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NEW SYNTHESES OF SPIROBENZYLISOQUINOLINE ALKALOIDS

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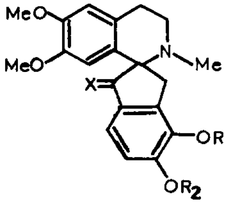
The spirobenzylisoquinoline alkaloids[1] comprise a group of about a dozen bases isolated from the Fumariaceae and characterized by the presence of an indane moiety spiro fused at the 1-position of the tetrahydroisoquinoline. Syntheses of these alkaloids by application of the Pictet-Spengler[2] and Pomeranz-Fritsch[3] reactions, and by means of biogenetically patterned conversions[4,5] from protoberberines have been reported.

We now report the development of a new synthetic route to provide alkaloids of both the ochotensimine (<u>1</u>) and ochrobirine (<u>2</u>) types. The indanone <u>4</u> was synthesised in a similar manner[6] to <u>3</u> and in comparable yields. [<u>4</u>, m.p. 189°; $\nu_{max}^{CHCl_3}$ 1635, 1705 cm^{-1}; λ_{max}^{MeOH} 239, 289 and 308 nm, log ε_{max} 5.48, 5.31 and 5.19 resp.; $\delta(CDCl_3)$[7] 2.07 (3H, s, N-Ac), 2.93 (3H, s, N-Me), 3.50 (br. d, CH_2), 4.17 (q, 1H, C<u>H</u>-CO), 3.77 and 3.90 (s, 2 x OMe), 6.13 (br. s, 2H, OCH_2O), 6.38 and 6.73 s, 2 x 1H, aromatic H), 6.90 and 7.45 (q, 2H, aromatic H, J_{AB} = 8.0 Hz.)] Both <u>3</u> and <u>4</u> upon hydrolysis with 2N hydrochloric acid followed by successive bromination with bromine-glacial acetic acid-sodium acetate and cyclisation with excess triethylamine provided the ketones <u>5</u> and <u>6</u> respectively in 28% of overall yield for the three steps. The latter was identical with a synthetic sample[8] which had previously been converted to ochotensimine[2a]. Thus a new total synthesis of ochotensimine has been achieved.

Base hydrolysis of <u>3</u> and <u>4</u> followed by oxidation as before[6] provided the enaminoketones <u>7</u> and <u>8</u> respectively which were hydrolysed with 4N hydrochloric acid, brominated with bromine-glacial acetic acid[3] and cyclised with triethylamine to the spirodiones <u>9</u> and <u>10</u>, this time in 76 and 67% overall yield respectively for the three steps. [<u>10</u>, m.p. 226°; $\nu_{max}^{CHCl_3}$ 1710, 1740 cm^{-1}; λ_{max}^{EtOH} 246, 297, 307 and 348 nm, log ε_{max} 4.38, 3.95, 3.93 and 3.81 resp.; $\delta(CDCl_3)$ 2.42 (s, 3H, N-Me), 2.87-3.47 (Sym. m. 4H, CH_2-CH_2), 3.55 and 3.90 (s, 2 x 3H, 2 x OMe), 6.00 and 6.70 (s, 2 x 1H, C_1-H and C_4-H), 6.34 (s, 2H, OCH_2O), 7.31 and 7.68 (q, 2H, J_{AB} = 8.0 Hz C_{11}-H and C_{12}-H). The spectral properties of both 9 and 10 were very similar to the closely related spirodione 11 previously synthesized in our laboratory[2d]]

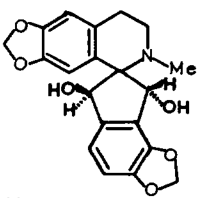
Thus a very convenient route to the ochrobirine type of alkaloid now becomes available. The present method, in contrast to the earlier laborious procedures[2d,f], allows the facile introduction of a second oxygen atom into ring C by a process that is essentially a conversion of a 1-indanone to a 1,3-indanedione. Investigations to determine the generality of this transformation are now underway.



1 ($R_1 + R_2 = X = CH_2$)

5 ($R_1 = R_2 = Me$, $X = O$)

6 ($R_1 + R_2 = CH_2$, $X = O$)



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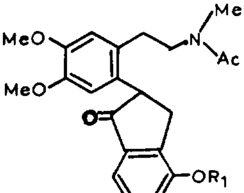
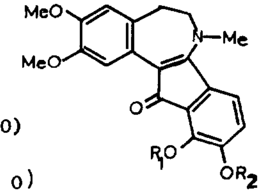


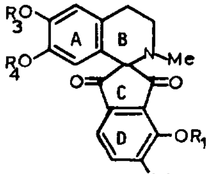
3 ($R_1 = R_2 = Me$)

4 ($R_1 + R_2 = CH_2$)



7 ($R_1 = R_2 = Me$)

8 ($R_1 + R_2 = CH_2$)



9 ($R_1 = R_2 = R_3 = R_4 = Me$)

10 ($R_1 + R_2 = CH_2$, $R_3 = R_4 = Me$)

11 ($R_1 + R_2 = R_3 + R_4 = CH_2$)

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7. Several signals are split, presumably as a result of the existence of amide tautomerism.
8. We thank Prof. S. McLean for a sample of synthetic 6. Acceptable elemental analyses were obtained for compounds 4, 8 and 10.