

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-azaisocarbostyrl (8).

In 1975, Hotellier and coworkers¹ isolated naucléfine (1) and nauclétine (2) together with the known alkaloids, angustoline² (3) and angustine² (4) from Naucléa latifolia, and reported a synthesis of naucléfine (1).

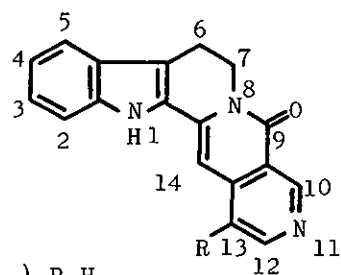
In a previous paper,³ we reported the synthesis of angustine by a biomimetic pathway using a gentianine-like compound as intermediate. Here we wish to report a total synthesis of naucléfine in a similar way.

4-Methylnicotinonitrile⁴ (5) was condensed with ethyl oxalate in the presence of potassium tert-butoxide in benzene⁵ and treated in situ with diluted hydrochloric acid to give lactone (6) in 10 % yield, m.p. 138 - 139°; $\nu_{\max}$ (CHCl₃) 1740, 1720, 1630 and 1575 cm⁻¹; δ (CDCl₃) 1.43 (3H, t, $\underline{J}$ 7 Hz, CH₂CH₃), 4.38 (2H, q, $\underline{J}$ 7 Hz, CH₂CH₃), 7.33 (1H, s, C₄-H), 7.36 (1H, d, $\underline{J}$ 6.5 Hz, C₅-H), 8.91 (1H, d, $\underline{J}$ 6.5 Hz, C₆-H)

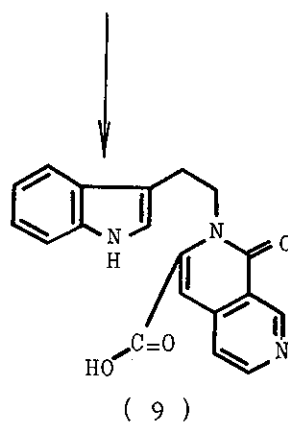
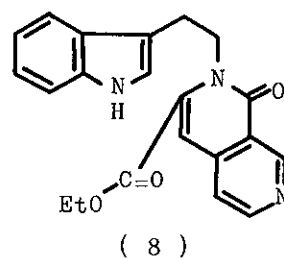
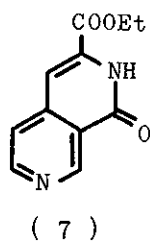
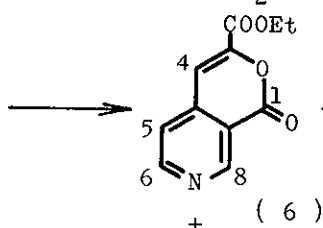
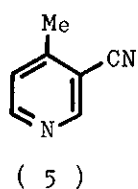
and 9.46 (1H, s, C₈-H), and the naphthyridine (7) in 10 % yield, m.p. 232 - 234° [lit.,⁶ m.p. 229 - 230°]; $\nu_{\max}$ (CHCl₃) 3350 (NH), 1718, 1664 and 1592 cm⁻¹; δ (CDCl₃) 1.51 (3H, t, $\underline{J}$ 7 Hz, CH₂CH₃), 4.46 (2H, q, $\underline{J}$ 7 Hz, CH₂CH₃), 7.02 (1H, s, C₄-H), 7.43 (1H, d, $\underline{J}$ 6.5 Hz, C₅-H), 8.80 (1H, d, $\underline{J}$ 6.5 Hz, C₆-H), and 9.56 (1H, s, C₈-H).

Refluxing an equimolecular amount of the above lactone (6) with tryptamine in glacial acetic acid for 3 hr gave, in 82 % yield, the azaisocarbostyryl (8), m.p. 158 - 159°; $\nu_{\max}$ (CHCl₃) 3460, 1720, 1650 and 1610 cm⁻¹. The nmr spectrum (δ in CDCl₃) showed the ethyl group at δ 1.35 (3H, t, $\underline{J}$ 7 Hz) and 4.00 (2H, q, $\underline{J}$ 7 Hz), two neighbouring methylene group at δ 3.23 and 4.70 (each 2H, each t, $\underline{J}$ 7.5 Hz), α proton of indole ring proton at δ 6.88 (1H, d, $\underline{J}$ 1.5 Hz) and the C₆ and C₈ protons of the azaisocarbostyryl ring at δ 8.68 (1H, d, $\underline{J}$ 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 [$\lambda_{\max}$ (EtOH) 390, 372, 300, 290, 250, and 220 nm], ir [$\nu_{\max}$ (KBr) 3500 (NH), 1650 (C=O), 1610 and 1538 cm⁻¹] and nmr [δ (DMSO-d₆) 4.92 (2H, t, $\underline{J}$ 7 Hz, C₇-H), 6.96 - 7.70 (6H, m, indole aromatic proton and C₁₃ and C₁₄-H), 8.56 (1H, d, $\underline{J}$ 6.5 Hz, C₁₂-H), 9.25 (1H, s, C₁₀-H)] spectra were superimposable with those of the natural product kindly given by Prof. F. Hotellier.



- (1) R=H
 (2) R=COCH₃
 (3) R=CH(OH)CH₃
 (4) R=CH=CH₂



(1)

Nauclefine (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 nauclefine (1) has been accomplished.

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