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STRUCTURE AND TOTAL SYNTHESIS OF DEPLANCHEINE, A NOVEL INDOLOQUINOLIZIDINE ALKALOID [1]

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Summary : The structure of deplancheine 5, an indoloquinolizidine alkaloid of a novel type, has been established from its spectral properties and also by an original synthesis.

From the ether extract of the New Caledonian plant (stem + bark) Alstonia deplanchei van Heurck and Mueller Arg. (Apocynaceae) [2], we have isolated a new indole alkaloid named deplancheine.

We present here spectral evidence indicating the structure 5 for deplancheine and an original synthesis confirming this formulation.

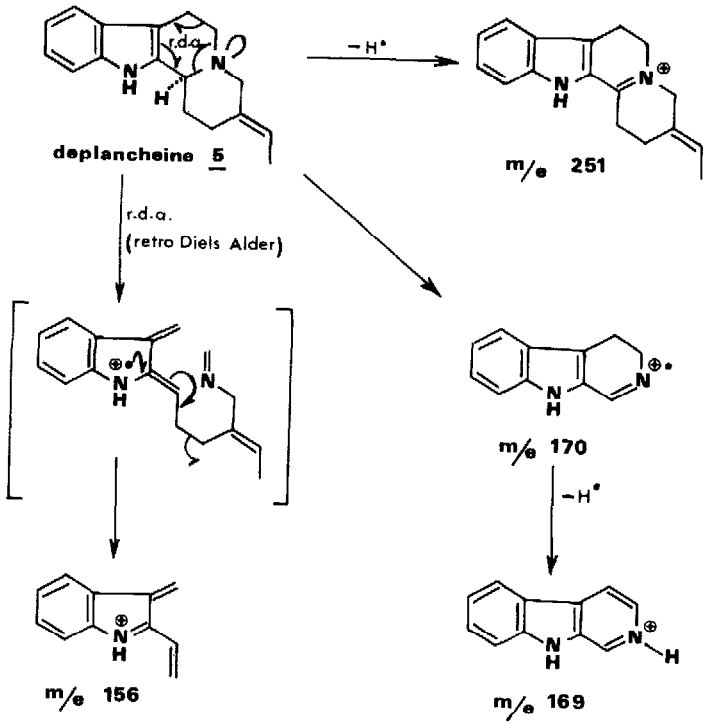
Deplancheine 5, $C_{17}H_{20}N_2$ (high resolution MS), m.p. 115° (crystallized from ether), $[\alpha]_D^{20}$ + 56° ± 2 ($CHCl_3$; c = 1) showed UV λ_{max}^{EtOH} nm (log ε) at 223 (4.60), 278 (3.53), 283 (3.54) and 291 (3.48) characteristic of a 2,3-disubstituted indole chromophore. The presence of the NH group was indicated by the IR absorption band at 3230 cm^{-1}. The ^1H NMR spectrum ($CDCl_3$, δ ppm) revealed the occurrence of an ethylidene chain [1.52 (3H, d, J = 6 Hz), 5.30 (1H, q, J = 6 Hz)], an indole NH (8.06) and four aromatic protons (between 6.8 and 7.5). Besides the intense $M^{+\cdot}$ and $(M-1)^+$ peaks at m/e 252 and 251, the mass spectrum exhibited (Scheme 1) the fragment ion peaks at m/e 156, 169 and 170 indicating a corynantheine-type skeleton [3].

Structure 5 lacking the usual 3-carbon substituent at $C_{(15)}$ position of the corynantheine group of indole alkaloids could therefore be proposed for deplancheine on the basis of the above spectral data.

The 3α configuration of structure 5 is supported by the presence of the characteristic Bohlmann bands [4] in the IR spectrum and also by the ^1H NMR chemical shift for the $C_{(3)}$ proton (m at δ < 3.7 ppm) [5].

The configuration of the ethylidene chain cannot be determined simply by an examination of the ^1H NMR of a single isomer although the E configuration may be assumed by analogy with the majority of indole alkaloids

having a similar unsaturation. A regio- and stereospecific total synthesis confirms the structure 5 of deplancheine [6].

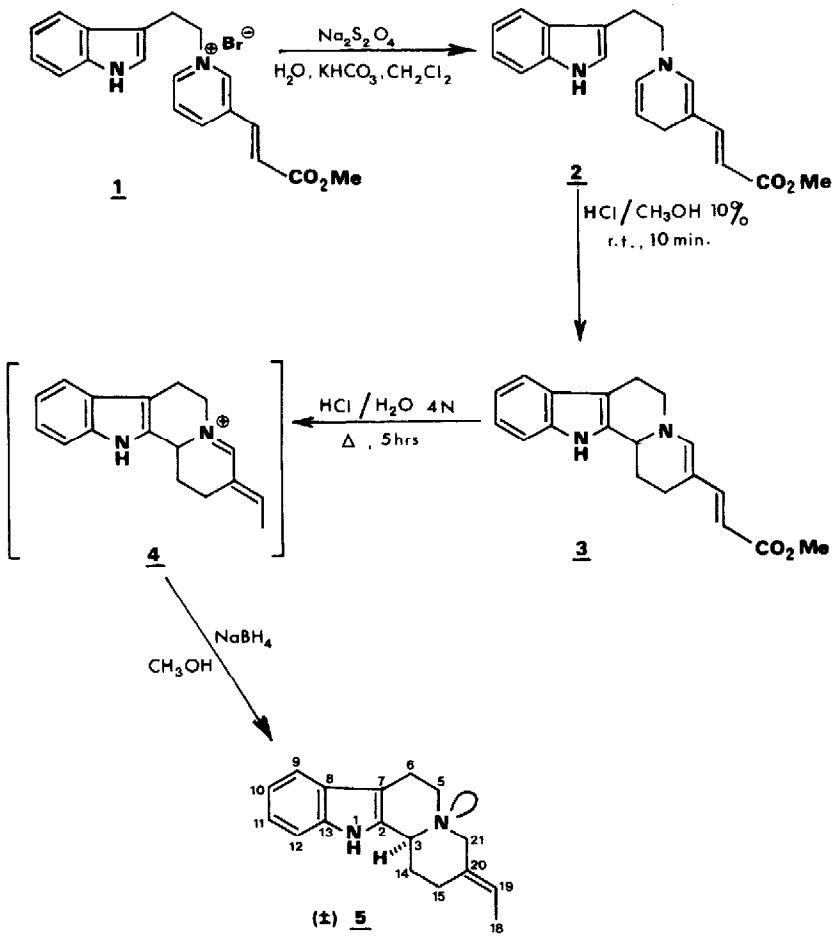


SCHEME 1

The synthesis of indoloquinolizidine alkaloids can be envisaged via an intramolecular cyclisation of a suitably substituted piperideinium ion onto the $C_{(2)}$ position of the indole nucleus. The piperidine ring of deplancheine 5 is particular in that it possesses a trisubstituted exocyclic double bond. Such a double bond of E configuration can be obtained by $NaBH_4$ reduction of the corresponding conjugated iminium ion [7].

Also, we have shown that this system could be synthesized by decarboxylation of 3-[3'-(2'-piperideine)] acrylic acid [8].

A 1,4-dihydropyridine of type 2 (Scheme 2) thus represents the key intermediate for the synthesis in mind since it is known that this type of enamine cyclises in a regioselective manner onto the simple iminium rather than the vinylogous amide system [9]. The sodium dithionite reduction [9,10] of the pyridinium salt 1 [11] in the presence of $KHCO_3$ in a two phase system (CH_2Cl_2, H_2O), yielded the desired enamine 2 (yield : 70%) [12,13].



SCHEME 2

The very unstable intermediate 2 was directly cyclised to the indoloquinolizidine 3 [14] in acid medium (10% yield of pure product ; not optimised). Treatment of 3 with refluxing 4N HCl accomplished the hydrolysis of the ester and the decarboxylation of the acid to the conjugated iminium 4 which was reduced directly to 5 [15] ($NaBH_4$, CH_3OH ; yield : 25% from 3) whose double bond possesses the E configuration [7]. This synthetic product was identical with natural deplancheine and thus the structure of the latter was

unambiguously established as 5.

References and Notes

1. Part 65 in the series "Plantes de Nouvelle-Calédonie" ; part 64 see F. Tillequin, M. Koch and T. Sévenet, J. Nat. Products, to be published.

2. The Authors thank Drs P. Boiteau and T. Sévenet for the plant material.

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6. (±) deplancheine has been synthesized as a model compound before it was known as a natural product : D. Thielke, J. Wegener and E. Winterfeldt, Angew. Chem. Int. Edit., 13, 602 (1974). We thank Prof. Dr. E. Winterfeldt for sending a sample for comparison.

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8. A. Husson and H.-P. Husson, unpublished results.

9. J.H. Supple, D.A. Nelson and R.E. Lyle, Tetrahedron Lett., 1645 (1963).

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13. 2 : amorphous, MS m/e (relative intensity) : $M^{+\cdot}$ 308 (32), 293 (24), 178 (32), 144 (100), 130 (19) ; ^1H NMR ($CDCl_3$, δ, ppm) : 3.65 (3H, s), 4.70 (1H, m), 5.15 (1H, d, J_{AB} = 15 Hz), 5.65 (1H, m), 6.30 (1H, s), 6.90 (1H, broad s), 7 - 7.60 (4H aromatic, m + 2H, d, J_{AB} = 15 Hz), 8.5 (1H, m).

14. 3 : m.p. 170° (CH_2Cl_2) ; MS m/e (relative intensity) : $M^{+\cdot}$ 308 (100), 307 (48), 293 (22), 277 (22), 249 (18), 170 (20), 156 (40) ; ^1H NMR ($CDCl_3$, δ, ppm) : 3.62 (3H, s), 5.30 (1H, d, J_{AB} = 15 Hz), 6.63 (1H, s), 7 - 7.60 (4H aromatic, m + 2H, d, J_{AB} = 15 Hz), 7.9 (1H, m).

15. ^{13}C NMR ($CDCl_3$, δ, ppm, 22.63 MHz) of synthetic deplancheine : 12.7 C-18, 21.6 C-6, 25.9 C-15, 30.2 C-14, 52.9 C-5, 60.2 C-3, 63.5 C-21, 108.3 C-7, 110.7 C-12, 118.2 C-9, 119.3 C-10 + C-19, 121.3 C-11, 127.4 C-8, 134 and 134.7 C-2 and C-20 (can be interchanged), 136.1 C-13.

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