Synthesis of 1-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]-3a,4-dihydro-1*H*-indole-2(3*H*), 6(5*H*)-dione: a Potential Intermediate for the Preparation of Erythrinan Alkaloids

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Summary A new synthetic route to erythrinan alkaloids was developed *via* the title compound (III) as the key intermediate from the enol methyl derivative (II) which was obtained by the Birch reduction of the benzyl amide (I).

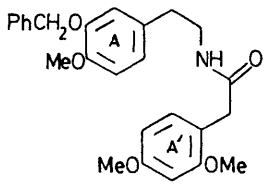
ALTHOUGH many syntheses of 3-oxoerythrinan have been reported[1a–f] the methods are either tedious or give low yields, except that reported by Stevens *et al.*[1e] The title compound (III) is the key intermediate in the synthesis of erythrinan alkaloids. We report here a convenient method for the preparation of (III) from the enol methyl derivative (II), which was obtained by Birch reduction of the benzyl amide (I) without cleavage of the amide bond.[2]

The benzyl amide (I), m.p. 152—153 °C, was prepared quantitatively by heating 2-(3-benzyloxy-4-methoxyphenyl) ethylamine and 2,4-dimethoxyphenylacetic acid in xylene under reflux for 3 h. Birch reduction of (I) with sodium and methanol in liquid ammonia caused cleavage of the benzyl group from the ring A and simultaneous reduction of the ring A′ to give the enol methyl derivative (II) [oil; *m/e* 347 (M^+); ν_{max} ($CHCl_3$) 3550 (OH), 3390 (NH), 1710 (enol-Me), and 1660 (N-C=O) cm^{-1}; δ ($CDCl_3$) 4·60 (1H, m, vinyl-H), and 3·84, 3·56, and 3·48 (9H, s, 3 × OMe)].

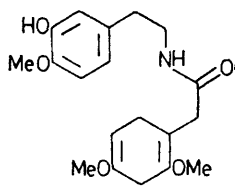
Hydrolysis of (II) with 10% H_2SO_4 in dimethylformamide afforded the β-enamidoketone (III) (85%) m.p. 181—183 °C; ν_{max} ($CHCl_3$) 1740 (N-C=O) and 1620 (conj. C=O) cm^{-1}; λ_{max} (EtOH) 230sh and 278 nm; δ($CDCl_3$) 5·50 (1H, d, *J* 2 Hz, vinyl-H), and 3·88 (3H, s, OMe); *m/e* 301 (M^+), 150]. On heating (III) under reflux in 98% HCO_2H for 16 h, the desired tetracyclic compound (IV) with a C/D-*cis*-ring junction was obtained (65%)† m.p. 223—225 °C; *m/e* 301 (M^+), 258, and 244; ν_{max} ($CHCl_3$) 3590 (OH), 1720 (C=O), and 1690 (N-C=O) cm^{-1}; δ ($CDCl_3$) 6·60 (1H, s, 17-H), 6·53 (1H, s, 14-H), and 3·88 (3H, s, OMe)], along with its positional isomer (V) (6%)[3] [oil; *m/e* 301 (M^+), 258 and 244; δ ($CDCl_3$) 6·76 (1H, d, *J* 9 Hz), 6·62 (1H, d, *J* 9 Hz), 3·90, and (3H, s, OMe)].

In order to confirm its structure, (IV) was *O*-methylated with diazomethane to yield the dioxoerythrinan (VI) (97%) which was identified by comparison of its i.r. spectrum with that of an authentic sample. Reduction of (IV) with $LiAlH_4$ in tetrahydrofuran gave the tetrahydroerysonine (VII) (65%) and its epimer at the 3-hydroxy group (VIII) (35%).

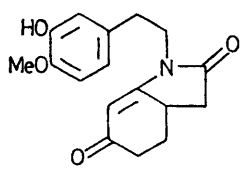
On methylation with diazomethane, (VII) was converted into the erythrinan-3α-ol (IX), the i.r. and ^1H n.m.r. spectra of which were identical with those of an authentic sample.[1f]



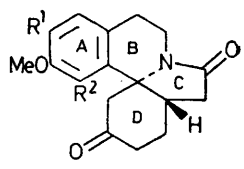
(I)



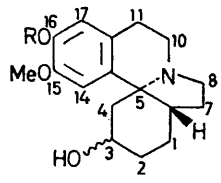
(II)



(III)



(IV) R^1 = OH, R^2 = H
(V) R^1 = H, R^2 = OH
(VI) R^1 = OMe, R^2 = H



(VII) R = H, (3α-OH)
(VIII) R = H, (3β-OH)
(IX) R = Me, (3α-OH)

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† Corrected yield.

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[2] A. J. Birch, J. Cymerman-Craig, and M. Slaytor, *Austral. J. Chem.*, 1955, **8**, 512.