STUDIES IN THE DIHYDROPYRIDINE SERIES. V.† SYNTHESIS OF PYRIDOCARBAZOLE ALKALOIDS: OLIVACINE AND GUATAMBUINE.

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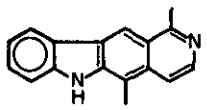
Abstract - The tricarbonylchromium(0) complex 8 effectively stabilized the very reactive dihydropyridine system during one carbon insertion. Release of the complex allowed cyclization to the pyridocarbazole product 13 which was elaborated to olivacine 1 and guatambuine 2.

The pyridocarbazole alkaloids, including olivacine 1 and guatambuine 2, have received considerable interest as a result of their anti-tumour activity[2-4]. Numerous syntheses of representatives of this family of alkaloids have been reported[5-20], and several routes employed cyclization of pyridyl-substituted indoles to generate the linear pyridocarbazole skeleton although the yields have generally been low. Our interest in the stabilization and use of very reactive dihydropyridine systems[1,21] led us to investigate the utility of tricarbonylchromium(0) complexes (eg. 8) in the synthesis of natural products. Here, the complex 8 was intended to provide a nucleophilic centre at the indole- 3- position and a masked enamine (dihydropyridine) for the introduction of a one carbon unit and subsequent cyclization to the pyridocarbazole skeleton.



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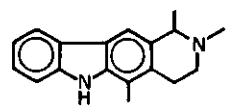

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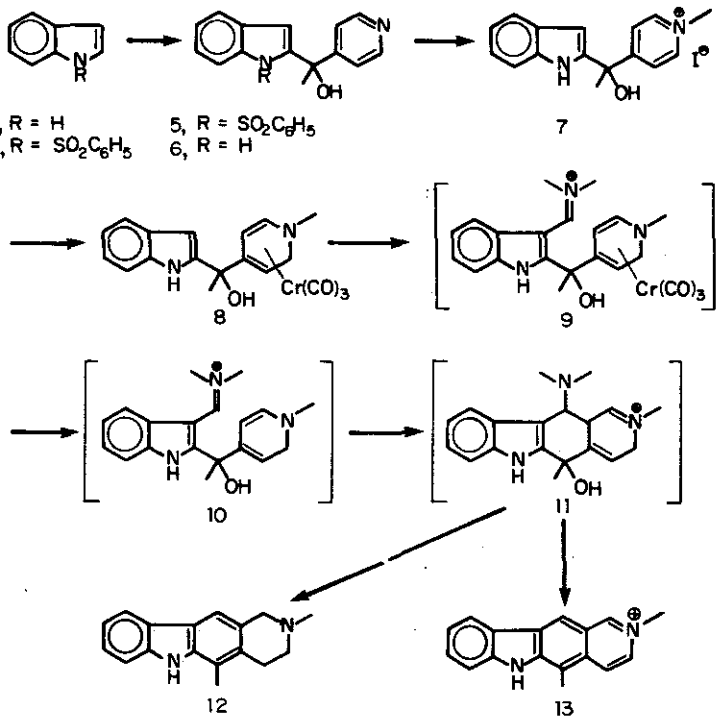
Condensation of 4, readily derived from indole 3, with 4-acetylpyridine gave 5 which was readily hydrolysed to 6[18,22]. Reaction with iodomethane produced the salt 7 in high yield. Reduction of 7 with sodium borohydride and protection of the resulting dihydropyridine, in the usual manner[21], gave the tricarbonylchromium(0) complex 8 (mp 64-65°; ν_{max} 3420, 1941, 1866, 1821; λ_{max} 218, 398) in 55% yield (Scheme 1).

† For Part IV, see reference 1.

The complex 8 reacted with the Vilsmeier salt from DMF and $POCl_3$ to give an intermediate (viz. 9) which on treatment with pyridine gave a mixture of yellow products (eg. 11; viz. 9 → 10 → 11). Subsequent reaction with sodium borohydride gave 1-desmethylguatambuine 12 (mp 274-276°; ν_{max}

scheme I.



3220, 1613; λ_{max} 232, 238, 248, 259, 287, 297, 326, 340) in 89% yield from 8. Alternatively, dehydrogenation of the crude mixture (eg. 11) using Pd/C at 300° gave a mixture of the salt 13 (60% from 8) and the pyridine derivative 14 (10% from 8). The former was easily demethylated to 14 using triphenylphosphine in DMF or HMPA (Scheme 2). Methyllithium, in dry THF, reacted with 14 and subsequent oxidation of the dihydropyridine intermediate with iodine gave olivacine[23] 1 in 54% yield. Reaction of 1 with iodomethane and reduction with sodium borohydride gave (±) guatambuine 2.

Chromium tricarbonyl complexing provided a good method for stabilizing very reactive dihydropyridines. Reaction with pyridine released the dihydropyridine from the complex, allowing cyclization and subsequent elaboration of the pyridocarbazole skeleton in a synthesis of olivacine and (±) guatambuine.

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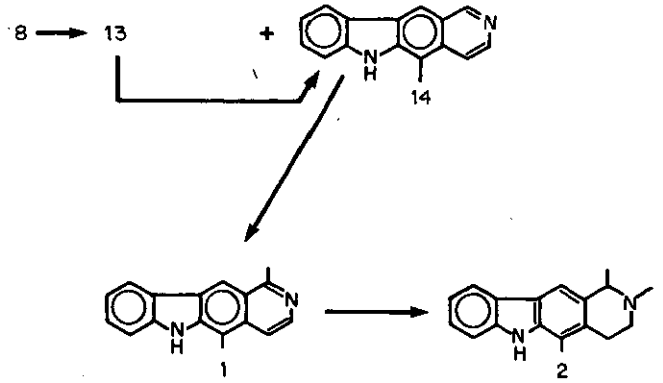
scheme 2.



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23. Synthetic samples of 1 and 2 were identical with authentic samples of the respective natural products. All compounds gave satisfactory spectral and analytical data.

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