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A TOTAL SYNTHESIS OF THE ALKALOID DEPLANCHEINE

W. R. Ashcroft and J. A. Joule*

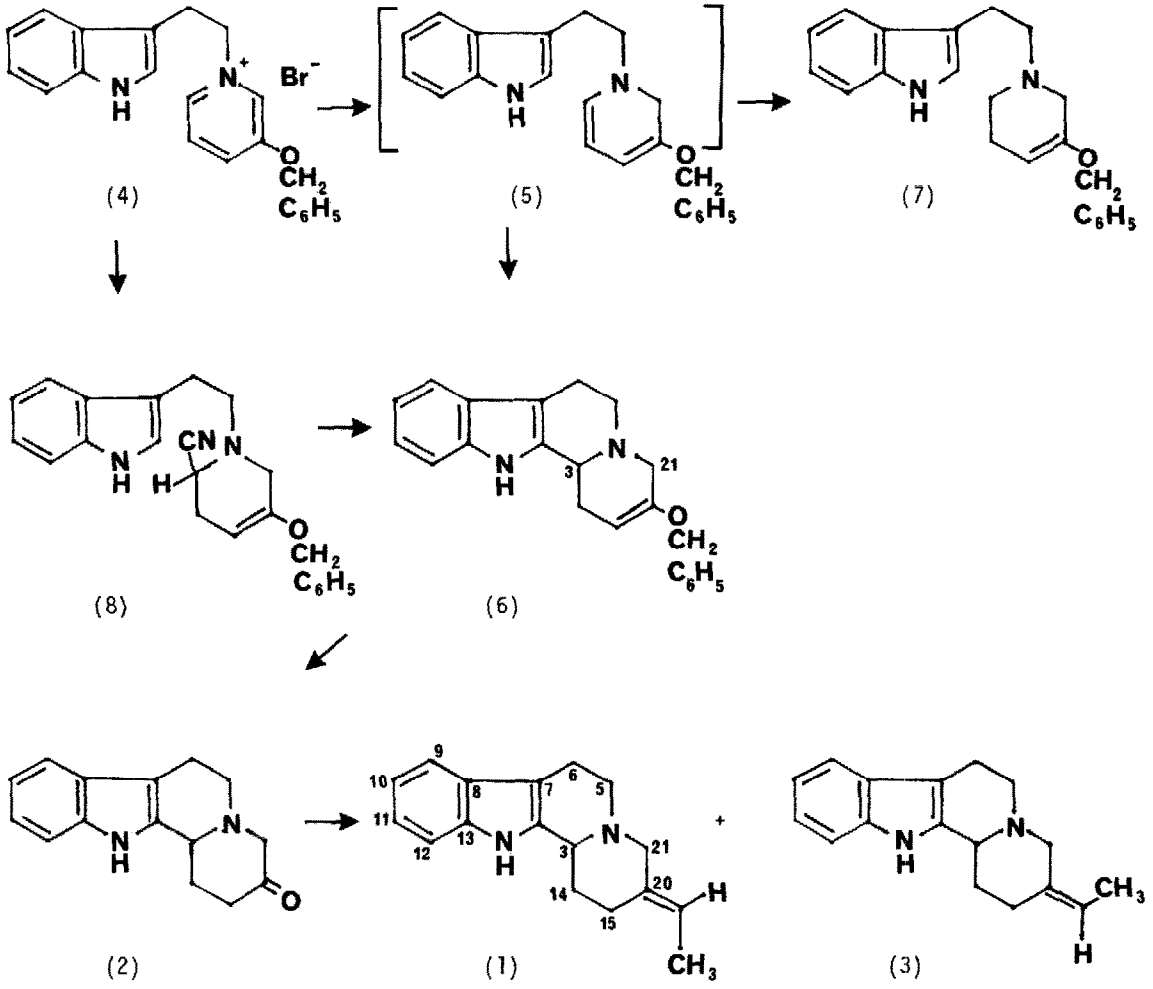
Chemistry Department, University of Manchester, Manchester, M13 9PL England

Summary: The indole alkaloid deplancheine (1) has been synthesised utilising a Wittig reaction on the octahydro[2,3-a]quinolizin-2-one (2) itself available in four synthetic steps from readily available materials.

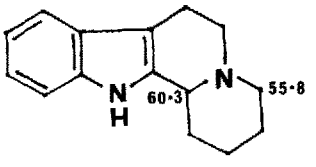
Deplancheine (1), isolated[1] from Alstonia deplanchei van Heurck and Mueller Arg., has an unusual structure in lacking the C-16/-17/-22 unit usually attached to C-15 in the corynantheine-type alkaloids. The (±)-form of deplancheine had been synthesised[2] as a model compound, by such a route that the E configuration of the ethylidene group was rigorously established, six years before the report[1] of the isolation of the (+)-base from a natural source. No yields were given for the steps in the first synthesis[2] and moderate to poor yields were obtained in those in the subsequent preparation[1]. We report here a simple, efficient synthesis of ketone (2) which on Wittig reaction gave (±)-deplancheine together with its geometrical isomer (3) in good yield, but in approximately equal proportions.

The partial reduction of indol-3-ylethylpyridinium salts to 1,2-dihydropyridines, coupled with subsequent acid treatment leading, via enamine protonation and intramolecular Mannich reaction, to tetracyclic materials, has been used[3] before for the formation of the octahydroindolo[2,3-a]quinolizine nucleus. Accordingly we undertook the preparation of salt (4), having an oxygen function at the future C-20, in the hope of converting it, via (5) into (6) where the C-20-oxygen would be present as a protected ketone to be then used to provide the means for introducing the ethylidene group.

Reaction[4] (100°C, 2 h, 83%) of tryptophyl bromide[5] with 3-benzyloxypyridine[6] gave the hygroscopic salt (4)[7] which on reduction with excess $LiAlH_4$ (THF, 20°C, 5 min) and immediate acid-catalysed cyclisation (50% aq AcOH, 20°C, 68h) gave the tetracyclic enol-ether (6)[7,8] (25% from (4)), m.p. 208-210°C (from MeOH). Unfortunately, because larger scale reductions (>100 mg) required longer reaction times, further reduction to the tetrahydropyridine (7)[7] then became competitive. This problem was avoided by trapping the dihydropyridine as the cyano-adduct (8) by "reductive cyanation"[9] (KCN, $NaBH_4$, MeOH, H_2O, Et_2O, 0°C, 100 min, 95% crude). The amorphous cyano-adduct (8)[7], though isolable, was somewhat unstable and was best utilised without purification for the next stage, cyclisation (50% aq AcOH, 20°C, 15 h) to the tetracyclic enol-ether (6) in 36% recrystallised overall yield from (4). The ^{13}C n.m.r. spectrum[8] of (6) ruled out the possibility that the cyano-adduct and thence the tetracyclic



product were regio-isomers by showing there to be an endocyclic homoallylic shielding effect[10] of 4 p.p.m. on C-3 rather than on C-21, by comparsion with the corresponding carbon resonances of the model tetracycle (9)[11].



(9)

Deprotection of the enol-ether (6N HCl, MeOH, 20°C, 1 h, 85%) gave the ketone (2)[7] (amorphous). Wittig reaction with ethylidenetriphenylphosphorane[12] (DMSO, 40°C, 15 h, 74%) gave a 1:1 mixture of two isomers which, after t.l.c. separation, were both crystallised from Et_2O, m.p.s 140-142°C and 148-153°C (lit[1], for (+)-deplancheine, 115°C (from Et_2O)). Comparison of the spectra of the two isomers with those of the natural material allowed us to identify the lower melting isomer, as the E isomer, (1), (±)-deplancheine It is worth noting that the unnatural, higher melting isomer (3) had an ^1H n.m.r. signal, as a doublet at τ6.1, J 12 Hz, for the equatorial C-21 proton, at considerably lower field[13] than any aliphatic proton signal shown by the natural E-isomer (no aliphatic proton signals below τ6.4). Further, the unnatural isomer had a higher olefinic proton signal (τ4.6 compared to τ4.5) and a lower methyl signal (τ8.2 compared to τ8.3)than the natural geometrical isomer.

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References and Notes

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7. All new compounds gave u.v., i.r., ^1H n.m.r. and m. spectra and elemental or high resolution m.s. analyses consistent with the proposed structures except for (4) which was characterised by u.v. and ^1H n.m.r. alone.

8. ^{13}C n.m.r. ($CDCl_3$) p.p.m., 21.6 t C-6, 29.6 t C-4, 52.2 t C-5, 55.8 t C-21, 56.1 d C-3, 69.1 t $\underline{O}CH_2Ph$, 91.8 d C-15, 108.7 s C-7, 110.9 d C-12, 118.4 d C-9, 119.7 d C-10, 121.6 d C-11, 127.7 C-8 and d ortho-$C_6H_5CH_2O$, 128.0 d para-$C_6H_5CH_2O$, 128.6 d meta-C_6

H_5CH_2O, 134.7 s C-2, 136.5 s C-13, 137.3 s OCH_2C, 153.0 s C-20.

9. This useful device permits the preparation of fairly stable masked dihydropyridines, c.f. J. A. Beisler and E. M. Fry, J. Org. Chem., 1970, 35, 2809 and R. Besselièvre, C. Thal, H.-P. Husson, and P. Potier, JCS Chem. Comm., 1975, 90; H.-P. Husson in "Indole and Biogenetically Related Alkaloids", J. D. Phillipson and M. H. Zenk, Eds, Academic Press Inc., London, New York, in press.

10. Many examples of this shielding effect on homoallylic carbon atoms by a double bond within a piperidine ring are known, e.g., see E. Wenkert, D. W. Cochran, E. W. Hagamann, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, J. Amer. Chem. Soc., 1973, 95, 4990.

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