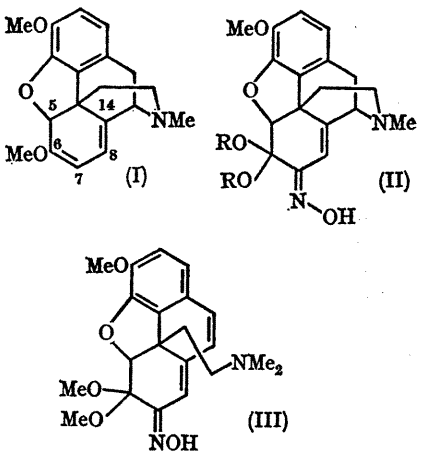
Nitrosation of Thebaine involving Electrophilic Attack at C-7

By K. W. BENTLEY, G. W. KIRBY*, A. P. PRICE, and SERJINDER SINGH
(*Department of Chemistry, University of Technology, Loughborough*)

THE methoxy-diene system of thebaine (I) is normally attacked by electrophilic reagents at C-14.[1] Thus, bromination gives 14-bromocodeinone and oxidation with peroxy-acids gives 14-hydroxycodeinone. We now report that nitrosation of thebaine in the presence of alcohols occurs predominantly at C-7 to give oximes of the type (II). This reaction provides a potential route to morphine derivatives, for example salutaridine,[2] with a functional group at C-7.

The nitrosation of thebaine in methanol or ethanol was earlier reported[3] to give products of composition $C_{20}H_{24}N_2O_5$ and $C_{22}H_{28}N_2O_5$, respectively. Structures were not assigned to these compounds. In our hands, treatment of thebaine hydrochloride in methanol at room temperature with an excess of nitrosyl chloride gave (II; R = Me), m.p. 247°, λ_{max} 234 nm (ϵ 22,100). The ethoxyl analogue (II; R = Et), m.p. 245—247°, λ_{max} 234 nm (ϵ 22,600), was similarly obtained when ethanol was used as solvent. The two products were interconverted by treatment with a solution of hydrogen chloride in the appropriate alcohol. Proof of the structures (II) is illustrated, as follows, for the dimethyl ketal (II; R = Me).

The n.m.r. spectrum, in $CDCl_3$, showed three *O*-methyl singlets at τ 6·12 (methoxy-aryl), 6·45, and 7·07, and an *N*-methyl singlet at τ 7·56. The singlet at τ 7·07 is expected[4] for an *O*-methyl group at C-6 *cis* to, and shielded by, the aromatic ring. Protons at C-5 and C-8 gave singlets at τ 5·25 and 3·56. The low-field position of the olefinic proton signal suggests that the oxime group has the *syn*-configuration. In hexadeuteriodimethyl sulphoxide the oximinohydroxy-group gave an n.m.r. signal τ −1·47. The acetal (II; R = Me) dissolved sparingly in aqueous sodium hydroxide and was reprecipitated by carbon dioxide but did not give a colour with ferric chloride. The u.v. spectrum showed a red shift to λ_{max} 273 nm. (ϵ 17,150) upon addition of sodium ethoxide to an ethanolic solution. A similar shift, presumably induced by ionisation of the oxime group, was observed with the *syn*-oxime of cholest-4-en-3-one:[5] λ_{max} 241 nm (ϵ 23,050) in EtOH, 262 nm. (22,480) in EtOH–EtONa.



The methiodide of (II; R = Me) underwent Hofmann elimination at room temperature with potassium t-butoxide in dimethylformamide. The extended chromophore in the resulting methine (III), m.p. 223—224°, was apparent from the u.v. absorption, λ_{max} 257 nm (ϵ 18,000) and 350 nm (ϵ 12,650) and the n.m.r. olefinic signals (in $CDCl_3$), τ 3·57 (singlet), 3·44 and 3·78 (doublets, J 9·7 Hz). The oximino-hydroxy-group absorbed at τ −1·8 in $(CD_3)_2SO$.

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