A Concise Synthesis of the Antitumour Alkaloid Ellipticine

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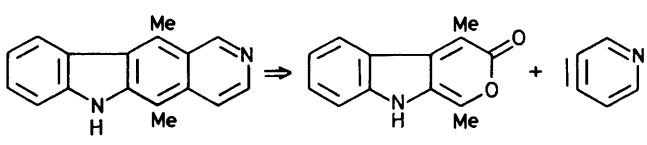
A short synthesis of the antitumour alkaloid ellipticine, based on the Diels–Alder reaction between 1,4-dimethylpyrano[3,4-*b*]indol-3-one (**2**) and 3,4-didehydropyridine, is described.

The 6*H*-pyrido[3,4-*b*]carbazole alkaloid ellipticine (**1**) and its 9-hydroxy- and methoxy-derivatives possess significant anti-cancer activity.[1] Consequently many synthetic routes to these compounds have been developed, and since the subject was comprehensively reviewed in 1977[2] many more syntheses have appeared.[3,4] We now describe a concise new synthesis of ellipticine (**1**) based on the strategy shown in Scheme 1.

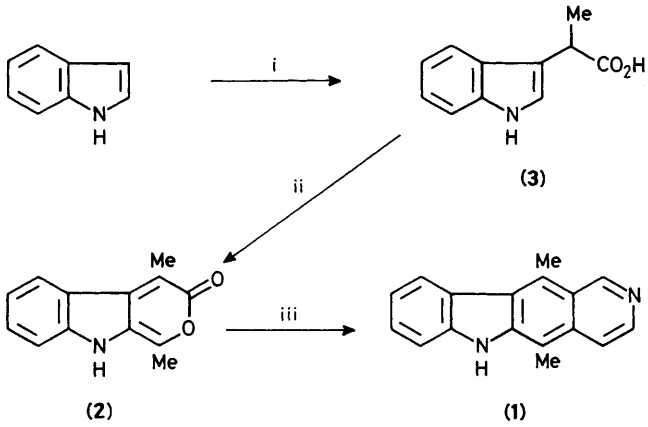
The strategy is based on the known Diels–Alder reaction of pyrano[3,4-*b*]indol-3-ones with alkynes which gives, with concomitant loss of carbon dioxide, carbazoles in moderate to good yield.[5,6] The requisite diene (**2**) was prepared from indole in two steps *via* the known[7] α-methylindole-3-acetic acid (**3**). Treatment of an acetic anhydride solution of (**3**) with boron trifluoride–diethyl ether gave the pyranoindolone (**2**) as an orange precipitate; it was isolated in 44% yield simply by filtration.



(1) (2)

Scheme 1

It was clear from earlier experiments[6] on the reaction of pyranoindolones with benzyne that a thermal source of 3,4-didehydropyridine would be needed to effect the required Diels–Alder reaction (Scheme 1). Although 3,4-



Scheme 2. *Reagents:* i, lactic acid, KOH, heat (ref. 7); ii, Ac_2O, BF_3–Et_2O; iii, (**4**), MeCN, heat; then chromatography.

didehydropyridine can be generated thermally from pyridine-3-diazonium-4-carboxylate,[8] this precursor is difficult to prepare and somewhat unstable. Therefore we developed a convenient new source of 3,4-didehydropyridine,[9] based on the thermal decomposition of 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid (**4**).[10] The triazene (**4**), a shelf-stable crystalline solid, m.p. 134 °C, is readily prepared (72%) by diazotisation of 3-aminopyridine-4-carboxylic acid[11] followed by treatment with alkaline dimethylamine.

The key Diels–Alder step was carried out by heating a mixture of the pyranoindolone (**2**) with excess of the triazene (**4**) in acetonitrile, and gave ellipticine (**1**) (20%), together with an equal amount of isoellipticine (**5**) which was separated by chromatography. No reactions of 3,4-didehydropyridine with unsymmetrical dienes have been reported, and therefore it is not clear whether the lack of regioselectivity, which is observed in the Diels–Alder reaction with (**2**), is intrinsic in the dienophilic properties of this reactive intermediate.

Nevertheless the synthesis of ellipticine (**1**) described herein is short, being only three steps from indole (Scheme 2), easy to carry out, and obviates the protection of the indole nitrogen.

We thank the S.E.R.C. for a studentship (to C. M.), Drs. M. Sainsbury and J. A. Joule for authentic samples of ellipticine, and the Central Research Fund of the University of London for an equipment grant.

Received, 19th April 1984; Com. 563

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