Cyclo-adducts of Thebaine with Nitrosoarenes

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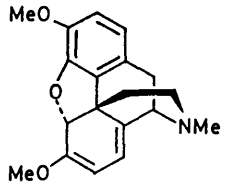
Thebaine (1) reacts reversibly with various nitroso-arenes to form cyclo-adducts by 1,4-addition of the nitroso-group to the conjugated diene system of the alkaloid. Adducts (2) of thebaine with nitrosobenzene and with 4-chloro-, 4-methyl-, 3-methoxy-, and 4-nitro-nitrosobenzene have been prepared in good yield. The adduct with nitrosobenzene was hydrolysed by hydrochloric acid to give 14β-(*N*-hydroxyphenylamino)codeinone (3; Ar = Ph) in high yield. Catalytic hydrogenation of this derivative afforded 7,8-dihydro-14β-phenylaminocodeinone (4). 14β-(*N*-Hydroxyphenylamino)codeinone rearranged readily in alkaline solution to give the phenol, 5,*O*-dihydro-5β,14β-(*N*-phenylepoxyimino)codeinone (5).

THE isolation of ' dimeric ' products from the nitrosation of thebaine (1) led to the suggestion [1] that the alkaloid might undergo Diels–Alder reactions with *C*-nitroso-compounds. We now report experiments [2] with nitroso-arenes which demonstrate this process and establish a convenient route to 14-arylaminocodeinone derivatives.

RESULTS AND DISCUSSION

Thebaine (1) reacted with nitrosobenzene in chloroform at room temperature to give the adduct (2; Ar = Ph) in high yield. The gross structural features of the product were discerned spectroscopically; in particular, n.m.r. signals at τ($CDCl_3$) 3.75 (dd, *J* 1 and 9 Hz, 7-H), 4.64 (d, *J* 9 Hz, 8-H), and 5.25 (d, *J* 1 Hz, 5-H) supported the formulation of (2; Ar = Ph) as a cyclo-adduct. Treatment of the adduct with 2N-hydrochloric acid caused hydrolysis of the acetal group and afforded the enone



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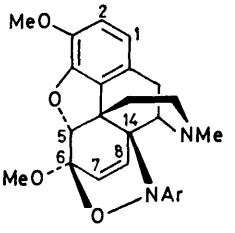

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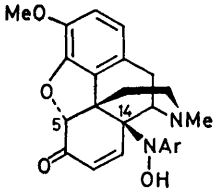

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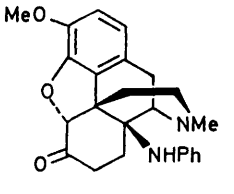

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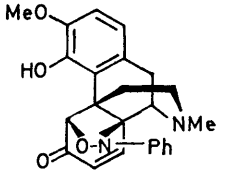

(5)

(3; Ar = Ph), $\nu_{max.}$ 1 687 cm^{-1}, in high yield. In principle, this enone might have been 14-(*N*-hydroxyphenylamino)codeinone (as shown) or 14-phenylamino-oxycodeinone, depending upon the orientation of the nitrosobenzene moiety in the parent adduct. This point was settled as follows. Acetylation of (3; Ar = Ph) gave a derivative judged to be an *O*-acetate, rather than an acetamide, from its i.r. absorption, $\nu_{max.}$ 1 773 and 1 688 cm^{-1}. Further, catalytic (Pd–C) hydrogenation of (3; Ar = Ph) afforded a dihydrodeoxy-derivative, which must be formulated as (4), thereby proving a direct connection between the phenylamino-residue and C-14.

The hydroxylamine (3) rearranged rapidly in alkaline solutions to give an isomeric enone (5), $\nu_{max.}$ 3 510 and 1 685 cm^{-1}. The phenolic character of (5) was revealed by the formation of an *O*-acetate, $\nu_{max.}$ 1 772 cm^{-1}, and by a change in u.v. spectrum induced by addition of base: $\lambda_{max.}$ (EtOH) 235 (ε 10 600), 317 (1 220), and 361 nm (872); $\lambda_{max.}$ (EtOH–EtONa) 254 (ε 12 200), 298 (4 370), and 361 nm (1 480). The rapid cyclisation of (3) must, at least in part, reflect the geometrical requirements [3] for intramolecular attack by an oxy-anion at C-5. Providing that (3) has the relative stereochemistry shown, then cyclisation may occur with a near collinear arrangement of the three relevant atoms, O–C(5)–O.

The formation of adducts (2) from thebaine and certain nitrosoarenes is reversible at ambient temperatures. Thus solutions of the colourless adduct (2; Ar = Ph) in methanol or chloroform showed a green tint due to partial dissociation. N.m.r. examination of a solution (0.5M) or (2; Ar = Ph) in deuteriochloroform revealed *ca.* 10% dissociation at 35 °C. Dissociation was diminished by electron-withdrawing substituents and enhanced by electron-donating substituents placed *para* to the nitroso-group in the nitrosoarene components. For example, the adduct (2; Ar = 4-NO_2-C_6H_4) showed (n.m.r.) no detectable dissociation at 35 °C and <10% at 100 °C, whereas 4-dimethylamino-nitrosobenzene and thebaine did not combine significantly in solution (0.5M). The following approximate dissociations (%) (0.5M solutions in $CDCl_3$ at 35 °C) were observed (n.m.r.) with various aryl groups [Ar in (2)]: 4-$NO_2C_6H_4$ (0), 4-ClC_6H_5 (0), 3-$MeOC_6H_4$ (0), C_6H_5

(10), 3-MeC_6H_4 (15), 4-MeC_6H_4 (35), 4-$MeOC_6H_4$ (45), and 4-$Me_2NC_6H_4$ (100).

The crystalline adducts (2; Ar = 4-ClC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, and 4-$NO_2C_6H_4$) were isolated and characterised. Hydrolysis of (2; Ar = 4-ClC_6H_4) and (2; Ar = 4-MeC_6H_4) gave the corresponding codeinone derivatives (3).

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were recorded at 60 MHz.

Reaction of Thebaine with Nitrosobenzene.—Thebaine (1) (7.44 g) in chloroform (20 ml) was added to nitrosobenzene (2.56 g) in chloroform (20 ml). The mixture was kept at room temperature until no further colour change occurred (*ca.* 0.5 h). The solvent was evaporated and the residue crystallised from methanol to give 6,14-*dihydro*-6β,14β-(N-*phenylepoxyimino*)*thebaine* (2; Ar = Ph) (8.8 g, 90%) as colourless needles, m.p. 115—118 °C (decomp.) (Found: C, 71.8; H, 6.4; N, 6.7. $C_{25}H_{26}N_2O_4$ requires C, 71.75; H, 6.3; N, 6.7%); τ($CDCl_3$ 2.87 (br s, Ph), 3.32 and 3.45 (AB q, *J* 8.5 Hz, 2-H and 1-H), 3.75 (dd, *J* 9 and 1 Hz, 7-H), 4.64 (d, *J* 9 Hz, 8-H), 5.25 (d, *J* 1 Hz, 5-H), 6.18 (s 3-OMe), 6.24 (s, 6-OMe), and 7.51 (s, NMe).

Preparation of Other Cyclo-adducts (2) *of Thebaine.*—The foregoing procedure was used to prepare the following cyclo-adducts (2) of thebaine and nitrosoarenes: (2; Ar = 4-ClC_6H_4) (76%), m.p. 125—130 °C (decomp.) (from CH_2Cl_2; crystallisation was difficult) (Found: C, 65.7; H, 5.5; N, 5.75. $C_{25}H_{25}ClN_2O_4$ requires C, 66.3; H, 5.5; N, 6.2%); τ($CDCl_3$) 2.8 (br s, NAr), 3.30 and 3.40 (AB q, *J* 8.5 Hz, 2-H and 1-H), 3.72 (dd, *J* 9 and 1 Hz, 7-H), 4.60 (d, *J* 9 Hz, 8-H), 5.25 (d, *J* 1 Hz, 5-H), 6.17 (s, 3-OMe), 6.26 (s, 6-OMe), and 7.53 (s, NMe); (2; Ar = 4-MeC_6H_4) (65%) (crystallised slowly from MeOH; decomposed gradually with heating) (Found: C, 71.8; H, 6.4; N, 6.0. $C_{26}H_{28}N_2O_4$ requires C, 72.2; H, 6.5; N, 6.5%), τ($CDCl_3$) 2.92 (br s, NAr), 3.35 (m, 1-H and 2-H), 3.73 (dd, *J* 9 Hz and 1.4 Hz, 7-H), 4.67 (d, *J* 9 Hz, 8-H), 5.26 (d, *J* 1.4 Hz, 5-H), 6.18 (s, 3-OMe), 6.26 (s, 6-OMe), 7.53 (s, NMe), and 7.73 (s, ArMe); (2; Ar = 3-$MeOC_6H_4$) (92%), m.p. 142—143 °C (decomp.) (from MeOH) (Found: C, 69.9; H, 6.5; N, 6.2. $C_{26}H_{28}N_2O_5$ requires C, 69.6; H, 6.3; N, 6.25%); τ($CDCl_3$) 2.70—3.60 (m, 1-H, 2-H, and NAr), 3.82 (q, *J* 8.5 and 1.5 Hz, 7-H), 4.70 (d, *J* 8.5 Hz, 8-H), 5.35 (d, 1.5 Hz, 5-H), 6.24 and 6.29 (overlapping singlets, 3-OMe, 6-OMe, and Ar-OMe), and 7.55 (s, NMe); (2; Ar = 4-$NO_2C_6H_4$) (97%), m.p. 166—167 °C (decomp.) (from MeOH) (Found: C, 64.5; H, 5.7; N, 8.8. $C_{25}H_{25}N_3O_6$ requires C, 64.8; H, 5.4; N, 9.1%); τ($CDCl_3$) 1.60 and 2.43 (q, *J* 9.5 Hz, 4-$NO_2C_6H_4$), 3.12 (m, 1-H and 2-H), 3.56 (dd, *J* 10 and 1.5 Hz, 7-H), 4.50 (d, *J* 10 Hz, 8-H), 5.17 (d, *J* 1.5 Hz, 5-H), 6.14 (s, 3-OMe), 6.20 (s, 6-OMe), and 7.52 (s, NMe).

Preparation of 14-(N-*Hydroxyphenylamino*)*codeinone* (3; Ar = Ph).—The cyclo-adduct (2; Ar = Ph) (8 g) was warmed and triturated with 2N-hydrochloric acid (20 ml) until the resulting pasty mass solidified. The solid crystallised from 96% aqueous ethanol to give needles (90%) of 14-(N-*hydroxyphenylamino*)*codeinone hydrochloride hydrate*, m.p. *ca.* 125 °C (decomp.) (Found: C, 63.2; H, 5.95; N, 6.15; Cl, 7.8. $C_{24}H_{24}N_2O_4$·HCl·H_2O requires C, 62.8; H, 5.9; N, 6.1; Cl, 7.7%); τ[$(CD_3)_2SO$] 2.62 (br s, Ph), 3.13 and 3.20 (AB q, *J* 8.5 Hz, 2-H and 1-H), 3.61 and 3.76 (AB q, *J* 10 Hz, 8-H and 7-H), 5.02 (s, 5-H), 6.25 (s, OMe), and 6.92 (br s, NMe); $\nu_{max.}$ (Nujol) 3 490, 1 683, and 1 620 cm^{-1}.

Hydrolysis of the Cyclo-adducts (2; Ar = 4-ClC_6H_4) *and* (2; Ar = 4-MeC_6H_4).—The foregoing procedure was used to prepare the following codeinone derivatives (3) from the corresponding cyclo-adducts (2). 14-(N-*Hydroxy*-4-*chlorophenylamino*)*codeinone hydrochloride hydrate* (88%) (from EtOH), decomposed slowly above 150 °C (Found: C, 58.8; H, 5.4; N, 5.4; Cl, 14.5. $C_{24}H_{23}ClN_2O_4$·HCl·H_2O requires C, 58.4; H, 5.3; N, 5.7; Cl, 14.4%); $\nu_{max.}$ (Nujol) 3 400, 1 678, and 1 515 cm^{-1}. The corresponding *free base* (3; Ar = 4-ClC_6H_4) had m.p. 108—108.5 °C (from EtOH) (Found: C, 64.0; H, 6.05; N, 5.9. $C_{24}H_{23}ClN_2O_4$·EtOH requires C, 64.4; H, 6.0; N, 5.8%); $\nu_{max.}$ ($CHCl_3$) 3 340 and 1 685 cm^{-1}; τ($CDCl_3$) 2.79 (br s, NAr), 3.40 (m, 1-H and 2-H), 3.70 (d, *J* 10 Hz, 8-H), 4.08 (d, *J* 10 Hz, 7-H), 5.10 (s, 5-H), 6.21 (s, OMe), 7.64 (s, NMe), and signals for EtOH (*ca.* 1 mol). 14-(N-*Hydroxy*-4-*methylphenylamino*)*codeinone hydrochloride hydrate* (82%) (from EtOH), decomposed above 150 °C (Found: C, 63.85; H, 6.1; N, 6.5; Cl, 7.4. $C_{25}H_{26}N_2O_4$·HCl·H_2O requires C, 63.5; H, 6.2; N, 5.9; Cl, 7.5%); $\nu_{max.}$ (Nujol) 3 260 and 1 682 cm^{-1}; τ[$(CD_3)_2SO$] 2.82 (br s, NAr), 3.15 (s, 1-H and 2-H), 3.60 (d, *J* 10 Hz, 8-H), 3.74 (d, *J* 10 Hz, 7-H), 5.05 (s, 5-H), 6.26 (s, OMe), 6.95 (s, NMe), and 7.72 (s, ArMe).

14-(N-*Acetoxyphenylamino*)*codeinone.*— 14-(*N*-Hydroxyphenylamino)codeinone (1 g) was acetylated with acetic anhydride (0.25 ml) in pyridine (25 ml) at room temperature overnight and the product was isolated in the usual way. 14-(N-*Acetoxyphenylamino*)*codeinone* had m.p. 167—168 °C (from C_6H_6) (Found: C, 69.7; H, 5.6; N, 6.1. $C_{26}H_{26}N_2O_5$ requires C, 69.9; H, 5.8; N, 6.3%); $\nu_{max.}$ ($CHCl_3$) 1 774 and 1 690 cm^{-1}; τ($CDCl_3$) 2.70 (m, NPh), 3.40 (m, 1-H and 2-H), 3.66 (d, *J* 10 Hz, 8-H), 3.78 (d, *J* 10 Hz, 7-H), 5.39 (s, 5-H), 6.20 (s, OMe), 7.65 (s, NMe), and 8.03 (s, COMe).

7,8-*Dihydro*-14-*phenylaminocodeinone.*— 14-(*N*-Hydroxyphenylamino)codeinone hydrochloride hydrate (290 mg) was hydrogenated in methanol (6 ml) using 10% Pd–C catalyst (40 mg) for 4 h at room temperature and pressure. The product was converted (aqueous $NaHCO_3$) into the free base which was crystallised from ethanol. 7,8-*Dihydro*-14-*phenylaminocodeinone* had m.p. 188—189 °C (Found: C, 72.9; H, 6.7; N, 6.7. $C_{24}H_{26}N_2O_3$·0.5EtOH requires C, 72.7; H, 7.0; N, 6.8%) (Found: *m/e* 390.194 5. $C_{24}H_{26}N_2O_3$ requires *M*, 390.194 3); $\nu_{max.}$ ($CHCl_3$) 3 360 and 1 721 cm^{-1}; τ($CDCl_3$) 2.85 (m, NPh), 3.34 (s, 1-H and 2-H), 5.32 (s, 5-H), 6.13 (s, OMe), and 7.68 (s, NMe).

Base-catalysed Rearrangement of (3; Ar = Ph).—The codeinone (3; Ar = Ph) hydrochloride hydrate (500 mg), dissolved in the minimum quantity of methanol, was treated with sodium methoxide [from sodium (50 mg)] in methanol (10 ml). Methanol (10 ml) was added to dissolve the precipitate which formed. After 10 min at room temperature the solvent was evaporated and the residue was dissolved in water. An excess of solid carbon dioxide was added and the resulting precipitate was collected and crystallised from ethanol to give 5,O-*dihydro*-5β,14β-(N-*phenylepoxyimino*)*codeinone* (5) (380 mg) as yellow needles, m.p. 207—208 °C (Found: C, 70.0; H, 6.8; N, 6.1. $C_{24}H_{24}N_2O_4$·EtOH requires C, 69.4; H, 6.7; N, 6.2%); *m/e* 404; $\nu_{max.}$ ($CHCl_3$) 3 550 and 1 687 cm^{-1}; τ($CDCl_3$) 2.82 (m, NAr), 3.33 (s, 1-H and 2-H), 3.89, (s, 7-H and 8-H), 4.12 (s, OH), 4.81 (s, 5-H), 6.20 (s, OMe), 7.45 (s, NMe), and signals for EtOH (*ca.* 1 mol); u.v. spectra are recorded in the main text. Solvation of the phenol seemed variable; in a separate preparation the product had m.p. 197 °C (from

EtOH) (Found: C, 70.5; H, 6.2; N, 6.8. $C_{24}H_{24}N_2O_5 \cdot 0.5$ EtOH requires C, 70.2; H, 6.3; N, 6.6%).

Treatment of the phenol (5) with acetic anhydride in pyridine at room temperature in the usual way gave the corresponding *O-acetyl derivative*, m.p. 221—223 °C (from EtOH) (Found: C, 70.0; H, 5.5; N, 6.4. $C_{26}H_{26}N_2O_5$ requires C, 69.9; H, 5.9; N, 6.3%); $\nu_{max.}$ ($CHCl_3$) 1 772 cm^{-1}; τ($CDCl_3$) *ca.* 3.0 (m, 1-H, 2-H, and Ph), 3.95 (s, 7-H and 8-H), 5.20 (s, 5-H), 6.31 (s, OMe), 7.50 (s, NMe), and 7.68 (s, COMe).

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