The Synthesis of De-ethyldasycarpidone

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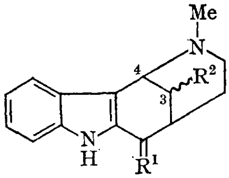
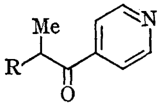
SINCE the elucidation[1] of the structure of uleine (Ia) by Büchi, six other alkaloids have been discovered[2] which are based on the same carbon skeleton. We present here the first synthesis of the basic four-ring system possessed by these alkaloids.

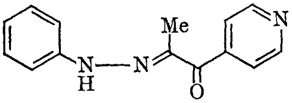
The Claisen condensation of methyl isonicotinate with methyl propionate, catalysed by sodium hydride, gave methyl 2-isonicotinylpropionate (IIa) as an oil, (b.p. 128—130°/1·5 mm.) in 65% yield. The β-keto-ester (IIa) was hydrolysed and decarboxylated in 80% yield by boiling with a mixture of acetic and sulphuric acids. The resulting ketone (IIb) was converted into an enamine with pyrrolidine in benzene and the enamine coupled,[3] without purification, with benzenediazonium chloride. The phenylhydrazone (III) was thus obtained in 50% yield, (m.p. 223—225°). Indolisation of the phenylhydrazone, using phosphoric acid, gave 2-isonicotinylindole (IV) in 33% yield, (m.p. 172—174°, λ_{max} 220, 265, and 329 mμ; log ϵ 4·31, 3·89, 4·24, ν_{max} 3300 and 1635 cm.$^{-1}$). The methiodide of (IV) was reduced with potassium borohydride, giving an unsaturated alcohol (Va) in 90% yield, (m.p. 160—162°, λ_{max} 220, 273, 282, 290 mμ; log ϵ 4·46, 3·90, 3·90, and 3·76, ν_{max} 3280 cm.$^{-1}$). Manganese dioxide oxidation converted the alcohol (Va) into the corresponding conjugated ketone (Vb) in 67% yield, (m.p. 161—162°, λ_{max} 241, 319 mμ; log ϵ 4·00, 4·23, ν_{max} 3140, 1640, 1615 cm.$^{-1}$). Deconjugation of the ketone (Vb) was achieved by successive treatment with dimsyl sodium and ammonium chloride and the enamine (VI) (m.p. 152—155°) obtained in 55% yield. Ring closure of the enamine to de-ethyldasycarpidone (Ib) was achieved in 50% yield by treatment with 50% aqueous acetic acid at 100°. This process is envisaged as involving initial protonation at the β-carbon of the enamine to produce an electrophilic immonium group. Mannich condensation of the immonium grouping at the indole β-position then gives de-ethyldasycarpidone (Ib), (m.p. 215—216°, λ_{max} 237, 314 mμ; log ε 4·02, 4·21, ν_{max} 3450, 1665 cm.$^{-1}$). The mass spectrum of de-ethyldasycarpidone (Ib) showed a fragmentation pattern completely in accord with expectation, based upon the fragmentation of dasycarpidone (Ic) itself. For example, the base peak in the spectrum of (Ib) is at *m/e* 183, corresponding to an ion (VII). The base peak in the spectrum of dasycarpidone (Ic) occurs[4] at *m/e* 211, an ion which is the 3-ethyl homologue of (VII). The n.m.r. spectrum of de-ethyldasycarpidone (Ib) is also completely consistent with the structure assigned. The most relevant features are (*a*) the presence of only four aromatic hydrogen signals and the absence of an indole β-proton signal; (*b*) a one-proton multiplet at τ 5·55, which is attributed to the hydrogen at C-4; and (*c*) a one-proton signal at τ 0·41 for the indole *N*-hydrogen. In the n.m.r. spectrum of dasycarpidone,[2b] the hydrogen at C-4 resonates at τ 5·65 and is a doublet due to coupling with the single hydrogen at C-3.



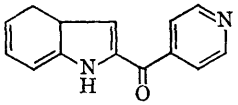
(I) a, $R^1{=}CH_2$, $R^2{=}Et$
b, $R^1{=}O$, $R^2{=}H$
c, $R^1{=}O$, $R^2{=}Et$



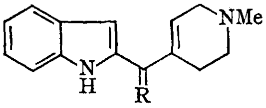
(II) a, $R{=}CO_2Me$
b, $R{=}H$



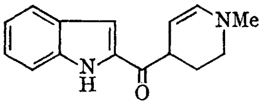
(III)



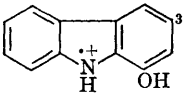
(IV)



(V) a, R=H,OH
b, R=O



(VI)



(VII)

This method is being extended to the synthesis of dasycarpidone and uleine.

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