A Simple Synthesis of Ellipticine and 11-Demethylellipticine

By MALCOLM SAINSBURY* and RAYMOND F. SCHINAZI
(*School of Chemistry, University of Bath, Claverton Down, Bath*)

Summary A new synthesis of 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines) is described which involves a minimum of steps and very mild reaction conditions.

DURING the last three years no less than five syntheses of 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines) have been described.[1] This interest has been stimulated by reports of the potentially useful anticancer activity of ellipticine and some of its derivatives.[2]

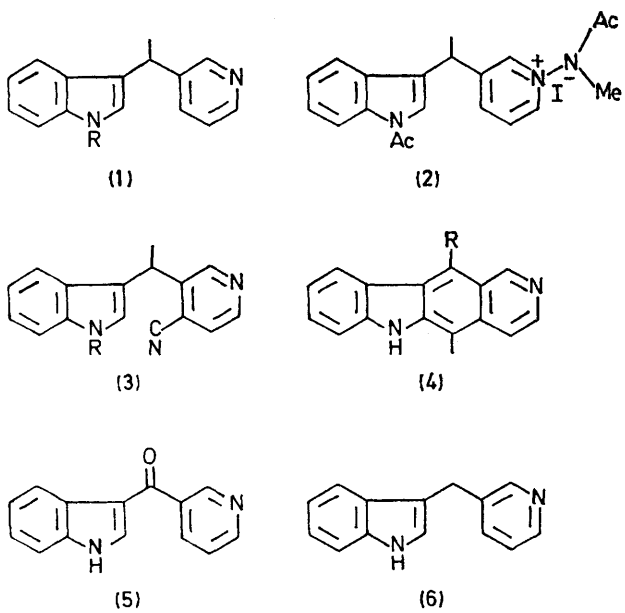
Although the new work represents a considerable advance on earlier studies,[3] as general methods all the syntheses have disadvantages either in the number of stages employed or in the severe conditions involved.

We now report a simple preparation of ellipticine (**4**, R = Me) and 11-demethylellipticine (**4**, R = H) which requires only very mild conditions and should provide an efficient general synthesis of 6*H*-pyrido[4,3-*b*]carbazoles.

Indolyl magnesium bromide is first combined with 3-(1-chloroethyl)pyridine[1d] to give 3-[1-(3-pyridyl)ethyl]-indole (**1**, R = H), m.p. 73—74 °C † (50%). The *N*(*a*)-acetyl derivative (**1**, R = Ac), m.p. 123—124 °C, is then treated in turn with *O*-mesitylsulphonylhydroxylamine, acetic anhydride and methyl iodide to give the salt (**2**), yield 75% overall; this, without purification, is treated with potassium cyanide and ammonium chloride[1e] to yield the nitrile (**3**, R = Ac) as an oil (98%). Purification and de-*N*-acetylation is effected by elution through a short column packed with basic alumina using chloroform as solvent to give (**3**, R = H), m.p. 118—119 °C (95%).

This product is treated with methyl lithium and the intermediate imine hydrolysed directly with 20% acetic acid in water (see ref. 1e) to form ellipticine (identical in m.p., i.r. spectrum, and chromatographic behaviour with an authentic specimen).[1d] Overall yield from (**1**, R = H) is 25—30%.

11-Demethylellipticine, m.p. 275—277 °C,[4] was obtained by a repetition of the above sequence using 3-(3-pyridylmethyl)indole (**6**), m.p. 157—158 °C, in place of (**1**, R = H).‡ The required starting material may be obtained from indolyl magnesium bromide and nicotinoyl chloride, followed by reduction of the product ketone (**5**), m.p. 250—251 °C with sodium borohydride, or less advantageous directly from indolyl magnesium bromide and 3-pyridylmethyl chloride. The best yield of 11-demethylellipticine from (**6**) was 28%.



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† Satisfactory analytical data are available for all compounds described.

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