A TOTAL SYNTHESIS OF NAUCLÉFINE

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A total synthesis of naucléfine (1) was accomplished by condensation of tryptamine with the lactone (16), prepared from nicotinonitrile (5), followed by cyclisation of the 7-azaisocarbostyril (8).

In 1975, Hotellier and coworkers[1] isolated naucléfine(1) and nauclétine (2) together with the known alkaloids, angustoline[2] (3) and angustine[2] (4) from Naucléa latifolia, and reported a synthesis of naucléfine (1).

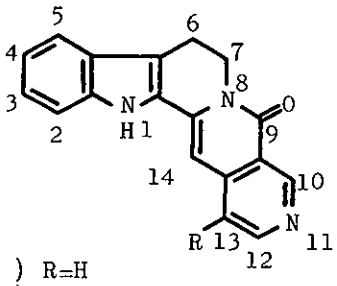
In a previous paper,[3] we reported the synthesis of angustine by a biomimetic pathway using a gentianine-like compound as intermediate. Here we wish to report a total synthesis of naucléfine in a similar way.

4-Methylnicotinonitrile[4] (5) was condensed with ethyl oxalate in the presence of potassium tert-butoxide in benzene[5] and treated in situ with diluted hydrochloric acid to give lactone (6) in 10 % yield, m.p. 138 - 139°; ν max ($CHCl_3$) 1740, 1720, 1630 and 1575 cm^{-1}; δ ($CDCl_3$) 1.43 (3H, t, J 7 Hz, $CH_2\underline{CH}_3$), 4.38 (2H, q, J 7 Hz, $\underline{CH}_2CH_3$), 7.33 (1H, s, C_4-H), 7.36 (1H, d, J 6.5 Hz, C_5-H), 8.91 (1H, d, J 6.5 Hz, C_6-H)

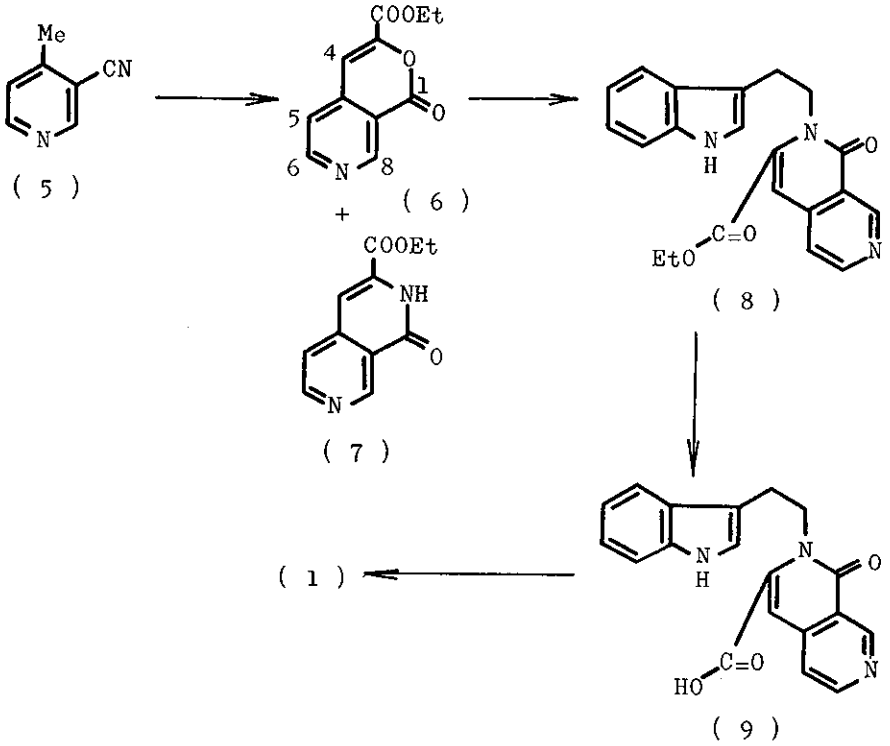
and 9.46 (1H, s, C_8-H), and the naphthyridine (7) in 10 % yield, m.p. 232 - 234° [lit.,[6] m.p. 229 - 230°]; ν max ($CHCl_3$) 3350 (NH), 1718, 1664 and 1592 cm^{-1}; δ ($CDCl_3$) 1.51 (3H, t, J 7 Hz, $CH_2\underline{CH}_3$), 4.46 (2H, q, J 7 Hz, $\underline{CH}_2CH_3$), 7.02 (1H, s, C_4-H), 7.43 (1H, d, J 6.5 Hz, C_5-H), 8.80 (1H, d, J 6.5 Hz, C_6-H), and 9.56 (1H, s, C_8-H).

Refluxing an equimolecular amount of the above lactone (6) with tryptamine in glacial acetic acid for 3 hr gave, in 82 % yield, the azaisocarbostyril (8), m.p. 158 - 159°; ν max ($CHCl_3$) 3460, 1720, 1650 and 1610 cm^{-1}. The nmr spectrum (δ in $CDCl_3$) showed the ethyl group at δ1.35 (3H, t, J 7 Hz) and 4.00 (2H, q, J 7 Hz), two neighbouring methylene group at δ 3.23 and 4.70 (each 2H, each t, J 7.5 Hz), α proton of indole ring proton at δ 6.88 (1H, d, J 1.5 Hz) and the C_6 and C_8 protons of the azaisocarbostyril ring at δ 8.68 (1H, d, J 5.6 Hz) and 9.68 ppm (1H, s), respectively.

After hydrolysis of 8 with ethanolic potassium hydroxide at room temperature, the crude acid (9) obtained was heated with a mixture of concentrated hydrochloric acid and glacial acetic acid (1 : 1 v/v) until carbon dioxide ceased to be evolved to afford naucléfine (1), m.p. 285 - 290° [lit.,[1] m.p. 285 - 290°], in 10 % overall yield from 8. During the reaction a spontaneous dehydrogenation occurred. The uv [λ max (EtOH) 390, 372, 300, 290, 250, and 220 nm], ir [ν max (KBr) 3500 (NH), 1650 (C=O), 1610 and 1538 cm^{-1}] and nmr [δ (DMSO-d_6) 4.92 (2H, t, J 7 Hz, C_7-H), 6.96 - 7.70 (6H, m, indole aromatic proton and C_{13} and C_{14}-H), 8.56 (1H, d, J 6.5 Hz, C_{12}-H), 9.25 (1H, s, C_{10}-H)] spectra were superimposable with those of the natural product kindly given by Prof. F. Hotellier.



(1) R=H
(2) R=$COCH_3$
(3) R=$CH(OH)CH_3$
(4) R=$CH=CH_2$



(5) (6) + (7) (8) (9) (1)

Naucléfine (1) was also synthesised in 15 % yield by direct treatment of 8 with a mixture of concentrated hydrochloric acid and glacial acetic acid (1 : 1 v/v).

Thus, a total synthesis of naucléfine (1) has been accomplished.

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REFERENCES

1 F. Hotellier, P. Delaveau, and J. L. Pousset, Phytochemistry, 1975, 14, 1407.

2 T. Y. Au, H. T. Cheung, and S. Sternhell, J. C. S. Perkin I, 1973, 13; J. D. Phillipson, S. R. Hemingway, N. G. Bisset, P. J. Houghton, and E. J. Shellard, Phytochemistry, 1974, 13, 973.

3 T. Kametani, M. Takeshita, M. Ihara, and K. Fukumoto, Heterocycles, 1975, 3, 627.

4 I. M. Bobbitt and D. A. Scola, J. Org. Chem., 1960, 25, 560.

5 E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, J. Amer. Chem. Soc., 1967, 89, 6741.

6 D. J. Sheffield and K. R. H. Wooldridge, J. C. S. Perkin I, 1972, 2506.

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