Diels–Alder Adducts from Thebaine and Nitroso-arenes

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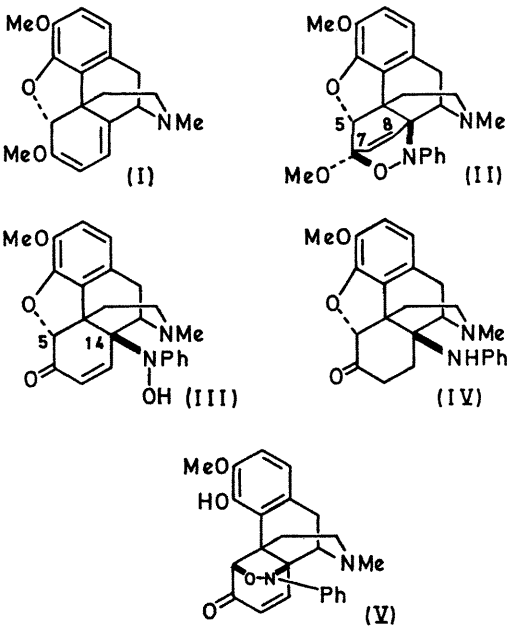
Summary Thebaine reacts reversibly with nitroso-arenes to form Diels–Alder adducts readily convertible into previously inaccessible derivatives of 14-aminocodeinone.

TREATMENT of thebaine (I) with nitrosobenzene in chloroform at room temp. gave, in high yield, the adduct (II), m.p. 115—118° (decomp.); τ 3·75 ($CDCl_3$) (q, J 1,9 Hz, 7-H), 4·64 (d, J 9 Hz, 8-H), 5·25 (d, J 1 Hz, 5-H), 6·18 and 6·24 (s, MeO), 7·51 (s, MeN). Solutions of the colourless adduct in methanol or chloroform showed a green tint due to partial dissociation; a solution in deuteriochloroform showed weak n.m.r. bands attributable to thebaine. Trituration of the adduct with 1N-hydrochloric acid gave 14-(*N*-hydroxyphenylamino)codeinone (III) as the dihydrochloride. The free base had m.p. 127—128°; ν_{max} ($CHCl_3$) 3540, 1687 cm.$^{-1}$; λ_{max} (EtOH) 240 (ϵ 9,230), 280 (2,510), 350 nm. (sh, 636); τ ($CDCl_3$) 3·71 and 4·08 (d, J 10 Hz, vinyl protons), 5·12 (s, 5-H). Tailing of the long-wavelength, u.v. absorption band of this compound accounted for its pale yellow colour. The mode of attachment of the phenylhydroxylamino-residue at C-14 was established as follows. Acetylation (Ac_2O, pyridine) of (III) gave an *O*-acetate, m.p. 157—158°; ν_{max} ($CHCl_3$) 1773, 1688 cm.$^{-1}$, and catalytic (Pd/C) hydrogenation of (III) gave 14-phenylaminodihydrocodeinone (IV), m.p. 189—190°; ν_{max} ($CHCl_3$) 1721 cm.$^{-1}$; τ ($CDCl_3$) 5·33 (s, 5-H). The ketone (III) rearranged at room temp. in ethanolic sodium ethoxide to the phenol (V), m.p. 197°; ν_{max} ($CHCl_3$) 3510, 1685 cm.$^{-1}$; λ_{max} (EtOH) 235 (ϵ 10,600), 317 (1220), 361 nm. (872); λ_{max} (EtOH/EtONa) 254 (ϵ 12,200), 298 (4370), 361 nm. (1480); τ ($CDCl_3$) 3·92 (vinyl protons, signals not separated at 60 MHz).

4-Chloro- and 4-methyl-nitrosobenzene also formed adducts with thebaine. Hydrolysis of the adduct from 4-chloronitrosobenzene gave the expected chloro-analogue of (III). The reactions recorded provide the first route to 14-aminocodeinone derivatives several of which have been found to possess analgaesic properties.



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