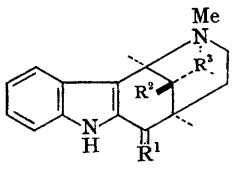
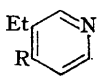
The Total Synthesis of Dasycarpidone and 3-*epi*-Dasycarpidone

By A. JACKSON, A. J. GASKELL, N. D. V. WILSON, and J. A. JOULE*
(*Chemistry Department, University of Manchester, Manchester* 13)

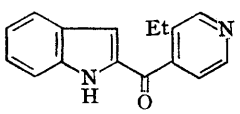
WE recently reported[1] the synthesis of the ring system of the group of indole alkaloids typified by uleine[2] (Ia) and dasycarpidone[3,2b](Ib). We have now succeeded in extending our synthetic approach and have obtained thereby racemic dasycarpidone and 3-*epi*-dasycarpidone[2b] (Ic), in each case identified by i.r., u.v., mass spectroscopic, and t.l.c. comparisons with the natural alkaloids.



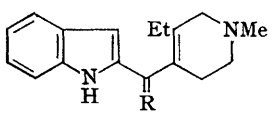
(I)	R^1	R^2	R^3
a	CH_2	Et	H
b	O	Et	H
c	O	H	Et



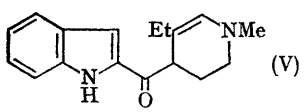
(II)	R
a	Me
b	CO_2H
c	CO_2Me
d	CO·CHMe·CO_2Me
e	CO·Et
f	CO·CMe:N·NHPh



(III)



(IV)	R
a	H,OH
b	O



(V)

Oxidation[4] of 3-ethyl-4-methylpyridine (IIa) with selenium dioxide in refluxing pyridine gave 3-ethylisonicotinic acid (IIb) in 72% yield (m.p. 198—200°). Transformation into the corresponding ester (IIc) (b.p. 90—94°/2 mm.) was achieved in 80% yield by successive treatment with thionyl chloride and methanol. Claisen condensation of this ester (IIc) with methyl propionate was effected with sodium hydride in 67% yield.

The resultant β-keto-ester (IId) (b.p. 102—110°/0·4 mm.) was hydrolysed and decarboxylated with refluxing aqueous H_2SO_4–HOAc to give the ketone (IIe) (b.p. 102—110°/4 mm.). Conversion into an enamine (pyrrolidine in refluxing benzene) was followed, without purification, by reaction[5] with benzenediazonium chloride to give the phenylhydrazone (IIf) (m.p. 212—213°). Fischer indolisation, catalysed by syrupy phosphoric acid, gave the indole (III) in 70% yield (amorphous, λ_{max} 227, 322 mμ; log ε 4·33, 4·26, ν_{max} 1640 cm.$^{-1}$). The methiodide of (III) gave a single alcohol (IVa) (m.p. 169—175°) on reduction with potassium borohydride. The production of only the desired Δ^3-piperideine is consistent with published data[6] on the reduction of 3-substituted pyridinium salts. The transformation of the conjugated ketone (IVb) (m.p. 96—100°, λ_{max} 236, 315 mμ; log ε 4·10, 4·28 ν_{max} 3200, 1625 cm.$^{-1}$), the manganese dioxide oxidation product of (IVa), into the required enamine (V) was more difficult than for the corresponding de-ethyl analogue.[1]

It was necessary to subject the compound to treatment with dimsyl sodium at 95° for 36 hr. followed by work-up using ammonium chloride in order to obtain the intermediate, (m.p. 151—153°, λ_{max} 242, 322 mμ; log ε 4·09, 4·20, ν_{max} 1665 cm.$^{-1}$).

Cyclisation of the intermediate resulted from treatment with 50% acetic acid at 100°. A readily separable mixture of dasycarpidone (Ib) and 3-*epi*-dasycarpidone (Ic) (m.p. 164—166°) was obtained in which the *epi*-base predominated to the extent of 5 : 1. Professor L. J. Dolby has kindly informed us that he has synthesised dasycarpidone and *epi*-dasycarpidone by a totally different approach.

(*Received, January 29th*, 1968; *Com.* 108.)

[1] A. Jackson and J. A. Joule, *Chem. Comm.*, 1967, 459.
[2] (a) G. Buchi and E. W. Warnhoff, *J. Amer. Chem. Soc.*, 1959, **81**, 4433; (b) A. J. Gaskell and J. A. Joule, *Chem. and Ind.*, 1967, 1089.
[3] M. Ohashi, J. A. Joule, B. Gilbert, and C. Djerassi, *Experientia*, 1964, **20**, 263; J. A. Joule, M. Ohashi, B. Gilbert, and C. Djerassi, *Tetrahedron*, 1965, **21**, 1717.
[4] D. Jerchel, J. Heider, and H. Wagner, *Annalen*, 1958, **613**, 153.
[5] V. I. Shvedov, L. B. Altukhova, and A. N. Grinev, *Zhur. org. Khim.*, 1965, **1**, 879 (*Chem. Abs.*, 1965, **63**, 6893).
[6] R. E. Lyle and P. S. Anderson, *Adv. Heterocyclic Chem.*, 1966, **6**, 45.