Total Synthesis of the Alkaloid Rhoeadine

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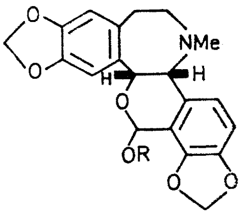
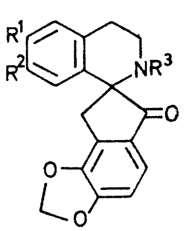
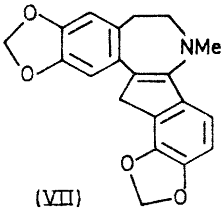
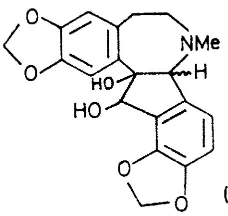
Summary Rhoeadine, an alkaloid from a variety of species of the genus Papaver, *Papaveraceae*, has been synthesised.

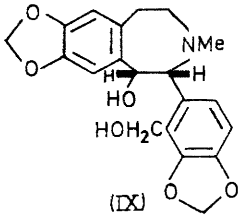
RHOEADINE (I), which occurs in a variety of plants of the genus Papaver of the *Papaveraceae*, is an alkaloid of the group characterised by its 3-benzazepine structure along with the presence of a six-membered acetal (or hemiacetal) ring in the molecule.[1,2] In connection with our synthetic studies of ochotensine and related alkaloids,[3] we have worked out a route to rhoeadine starting from the intermediate (II) for the synthesis of ochotensine and applying a Wagner–Meerwein rearrangement which resulted in enlargement of the isoquinoline ring in the intermediate (II). The spiro-isoquinoline (II) was treated with ethyl chloroformate and triethylamine to give, after alkaline hydrolysis of the (partly) formed *O*-ethoxycarbonyl group, the urethane (III). This was methylenated with methylene iodide and potassium carbonate in dimethyl sulphoxide to furnish the dimethylenedioxy-spiro-isoquinoline (IV). Treatment of this with lithium aluminium hydride gave, as the sole product, the *N*-methylamino-alcohol (V) in which the hydroxy- and the nitrogen groups were *trans*-orientated as shown by the i.r. spectrum in a dilute carbon disulphide solution (non-hydrogen-bonded hydroxy band at 3605 cm^{-1}).

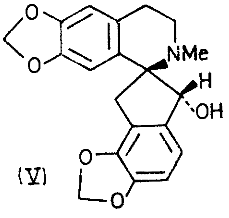

(I) R = Me
(X) R = H

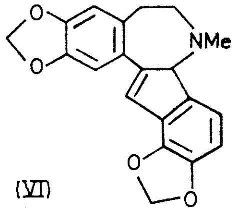

(II) $R^1 = R^2 = OH$; $R^3 = H$
(III) $R^1 = R^2 = OH$; $R^3 = CO_2Et$
(IV) $R^1, R^2 = O-CH_2-O$; $R^3 = CO_2Et$


(VII)


(VIII)


(IX)


(V)


(VI)

The *N*-methylamino-alcohol (V) was treated with methanesulphonyl chloride and triethylamine in dry tetrahydrofuran with cooling to give a mixture of unsaturated amines (VI) and (VII) in a ratio of 1 : 1. The required allylamine (VI) was isolated as the hydrochloride (easily soluble in chloroform), n.m.r. ($CDCl_3$) τ 2·49 (s, 1H), 3·37 (s, 1H), 2·16 (d, 1H, J 8 Hz), 3·26 (d, 1H, J 8 Hz), 2·81 (s, 1H, olefinic proton), 3·37 and 3·96 (s, 2H each, $O{\cdot}CH_2{\cdot}O$), and 7·26 (s, 3H, N-CH_3); λ_{max} (EtOH) 230, 249 (sh), 257 (sh), and 335 nm (ϵ 19,500, 15,300, 13,600, and 16,300). The corresponding free base is rather unstable and converted gradually into the enamine (VII) on chromatography on alumina or on standing in an alkaline solution. The enamine (VII) is a stable base with the following physical properties: n.m.r. τ 3·02 (s, 1H), 3·37 (s, 1H) 3·25 (d, 1H, J 8 Hz), 3·01 (d, 1H, J 8 Hz), 6·23 (s, 2H, benzylic protons) and 7·62 (s, 3H, N-CH_3); λ_{max} (EtOH) 275 and 348 nm (ϵ 10,000 and 24,300), λ_{max} (EtOH + HCl) 244, 318, and 346 nm (ϵ 23,000, 16,500, and 18,000).

Oxidation of the allylamine (VI) with osmium tetroxide in ether gave the diol (VIII), n.m.r. ($CDCl_3$) τ 2·55 (1H, s), 3·39 (s, 1H), 3·15 (s, 2H), 4·50 (s, 1H, $CH{\cdot}O$) 5·52 (s, 1H, $N{\cdot}CH{\cdot}$), and 7·72 (s, 3H, N-CH_3). Treatment of (VIII) with sodium metaperiodate for 5 min. with ice-cooling, followed by sodium borohydride, gave (±)-rhoeagenine diol (IX), m.p. 142—143° whose i.r. ($CHCl_3$), mass, and n.m.r. spectra were superimposable upon those of the rhoeagenine diol from natural sources.† Since rhoeagenine diol had already been re-converted into rhoeagenine (X) and rhoeadine (I),[4] we have completed the first synthesis of rhoeadine.

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† Supplied by Professor F. Šantavý.

[1] F. Şantavý, M. Maturová, A. Němečková, H. B. Schröter, H. Proestisilova, and V. Preininger, *Planta. Med.*, 1960, **8**, 167.
[2] F. Šantavý, M. Maturová, A. Němečková, and M. Horak, *Coll. Czech. Chem. Comm.*, 1960, **25**, 1901.
[3] H. Irie, T. Kishimoto, and S. Uyeo, *J. Chem. Soc.* (*C*), 1968, 3051.
[4] F. Šantavý, J. L. Kaul, L. Hruben, L. Dolejš, V. Hanuš, K. Bláha, and A. D. Cross, *Coll. Czech. Chem. Comm.*, 1965, **30**, 3479.