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SYNTHESIS OF THE INDOLE ALKALOID ELLIPTICINE.[+]

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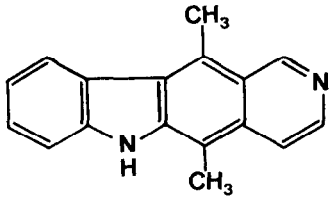
The potentially useful anti-cancer activity of ellipticine (1) and some of its derivatives, has triggered considerable synthetic efforts[1-6] in this area. In spite of the fact that no less than 20 routes are available at present no convenient method suitable for large-scale preparations does exist. Actually the inaccessability[7] of ellipticine derivatives has hampered the development of biological evaluation.

Some years ago we showed[8] that 2-ethylindole[9] and 3-acetylpyridine[10] could be condensed in acetic acid (or methanolic HBr) to give 2 rather than the expected compound 3 (cf. ref 11). At the time the idea was to cyclize 2 or 4a by introducing a suitable strongly electron-withdrawing substituent such as CH_3CO-, C_6H_5CO- or CH_3SO_2-, on the nitrogen atom in the pyridine ring, which would induce desired electrophilicity in the 4-position of the pyridine ring. This electrophilic centre should then attack the enamine system in the exocyclic tautomer of e.g. 4a (i. e. 4b) to give the desired cyclization.

A few examples of tautomerization of 2-alkylindoles followed by electrophilic attack are recorded in the literature. Thus, Thesing and Semler have shown[12] that 1,2,3-trimethylindole, on treatment with formaldehyde and dimethylamine, yielded the Mannichs base 5. More recently, Hutzinger and Raj found[13] that 2,3-dimethylindole when treated with 2,4-dinitrosulfenylchloride gave 3-methylindole-2-methylene-2',4'-dinitrophenyl sulfide (6). The fact that the 2-CH_3 group in 2,3-dimethylindole is completely deuteriated under mild acidic conditions[14] gave further support to the suggested approach.

[+] Presented in part at The 16th Nordiska Kemistmötet, Bergen, Norway, June 19-22, 1977.



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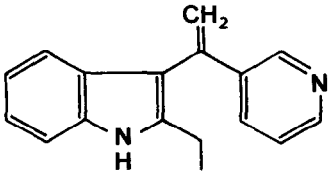

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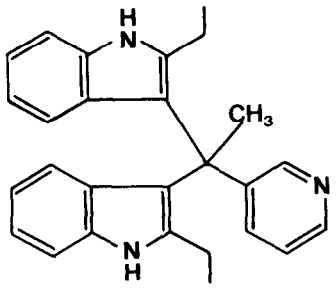

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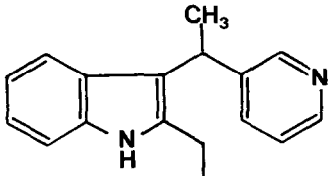

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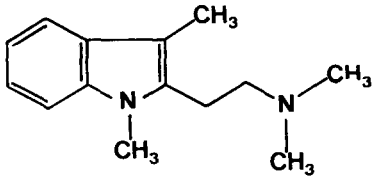

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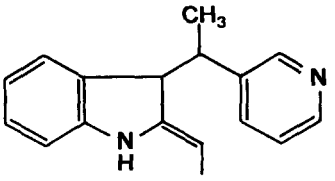

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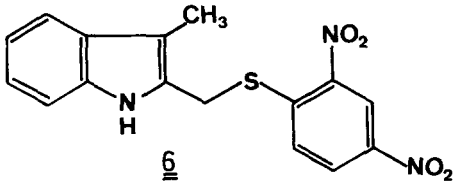

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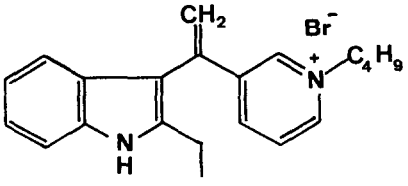

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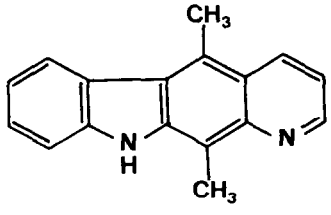

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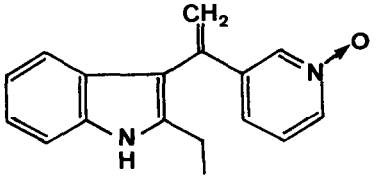

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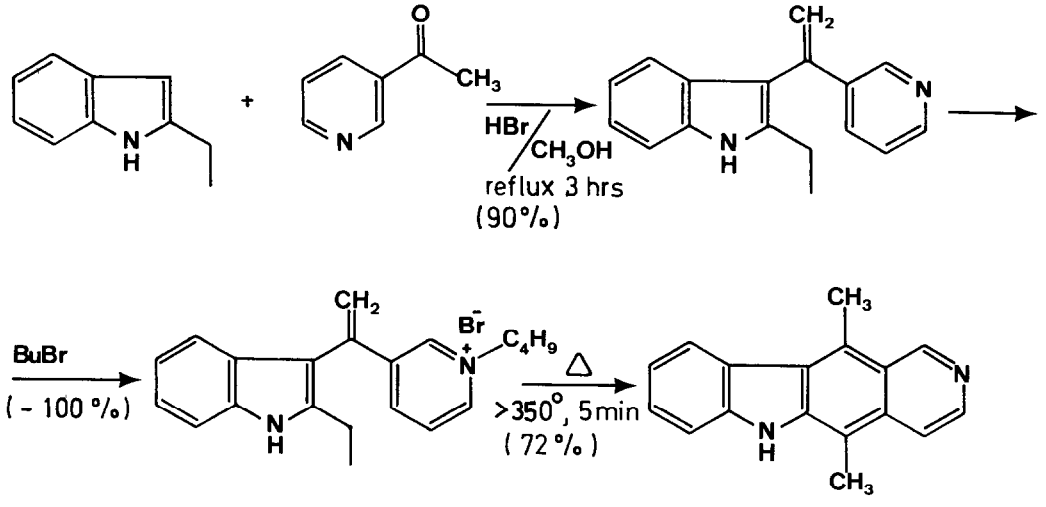
In spite of considerable efforts to effect the desired cyclization in various solvents in the temperature range 0-100° the yields were invariably low (0-0.5 %). However, pyrolysis (5 min, > 350°) of N-alkylated derivatives, e.g. 7 gave ellipticine in high yield (72 %). The desired product could readily be separated from the minor products, which included 2-ethylindole, 2, and an isomer assigned structure 8[15]. It was also found that pyrolysis of 9[16] (and even 2) likewise afforded ellipticine (albeit in relatively low yields). The heating technique during the pyrolysis is essential. Thus rapid heating of 7 gave good yields of ellipticine (and less than 10 % of 8), whereas slow heating (e.g. 220° for 30 min) gave 8 as the predominant product. Similar results were obtained by heating (80°) 7 with $NaOC_2H_5$ in ethanol.

To sum up ellipticine (and several derivatives[17]) can very efficiently be synthesized by the following route



The possibility to integrate all the steps to a one-pot synthesis has not been explored but does indeed look promising.

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