Total Synthesis of the Alkaloids Corynoline and 12-Hydroxycorynoline

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Summary Photocyclisation of the enamide (III) followed by stereospecific functionalisation of the *cis*-lactam (VI) completed the first total synthesis of the alkaloids corynoline (I) and 12-hydroxycorynoline (II).

Corynoline, isolated from *Corydalis* plants and shown by Takao[1] to possess structure (I), is a representative of the hexahydro-10b-methylbenzo[*c*]phenanthridine alkaloids.[2] However, syntheses of corynoline (I) and related alkaloids including (II)[3] are limited to the syntheses of an analogue of corynoline by Onda *et al.*[4]

In connection with our synthetic studies[5] on benzo[*c*]-phenanthridine alkaloids, we now report the first total synthesis of corynoline (I) and 12-hydroxycorynoline (II), by enamide photocyclisation.[6]

The enamide (III), m.p. 186—187·5 °C, ν_{max} 1635 cm^{-1}, was readily prepared (66% yield) from 1-methylimino-2-methyl-6,7-methylenedioxytetralin with 6-methoxy-2,3-methylenedioxybenzoyl chloride.[7] Photocyclisation of a methanolic solution (0·003 M) of (III) proceeded smoothly upon irradiation with a high-pressure mercury lamp to afford the lactam (IV) (20%), m.p. 128—130 °C, ν_{max} 1645 cm^{-1}, and the phenolic lactam (V) (10%), ν_{max} 3350 and 1640 cm^{-1} as a result of cyclisation at the *ortho*-methoxy and methylenedioxy group, respectively, as described previously.[7]

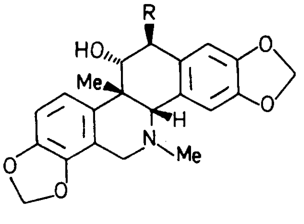
Hydrogenolysis (H_2, 40% Pd–C) of the lactam (IV) afforded the *cis*-lactam (VI) (21%), m.p. 277—279 °C, and the *trans*-lactam (VII) (60%), m.p. 195—197 °C, their stereochemistry being deduced from comparison (n.m.r. spectra) with previously reported compounds.[5b]

The *cis*-lactam (VI) was dehydrogenated with dichlorodicyanobenzoquinone in $CHCl_3$ to give the 11,12-dehydrolactam (VIII) (28%), m.p. 281—282 °C, δ ($CDCl_3$) 6·40 and 6·08 (2H, ABq, *J* 10 Hz), which was converted into deoxycorynoline (IX) (56%) by reduction with $LiAlH_4$.

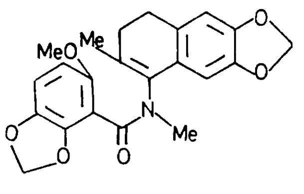
Treatment of deoxycorynoline (IX) with peroxyformic acid,[3] followed by alkali, furnished stereospecifically 12-hydroxycorynoline (II) (91%), m.p. 238—240 °C, which was identical with the natural alkaloid upon comparisons of their i.r. spectra and R_F values.

Hydrogenolysis (H_2, 40% Pd–C) of the glycol (II) in 10% HCl with a small amount of 70% $HClO_4$ proceeded slowly (48 h at 5 atm) to afford corynoline (I) (35%) which was identical with the natural alkaloid upon comparisons of their i.r. and mass spectra and R_F values.

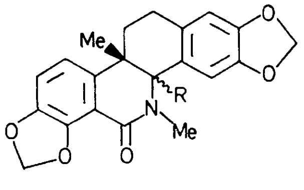
Since corynoline has been converted into 6-oxocorynoline[3] and corynoloxine,[8] this synthesis formally completes the total synthesis of all these alkaloids.



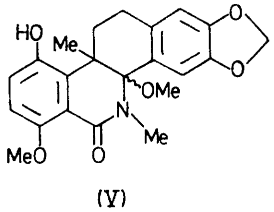
(I); R = H
(II); R = OH



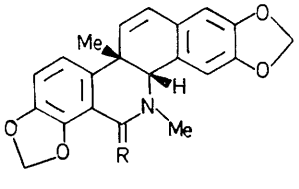
(III)



(IV); R = OMe
(VI), R = ◄H
(VII), R = ⋯H



(V)



(VIII); R = O
(IX); R = H_2

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[1] N. Takao, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 1306 and 1312.

[2] M. Shamma, 'The Isoquinoline Alkaloids,' Academic Press, New York, 1972, p. 315.

[3] G. Nonaka and I. Nishioka, *Chem. and Pharm. Bull.* (*Japan*), 1975, **23**, 521.

[4] M. Onda, K. Yuasa, and J. Okada, *Chem. and Pharm. Bull.* (*Japan*), 1974, **22**, 2365.

[5] (a) I. Ninomiya, T. Naito, H. Ishii, T. Ishida, M. Ueda, and K. Harada, *J.C.S. Perkin I*, 1975, 762; (b) I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles*, 1976, **4**, 743.

[6] I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, *J.C.S. Perkin I*, 1973, 1696.

[7] I. Ninomiya, T. Naito, and H. Takasugi, *J.C.S. Perkin I*, 1975, 1791.

[8] N. Takao, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 247.