

A Simple Synthesis of Ellipticine and 11-Demethylellipticine

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Summary A new synthesis of 6H-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 6H-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

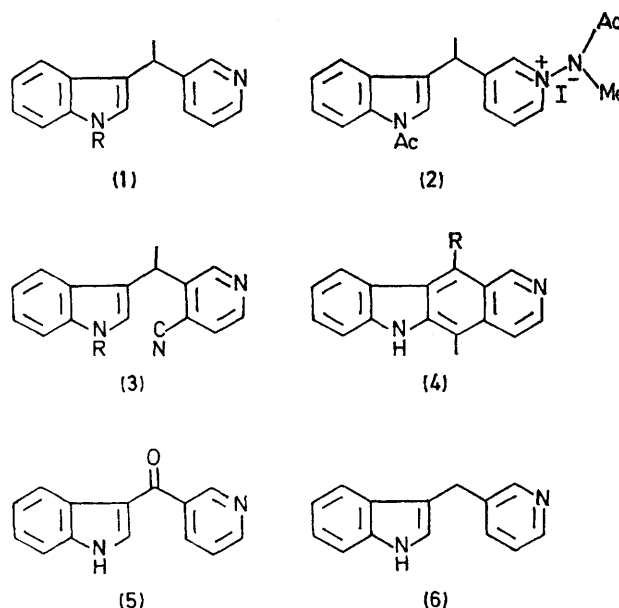
Although the new work represents a considerable advance on earlier studies,³ as general methods all the syntheses have disadvantages either in the number of stages employed or in the severe conditions involved.

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 6H-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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