A Novel Ring Closure Leading to 3-Hydroxyaporphines[1]

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Summary A novel ring closure leading to the 3-hydroxyaporphine species is described and evidence for the reaction mechanism is presented.

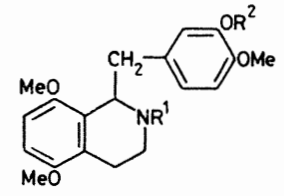
WE have found that the attempted demethylation of 1,2,3,4-tetrahydro-1-(3,4-dimethoxybenzyl)-5,8-dimethoxyisoquinolines (**1**; R^1 = H or Me, R^2 = Me) in concentrated hydrobromic acid at 140 °C gave the 3-hydroxyaporphines (**2**; R = H or Me) (91·5 and 95·8%, respectively†) rather than simple demethylation products.‡

This unexpected outcome of the above demethylation was first established for (**2**; R = Me) which was obtained as a crystalline solid, m.p. 297—299 °C (decomp.), homogeneous by t.l.c. Elemental analysis gave the empirical formula $C_{17}H_{17}NO_3$·HBr and the molecular formula was confirmed by mass spectroscopy [parent ion at *m/e* 283 (base peak); accurate mass measurement *m/e* 283·1206, $C_{17}H_{17}NO_3$ requires *m/e* 283·1208].§ Two fragments (*m/e* 152 and 165) in the mass spectrum of (**2**; R = H or Me) were identified by accurate mass measurement as the biphenyl radical ion ($C_{12}H_8$) and the fluorene radical ion ($C_{13}H_9$); these fragments have been observed in the mass spectra of all aporphines studied to date.[2] The u.v. spectrum of (**2**; R = Me), λ_{max} (0·1N HCl–EtOH) 280·9 mm (ϵ mol 16,130) and 241·0 mm (ϵ mol 8350), is consistent with those of the characterised aporphines such as nuciferine,[3] apomorphine,[4] and ovigerine.[5]

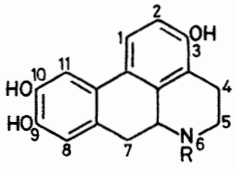
† Unless otherwise stated, all compounds described are the corresponding hydrobromides.

‡ 1,2,3,4-Tetrahydro-1-(3,4-dihydroxybenzyl)-5,8-dihydroxyisoquinoline and the 2-methylisoquinoline respectively.

§ This is in marked contrast to the mass spectrum of the 1,2,3,4-tetrahydro-1-benzyl-isoquinolines which exhibit very low molecular ion peaks (C. Djerassi, H. W. Brewer, C. Clarke, and L. J. Durham, *J. Amer. Chem. Soc.*, 1962, **84**, 3210; M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk, and C. Djerassi, *ibid.*, 1963, **85**, 2807).



(1)



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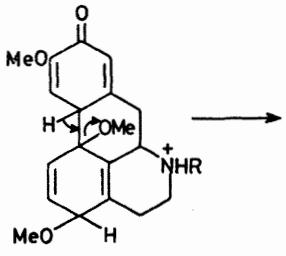

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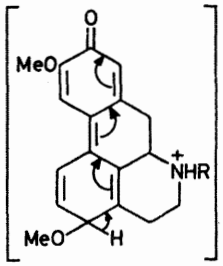

(4)

The ^{1}H n.m.r. spectrum [90 MHz, $(CD_3)_2SO$, 27 °C] of (**2**; R = Me) consisted of a broad complex multiplet (δ 2·76—3·88, 6H) containing a sharp 3-proton singlet (δ 3·10, 6-Me), a 1-proton doublet of doublets (δ 4·42, J_{cis} 4·0 and J_{trans} 13·0 Hz) which was consistent with the 6a-methine proton coupled to the non-equivalent 7-methylene protons, a pair of 1-proton doublets (δ 6·87 and 7·34, 1,2-CH, $J_{1,2}$ 8·5 Hz) which is a characteristic feature for all compounds in this series, a pair of 1-proton singlets (δ 6·77 and 7·09, 8- and 11-CH), and broad signals due to phenolic protons (δ 9·00, 9·78, and 10·22).

We have further shown that the treatment of (**1**; R^1=H, R^2 = Me) with concentrated hydrobromic acid at 60 ± 2 °C has led to selective mono-demethylation to yield the corresponding 3′-hydroxy derivative (**1**; $R^1 = R^2$ = H). Further treatment of this compound with concentrated hydrobromic acid at 140 °C afforded (**2**; R = H).¶

The formation of (**1**; $R^1 = R^2$ = H) is seen as the first step in the reaction sequence leading to (**2**; R = H). It seems likely that the protonation of the 5-methoxy group in (**1**; $R^1 = R^2$ = H) produces an electron-deficient centre at C-8 and subsequent nucleophilic attack at this position by the adjacent electron-rich phenolic residue leads to the quinol-methine (**3**). Elimination of methanol followed by a rapid acid catalysed proton shift in (**4**) and further demethylation would then afford (**2**; R = H).

The easy formation of a biphenyl system by an S_NAr mechanism in which an aromatic species is a nucleophile is further supported by the work of Buncel, *et al.*[6] Investigations are currently in progress to explore this novel reaction.

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¶ Fully characterised by elemental analysis, and u.v., mass, and ^{1}H n.m.r. spectroscopy. The 1,2,3,4-tetrahydro-1-(3,4-dihydroxybenzyl)-5,8-dihydroxyisoquinoline, prepared by an alternative route, does not cyclise under these conditions.

[1] Abstracted from the Ph.D. thesis of K. W. Franzmann, University of London, 1979.
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[6] E. Buncel, A. Jończyk, and J. G. K. Webb, *Canad. J. Chem.*, 1975, **53**, 3701.