.r., u.v., and ^{1}H- and ^{13}C-n.m.r. data were recorded for (**3**) and its various degradation products. Only the more significant degradations are reported here. Satisfactory elemental analyses were obtained for all new compounds.



(1)

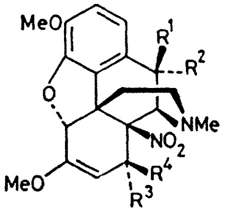


(2)

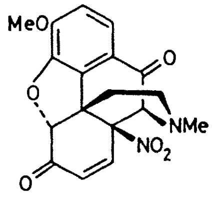


(3)

Dry oxygen was passed slowly through a solution of thebaine and tetranitromethane (1 mol. equiv.) for 3 h at room temperature to yield the trinitromethane salt of thebaine (*ca.* 50%), 14β-nitrocodeinone (8%), and 8α,10α-epidioxy-8,14-dihydro-14β-nitrothebaine (**3**) (31%), m.p. 160—161 °C (from EtOH or EtOAc). The yield of (**3**) was greatly reduced when the nitration was conducted in a nitrogen-flushed system. The presence of a peroxide bridge in (**3**) was shown in the following way. Treatment with triphenylphosphine (1 mol. equiv.) in benzene under reflux gave triphenylphosphine oxide (98%) and 8α,10α-epoxy-8,14-dihydro-14β-nitrothebaine [as (**3**) with – – – O – – – replacing – – – O_2 – – –] (84%). With sodium iodide in acetic acid, at room temperature, (**3**) afforded the diol (**4**; $R^1 = R^4 = H$, $R^2 = R^3 = OH$) (46%) and iodine (37% by titration). This diol readily epimerised in ethanolic sodium hydroxide, to yield (**4**; $R^1 = R^3 = H$, $R^2 = R^4 = OH$), thus suggesting the location of one hydroxy-group β to a nitro-group. The unexpected presence of an oxygen atom at C-10 was revealed by isomerisation of (**3**) in dilute ethanolic sodium hydroxide to give the hydroxy-ketone (**4**; $R^1R^2 = O$, $R^3 = H$, $R^4 = OH$), which had a characteristic[3] u.v. spectrum, λ_{max} 241 (ϵ 12,400), 288 (11,000), and 320 nm (6900). The epimeric diols and the hydroxy-ketone were each oxidised with manganese dioxide to give the same diketone (**4**; $R^1R^2 = O$, $R^3R^4 = O$). Finally, hydrolysis of the hydroxy-ketone (**4**; $R^1R^2 = O$, $R^3 = H$, $R^4 = OH$) with hot, dilute hydrochloric acid gave 14β-nitro-10-oxocodeinone (**5**), thereby indicating the relative positions of the enol-ether and hydroxy groups in ring C.



(4)



(5)

It was not possible to convert (**3**) or any of its degradation products into compounds of unequivocally known structure. Also, the formation of the peroxide bridge in (**3**) lacked any clear mechanistic precedent. Accordingly, confirmation of this unusual structure was sought by *X*-ray diffraction analysis. The peroxide (**3**) crystallised from ethyl acetate as a solvate‡ which yielded the following crystal data: $C_{19}H_{20}N_2O_7$, monoclinic, space group $P2_1$, $Z = 4$, $a =$ 8·053(1), $b =$ 19·494(6), $c =$ 13·354(2) Å, $\beta =$ 90·54(1)°. Associated with each pair of alkaloid molecules in the asymmetric unit was a molecule of ethyl acetate solvent with a partial occupancy of *ca.* 0·67. Cell dimensions and intensity data were obtained using monochromated Mo-K_α radiation. The structure was solved by direct methods using a version of MULTAN 78 into which quartet and quintet invariants had been incorporated. Full details will be published elsewhere. The structure was refined to $R =$ 0·051 for 2080 unique reflections having $I >$ 2·5$\sigma(I)$.§

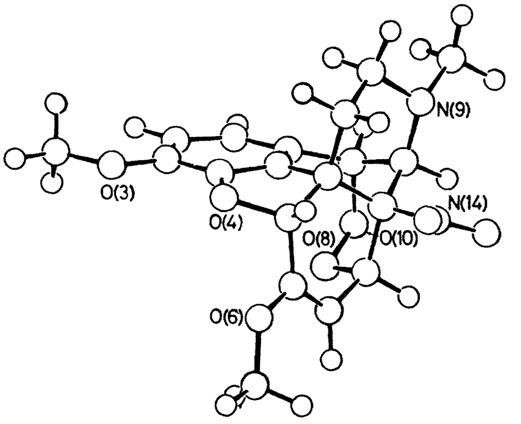


FIGURE. A view of 8,14-dihydro-8α,10α-epidioxy-14β-nitrothebaine (**3**). For clarity the atoms are shown as spheres of arbitrary radius.

There are no important differences in the geometries of the two molecules in the asymmetric unit. The Figure shows a view of one molecule. The peroxide ring has a chair conformation with a C–O–O–C dihedral angle of –70·4°; the remaining rings have conformations that parallel those found in other codeine derivatives.[4]

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‡ Solvent was lost from the crystals above *ca.* 80 °C.

§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratories, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

[1] 'The Chemistry of the Nitro and Nitroso Groups,' ed. H. Feuer, Interscience, New York, 1970, part 2.
[2] Full details of this reaction will be described elsewhere; see also R. M. Allen and G. W. Kirby, *Chem. Comm.*, 1970, **1346**; R. J. Kobylecki, I. G. Guest, J. W. Lewis, and G. W. Kirby, DTOLS 2,812,580/1978; *Chem. Abs.*, 1979, **90**, 87709t.
[3] H. Rapoport and G. W. Stevenson, *J. Amer. Chem. Soc.*, 1954, **76**, 1796.
[4] A. A. Freer, G. A. Sim, I. G. Guest, A. C. B. Smith, and S. Turner, *J.C.S. Perkin II*, 1979, 401.