Nitrosation of Thebaine leading to 7-Substituted Neopinone Derivatives

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Nitrosation of thebaine hydrochloride with nitrosyl chloride or pentyl nitrite in methanol or ethanol has been shown to give 7-hydroxyiminoneopinone dimethyl or diethyl acetal. Other, bimolecular, products, best prepared by use of nitrosylsulphuric acid as nitrosating agent, arise *via* Diels–Alder addition of a transient 7-nitrosoneopinone derivative to a second molecule of thebaine.

ELECTROPHILIC attack on the methoxy-diene system of thebaine (1) normally gives 14-substituted codeinone derivatives (2).[1] Thus, halogenation yields 14-bromo- and 14-chloro-codeinone, or the corresponding acetals, and oxidation with peroxy-acids gives 14-hydroxycodeinone. Nitrosation of thebaine therefore appeared to present an attractive route to the inaccessible derivatives of 14-aminocodeine. Nitrosation of the alkaloid in methanol or ethanol was earlier reported [2] to give closely related 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, and we now report [3] a reinvestigation showing that nitrosation occurs, apparently exclusively, at C-7 rather than C-14.

Treatment of thebaine hydrochloride in methanol at room temperature with nitrosyl chloride gave the methoxy-oxime (3; R = Me). The same compound was obtained, in varying yield, when nitrosylsulphuric acid and pentyl nitrite were used as nitrosating agents. Nitrosation in ethanol gave the analogous ethoxy-oxime (3; R = Et). The chemical and spectroscopic properties of these oximes were closely similar; moreover, treatment of the methoxy-oxime with ethanolic hydrogen chloride gave the ethoxy-oxime. Discussion will be confined hereafter to the methoxy-derivative (3; R = Me).

The n.m.r. spectrum of this oxime (3; R = Me) showed three methoxy-singlets, τ ($CDCl_3$) 6·12, 6·45, and 7·07. The highest field signal was assigned to a methoxy-group at C-6 *cis* to, and shielded [4] by, the aromatic ring. The *N*-methyl group gave rise to a singlet, τ 7·56. Protons at C-5 and C-8 gave singlets, τ 5·25 and 3·56, respectively, the low-field position of the latter suggesting a *syn*-configuration for the oxime hydroxy-group. A hydroxy-proton, exchangeable with deuterium oxide, absorbed at τ −1·47 in [$^2H_6$]dimethyl sulphoxide, although no corresponding signal was detectable in [^2H]chloroform. The methoxy-oxime was sparingly soluble in aqueous sodium hydroxide and was reprecipitated by carbon dioxide, but did not give a colour with iron(III) chloride. Confirmation of the presence of an oxime function came from u.v. spectra. The band at 234 nm (ε 22,100), observed in neutral ethanol shifted to 273 nm (ε 17,150) upon addition of sodium ethoxide. That ionisation of an αβ-unsaturated oxime rather than a phenol was occurring was shown by the similar behaviour of the *syn*-oxime [5] of cholest-4-en-3-one (4): $\lambda_{max.}$ (EtOH) 241 nm (ε 23,050), $\lambda_{max.}$ (NaOEt–EtOH) 262 nm (ε 22,480). The oxime group was only slowly cleaved by nitrosating agents, presumably because attack at the nitrogen atom in the *syn*-form was hindered by the neighbouring acetal function. However, treatment of the oxime (3; R = Me) with a large excess of pentyl nitrite in acetic acid gave a low yield of the corresponding enone, $\nu_{max.}$ ($CHCl_3$) 1694 cm^{-1}, having physical properties in close agreement with those of material prepared recently [6] by an entirely different route. Cleavage in the presence of mineral acids was not observed, thus explaining the survival of the oxime during its formation from thebaine: no doubt under these conditions the oxime group was protected from nitrosation by protonation. The methoxy-oxime readily formed a methiodide which underwent Hofmann elimination with potassium t-butoxide in dimethylformamide. The extended chromophore in the product (5), revealed by u.v. absorption [$\lambda_{max.}$ 257 (ε 18,000) and 350 nm (12,650)], and n.m.r. olefinic signals [τ ($CDCl_3$) 3·57 (s), 3·44 (d) and 3·78 (d) (*J* 9·7 Hz)] established the relationship of the oxime function to the rest of the molecule. The oxime hydroxy-group absorbed at τ [$(CD_3)_2SO$] −1·8.

The earlier workers [2] reported that nitrosation of thebaine in ethanol gave a third product, $C_{22}H_{28}N_2O_5$, m.p. 238—240°, apparently an isomer of the ethoxy-oxime (3; R = Et). From experiments involving nitrosation of thebaine in the presence of a limited quantity of ethanol, we isolated a substance, m.p. 234—238°, showing n.m.r. absorption attributable to both methoxy and ethoxy acetal groups. This substance was therefore taken to be a mixture of the ethoxy-oxime (3; R = Et) and a mixed acetal [3; $(RO)_2C$ = MeO·C·OEt], and was not investigated further. The product recorded earlier may likewise have been a mixture or, less probably, the hindered *anti*-form of the oxime (3; R = Et).

Nitrosation of thebaine under various conditions in methanol or ethanol gave, besides the oximes (3), varying amounts of new ketonic products (6; R = Me or Et). Highest yields were obtained with nitrosyl-

[1] K. W. Bentley, 'The Chemistry of the Morphine Alkaloids,' Clarendon Press, Oxford, 1954, p. 188; W. Fleischhaker, F. Vieböck, and F. Zeidler, *Monatsh.*, 1970, **101**, 1215; J-P. Gavard, F. Krausz, and T. Rüll, *Bull. Soc. chim. France*, 1965, 486.

[2] C. H. Boehringer Sohn, D.R.P. 437,451/1926.

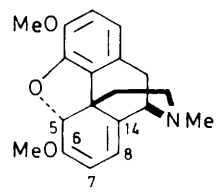
[3] *Cf.* K. W. Bentley, G. W. Kirby, A. P. Price, and Serjinder Singh, *Chem. Comm.*, 1969, 57.

[4] U. Eppenberger, M. E. Warren, and H. Rapoport, *Helv. Chim. Acta*, 1968, **51**, 381.

[5] C. W. Shoppee, G. Krüger, and R. N. Mirrington, *J. Chem. Soc.*, 1962, 1050.

[6] W. Fleischhaker, *Monatsh.*, 1971, **102**, 558.

sulphuric acid. Again, discussion will be confined to the methoxy-derivative. The composition, $C_{38}H_{43}N_3O_8$, was established by mass spectrometry and elemental



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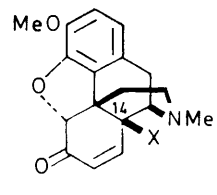

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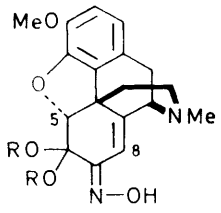

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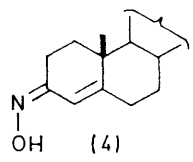

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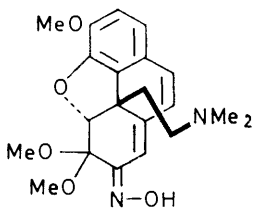

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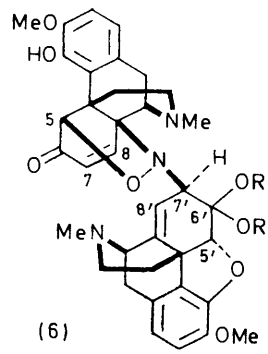

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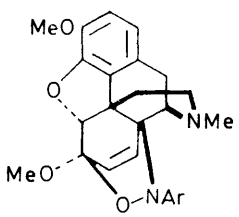

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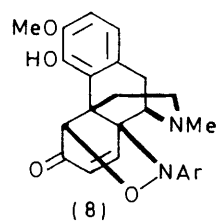

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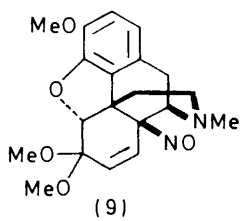

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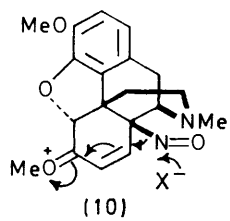

(10)

analysis, and the presence of an αβ-unsaturated ketone function was inferred from an i.r. band at 1682 cm^{-1} (chloroform) which had disappeared after reduction of the compound with sodium borohydride. The compound (6; R = Me) gave an ill-defined blue colour with an ethanolic iron(III) chloride, dissolved slowly in warm aqueous sodium hydroxide, and was recovered therefrom upon treatment with an excess of carbon dioxide. The u.v. absorption (ethanol) [$\lambda_{max.}$ 215, 278, and 360 nm (ε 34,100, 4680, and 1060)] showed a red shift characteristic of a phenol, [to $\lambda_{max.}$ 223, 292, and 360 (ε 49,500, 6980, and 1610)] upon addition of sodium ethoxide. Treatment with acetic anhydride in pyridine gave a mono-*O*-acetyl derivative, $\nu_{max.}$ ($CHCl_3$) 1772 cm^{-1}, confirming the phenolic character of the compound. The n.m.r. spectrum ($CDCl_3$) showed a pair doublets, τ 3·30 and 3·90 (*J* 9·5 Hz), assigned to protons (8-H and 7-H, respectively) of the enone system. Fine splitting (*J* 1·8 Hz) of the high-field pair was associated with a doublet, τ 5·13, which must arise from the proton at C-5. The position of this band and that of a singlet, τ 4·69 (5′-H), showed that both C-5 and C-5′ still carried oxygen functions, despite the phenolic nature of the compound. A doublet, τ 4·48 (*J* 6·0 Hz), suggested the presence of an olefinic proton (8′-H) coupled to a neighbouring proton absorbing in the congested, high-field region of the spectrim. Four methoxy-singlets, τ 6·14, 6·23, 6·44, and 7·16, were present, the highest-field signal being characteristic (see before) of a 6′-acetal function. Two *N*-methyl singlets were observed at τ 7·50 and 7·59. The aryl multiplet, τ *ca.* 3·4, was consistent with overlapping signals from the two different aromatic rings. Reduction of compound (6; R = Me) with zinc in acetic acid gave the methoxy-oxime (3; R = Me) thus allowing an NO unit to be located at C-7′ in one portion of the methoxy-ketone. Mechanistically, reductive cleavage of the C(5)–O bond, α to the keto-group, would give a 14-hydroxyamino-enone which, by a process analogous to a retro-aldol reaction, might collapse to an enol and the nitroso-tautomer of the oxime (3; R = Me). These data strongly suggested that, during the nitrosation of thebaine, an intermediate 7-nitroso-compound was trapped by Diels–Alder addition to another molecule of the alkaloid. Confirmation of this idea came from model studies,[7] showing that thebaine and nitrosoarenes form adducts (7) of this type which, by successive treatment with acid and alkali, give phenolic ketones (8). The stereochemistry at C-7′ in (6; R = Me) follows from the magnitude (6·0 Hz) of $J_{7',8'}$, which takes similar values[8] in simpler 7β-substituted neopinone acetals.

All products so far isolated from the nitrosation of thebaine thus arise from attack by the reagent at C-7. This is puzzling in that other common electrophiles attack at C-14. Nitrosation at C-14 might however be reversible. The hypothetical product (9) could neither tautomerise to an oxime nor, since it is a hindered, tertiary nitroso-compound, readily add to thebaine. It might merely revert to its progenitor (10), which could reasonably be cleaved, as indicated, to regenerate thebaine and a nitrosating species and thence the observed products (3) and (6). Support for this idea

[7] K. W. Bentley, P. Horsewood, G. W. Kirby, and Serjinder Singh, *Chem. Comm.*, 1969, 1411.

[8] R. M. Allen and G. W. Kirby, *Chem. Comm.*, 1970, 1346; W. Fleischhaker, *Monatsh.*, 1971, **102**, 558.

comes from the observation [9] that oxidation of 14-hydroxyaminocodeinone (2; X = NH·OH) with periodic acid leads not to 14-nitrosocodeinone (2; X = NO) but to 7-hydroxyiminoneopinone, the ketonic parent of the acetals (3). Recently two further examples of electrophilic attack at C-7 in thebaine have been reported. Iodination of thebaine in methanol gave [10] 7-iodoneopinone dimethyl acetal, and bromination of thebaine metho-salts gave [11] the analogous 7-bromoneopinone derivatives. In the latter example, the presence of an additional methyl group on the nitrogen atom presumably hindered attack at C-14. However, the reason why iodination, like nitrosation but unlike chlorination and bromination, takes place apparently exclusively at C-7 is not yet clear.

EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus. N.m.r. spectra were measured at 60 and 100 MHz and mass spectra at an ionising voltage of 70 eV.

Nitrosation of Thebaine with Pentyl Nitrite: the Methoxy-oxime (3; R = Me).—Thebaine (2·5 g) in methanol (6 ml) and chloroform (6 ml) was treated at 0 °C with methanolic 1·4N-hydrogen chloride (27·5 ml) followed by pentyl nitrite (3·75 ml), and the mixture was kept overnight at 5 °C. The solvent was evaporated off and the gummy residue treated with 2N-sodium hydroxide (17 ml). A precipitate was filtered off, washed with water, and crystallised from ethanol to give the methoxy-ketone (6; R = Me) (see later) (250 mg). The combined filtrate and washings were treated with an excess of solid carbon dioxide and the resulting precipitate was collected, washed with water, and crystallised from ethanol to give *7-hydroxyiminoneopinone dimethyl acetal* (3; R = Me) (1·1 g), m.p. 247° (Found: C, 64·8; H, 6·7; N, 7·3. $C_{20}H_{24}N_2O_5$ requires C, 64·5; H, 6·5; N, 7·5%).

Nitrosation of Thebaine with Pentyl Nitrite: the Ethoxy-oxime (3; R = Et).—Thebaine (5·25 g) in ethanol (11 ml) and chloroform (11 ml) containing ethanolic 2·75N-hydrogen chloride (11·3 ml) was treated with pentyl nitrite (1·8 ml) as just described. The mixture was shaken with water (25 ml) and ether (25 ml). The aqueous layer was shaken with 2N-sodium hydroxide (37·5 ml) and kept at 5 °C for 2 h. The resulting crystalline precipitate was filtered off and digested with water; the soluble component was treated with an excess of solid carbon dioxide to give the 'mixed acetal' (see text) (1·16 g), m.p. 234—238° (from ethanol). The original alkaline filtrate was treated with carbon dioxide to liberate *7-hydroxyiminoneopinone diethyl acetal* (3; R = Et) (800 mg), m.p. 232—235° (from ethanol) (Found: C, 66·0; H, 7·25; N, 6·8. $C_{22}H_{28}N_2O_5$ requires C, 66·0; H, 7·05; N, 7·0%). The spectra resembled those of the methoxy-oxime (see text) but n.m.r. triplets appeared at τ ($CDCl_3$) 8·74 and 9·29 (*J* 7·0 Hz) [$(CH_3{\cdot}CH_2{\cdot}O)_2C$].

Nitrosation of Thebaine with Nitrosyl Chloride.—Nitrosyl chloride was passed into a solution of thebaine hydrochloride in ethanol or methanol at room temperature until all the thebaine had reacted (disappearance of u.v. band at 280 nm). The solvent was evaporated off and the residue treated with aqueous sodium hydrogen carbonate and extracted with chloroform. The extract was chromatographed on neutral, grade V alumina, elution with chloroform, giving, successively, two minor products, the ketones (6), and the oximes (3). Alternatively, the residue was dissolved in water and treated with an excess of sodium hydroxide. The mixture was filtered and the oximes (3) were liberated by addition of an excess of solid carbon dioxide. This latter procedure was preferred for preparing the ethoxy-oxime (3; R = Et).

Hofmann Degradation of the Methoxy-oxime (3; R = Me).—The methoxy-oxime (3; R = Me) was treated with an excess of methyl iodide in methanol overnight. Evaporation left the corresponding methiodide, m.p. 231° (decomp.). This methiodide (800 mg) was treated with potassium t-butoxide (230 mg) in dimethylformamide (75 ml) at room temperature for 0·5 h. The solvent was evaporated off and the residue shaken with water and chloroform. The chloroform layer was dried (Na_2SO_4) and evaporated to give the *methine* (5) which crystallised from methanol as plates (330 mg), m.p. 223—224° (Found: C, 65·1; H, 7·0; N, 7·45. $C_{21}H_{26}N_2O_5$ requires C, 65·3; H, 6·8; N, 7·25%).

Nitrosation of the Methoxy-oxime (3; R = Me).—The methoxy-oxime (790 mg) was heated at 50—60 °C for 0·5 h in acetic acid (25 ml) and pentyl nitrite (25 ml). The mixture was kept overnight at room temperature, then evaporated. The residue was chromatographed on neutral, grade III alumina (50 g). Elution with benzene–ethyl acetate (1 : 1) gave a gum (400 mg) which was purified on alumina plates (Merck GF_{254}) developed with ethyl acetate–methanol (95 : 5). The major component (R_F *ca.* 0·65), 7-oxoneopinone dimethyl acetal, crystallised from ether–light petroleum (b.p. 40—60°) as plates (100 mg), m.p. 137—138° (lit.,[6] 135—136·5°); $\nu_{max.}$ ($CHCl_3$) 1694 cm^{-1}; τ ($CDCl_3$) 4·12 (s, 8-H), 5·18 (s, 5-H), 6·10, 6·46, and 7·0 (each s, MeO), and 7·55 (s, MeN); *m/e* 357·1573 (M^+, $C_{20}H_{23}NO_5$ requires *M*, 357·1576). Elution with benzene–ethyl acetate (9 : 1) gave a compound (63 mg), m.p. 181°, *m/e* 372·1321 (M^+, $C_{19}H_{20}N_2O_6$ requires *M*, 372·1321), possibly the *N*-nitroso-*N*-nor-derivative of the ketone, which was not investigated further.

Nitrosation of Thebaine with Nitrosylsulphuric Acid: the Alkoxy-ketones (6).—Thebaine (1·04 g) in methanol (21 ml) containing 1 mol. equiv. of hydrogen chloride was treated with nitrosylsulphuric acid (2·2 g) at room temperature for 4 h. The solvent was evaporated off and the residue dissolved in water then treated with an excess of sodium hydrogen carbonate. The resulting precipitate was dissolved in chloroform and the solution washed with water and dried (Na_2SO_4). Evaporation and crystallisation of the residue from ethanol gave the *methoxy-ketone* (6; R = Me) *diethanolate* (210 mg), m.p. 189—190°, *m/e* 669·302 (M^+, $C_{38}H_{43}N_3O_8$ requires *M*, 669·305) (Found: C, 66·4; H, 7·2; N, 5·6. $C_{38}H_{43}N_3O_8,2C_2H_5OH$ requires C, 66·4; H, 7·2; N, 5·5%) (see text for spectroscopic data). Similarly, nitrosation of thebaine in ethanol gave ethoxy-ketone (6; R = Et) (20%), m.p. 189—190°, *m/e* 697 (M^+), τ ($CDCl_3$) 8·76 (t) and 9·42 (t) (*J* 7·0 Hz, $CH_3{\cdot}CH_2{\cdot}O$).

Acetylation of the Methoxy-ketone (6; R = Me).—Acetylation was effected with acetic anhydride in pyridine overnight at room temperature. The O-*acetate* had m.p. 246° (from ethanol); $\nu_{max.}$ ($CHCl_3$) 1772 cm^{-1}; τ ($CDCl_3$) 2·96 (d, *J* 10 Hz, 8-H), 3·19—3·35 (m, aryl H), 3·82 (q,

[9] P. Horsewood and G. W. Kirby, unpublished work.
[10] R. M. Allen and G. W. Kirby, *Chem. Comm.*, 1970, 1346.
[11] H. Bach, W. Fleischhaker, and F. Vieböck, *Monatsh.*, 1970, **101**, 362.

J 10 and 1·8 Hz, 7-H), 4·48 (d, *J* 6·0 Hz, 8′-H), 4·70 (s, 5′-H), 5·43 (d, *J* 1·8 Hz, 5-H), 6·12, 6·26, 6·44, and 7·14 (s, MeO), 7·50 and 7·58 (s, MeN), and 7·64 (s, MeCO) (Found: C, 67·2; H, 6·45; N, 6·0. $C_{40}H_{45}N_3O_9$ requires C, 67·5; H, 6·3; N, 5·9%).

Reduction of the Methoxy-ketone (6; R = Me) *with Zinc Dust.*—The methoxy-ketone (148 mg) and zinc dust (152 mg) in acetic acid (5 ml) were heated briefly until the mixture became reddish brown. The product was poured into an excess of aqueous sodium hydrogen carbonate and extracted with chloroform. Chromatography on alumina (as before) gave the methoxy-ketone (16 mg) and the methoxy-oxime (3; R = Me) (35 mg).

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