Novel Synthesis of the Indole Alkaloid Ellipticine†

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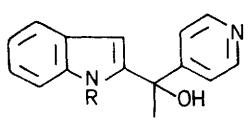
Summary A novel synthesis of the indole alkaloid ellipticine is described, the last step of which follows a possible biogenetic pathway.

THE indole alkaloids of the ellipticine series have aroused interest owing to their antitumour properties.[1] Several syntheses have been published.[2] We describe a novel

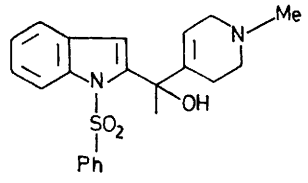
† For numbering used in this paper see ref. 3.

synthesis of ellipticine (**10**) which is reminiscent of a possible biosynthetic pathway[3] through an intermediate immonium ion like (**6**) or (**7**).

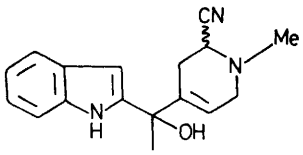
Compound (**1**) was synthesized by condensation of 2-lithio-1-sulphobenzoylindole with 4-acetylpyridine.[4] *N*-methyltetrahydroellipticine (**9**)[5] was obtained from (**1**) by two different routes. (a) Iodomethylation of (**1**) provides the corresponding pyridinium salt which is reduced with $NaBH_4$ to (**3**) (97%) [oil; $C_{22}H_{24}N_2O_3S$; M^+ 396, ^1H n.m.r., $\delta(CDCl_3$; $Me_4Si)$ 1·87 (3H, s, 17-Me), 2·37 (3H, s, NMe), 5·46 (1H, m, 20-H) and 6·86 (1H, s, 7-H)]. Treatment of (**3**)



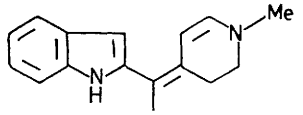
(1) R = SO_2Ph
(2) R = H



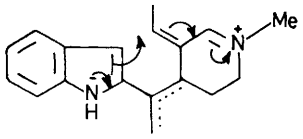
(3)



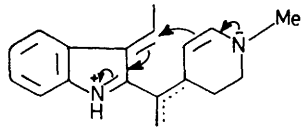
(5)



(4)



(6)



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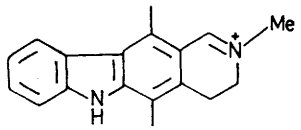

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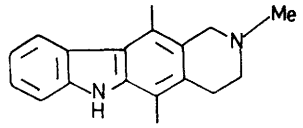
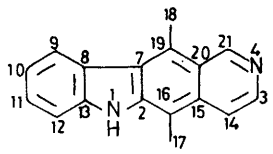


(9)



(10)

with KOBu^t in Me_2SO leads to the isomeric (*Z* and *E*) dienamines (**4**) (89%) [oil; $C_{16}H_{18}N_2$; M^+ 234; ^1H n.m.r., δ ($CDCl_3$; Me_4Si) 2·01 br (3H, s, 17-Me), 2·68 (3H, s, NMe), 5·50 (1H, d, J_{AB} 8 Hz, 20-H), 6·00 (1H, d, J_{AB} 8 Hz, 21-H), and 6·41 (1H, d, 7-H)]. Treatment of (**4**) in acetic acid with a Mannich reagent prepared by condensation of dimethylamine with acetaldehyde[6] affords *N*-methyltetrahydroellipticine (**9**) (2·2%).

(b) Compound (**1**) was hydrolysed to (**2**) (63%), m.p. 221, $C_{15}H_{14}N_2O$, M^+ 238 the iodomethylate of which was reduced with $NaBH_4$ in the presence of a large excess of KCN[7] to (**5**) (56%) [$C_{17}H_{19}N_3O$; M^+ 281; ν_{max} ($CHCl_3$) 2225 cm^{-1} (C ≡ N)]. The same Mannich reaction used in the case of compound (**4**) gives the immonium salt (**8**) *via* (**6**) or (**7**).[9] Compound (**8**) was treated without isolation with $NaBH_4$ affording *N*-methyltetrahydroellipticine (**9**) [24% yield from (**5**)].

Treatment of (**9**) with Pd–C in boiling decalin leads to ellipticine (**10**) (36%).

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[1] M. Hayat, G. Mathé, E. Chenu, M. M. Janot, P. Potier, N. Dat-Xuong, A. Cave, T. Sévenet, C. Kan-Fan, J. Poisson, J. Miet, J. Le Men, F. Le Goffic, A. Gouyette, A. Ahond, L. K. Dalton, and T. A. Connors, *Biomedicine*, 1974, **21**, 101.
[2] R. B. Woodward, G. A. Iacobucci, and F. A. Hochstein, *J. Amer. Chem. Soc.*, 1959, **81**, 4434; P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, 1962, 3482; T. R. Govindachari, S. Rajapa, and V. Sudarsanam, *Indian J. Chem.*, 1963, **1**, 247; R. N. Stillwell, Ph.D. Thesis, Harvard University, 1964; L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Austral. J. Chem.*, 1967, **20**, 2715; K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264; F. Le Goffic, A. Gouyette, and A. Ahond, *Tetrahedron*, 1973, **29**, 3357.
[3] P. Potier and M.-M. Janot, *Compt. rend.*, 1973, **276**, 1727.
[4] R. J. Sundberg and H. F. Russell, *J. Org. Chem.*, 1973, **38**, 3324.
[5] S. Goodwin, A. F. Smith, and E. C. Horning, *J. Amer. Chem. Soc.*, 1959, **81**, 1903.
[6] H. Kuhn and O. Stein, *Chem. Ber.*, 1937, **70**, 567; A. Ek and B. Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5579.
[7] (a) J. A. Beisler and E. M. Fry, *J. Org. Chem.*, 1970, **35**, 2809; (b) J. A. Beisler, *Tetrahedron*, 1969, **26**, 1961; (c) E. M. Fry, *J. Org. Chem.*, 1964, **29**, 1647.