INDOLE ALKALOID SYNTHESIS

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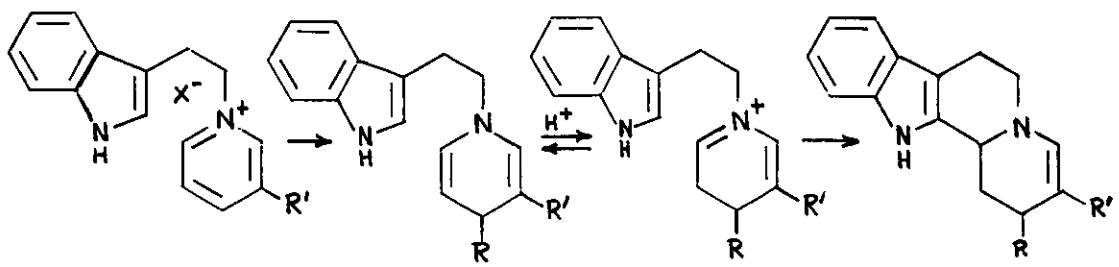
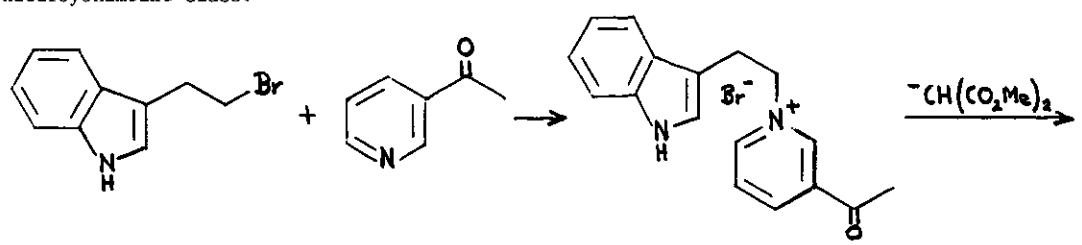
The lecture describes the total synthesis of pseudoyohimbine and an approach to the deserpidine group of indole alkaloids by way of the route of nucleophilic addition to a pyridinium salt followed by acid-induced ring closure.

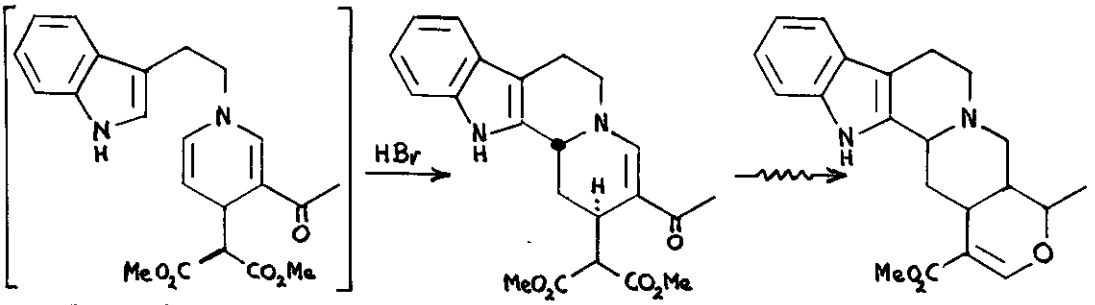
I wish to express my sincere thanks to the organizers of the Ninth International Congress of Heterocyclic Chemistry for their kind invitation to me to present this lecture in Tokyo.

For some time the two-step reaction sequence depicted below has served as the basis of a general alkaloid synthesis scheme. It involves carbon nucleophile addition to an N-alkylpyridinium salt possessing an electron-withdrawing group at its β-carbon site (R' below) and subsequent acid-induced ring closure of the resultant γ-alkylated 1,4-dihydropyridine.[1,2] Whereas exploitation of this method of polyfunctional, fused piperidine construction can be envisaged for a majority of alkaloids, it has been applied in my research group to the synthesis of only tetrahydrocarboline-containing indole alkaloids thus far.

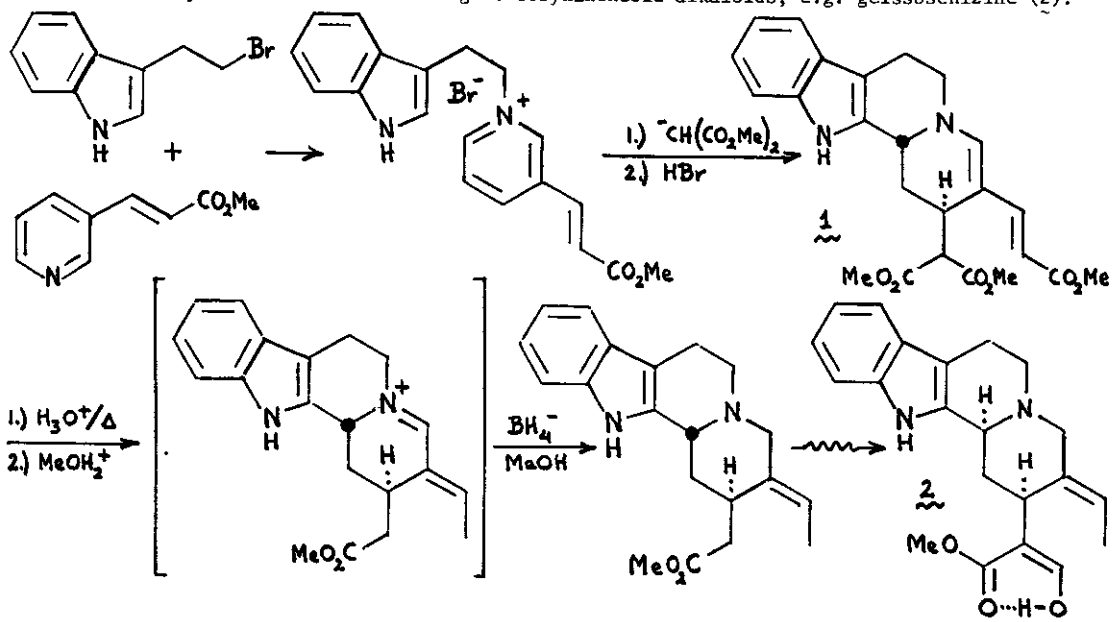


The following scheme illustrates the first application of the method. The two-step reaction sequence evolved in this instance into short syntheses of a variety of natural bases of the heteroyohimbine class.[3,4]

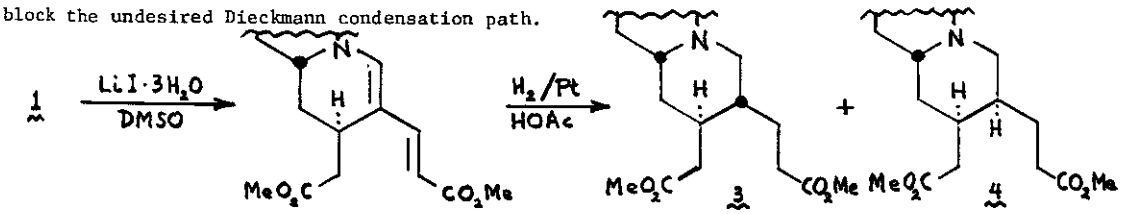


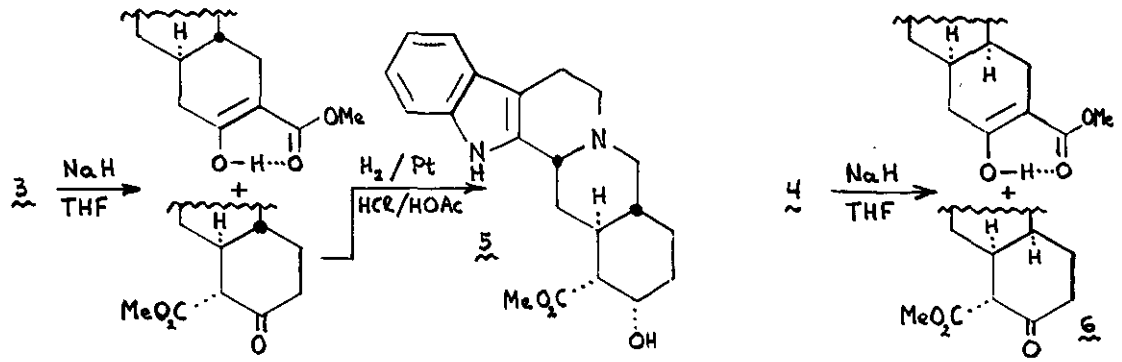


Whereas the acetyl function had served as the electron-withdrawing group in the above syntheses, its replacement by an acrylic ester moiety had no undue effect on the reaction scheme, as illustrated by the short route leading to corynantheoid alkaloids, e.g. geissoschizine (2).[5]

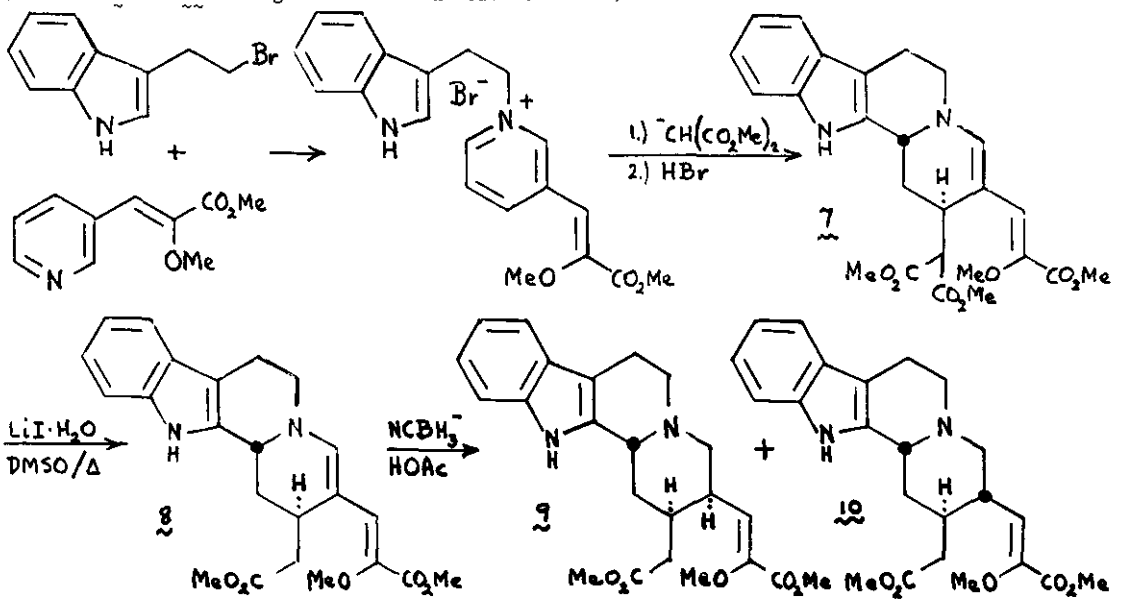


Tetracycle 1, the product of the initial two-step reaction scheme in the corynantheoid alkaloid syntheses, proved to be an excellent starting substance for short yohimboid alkaloid syntheses.[6] Thus its decarbomethoxylation and subsequent hydrogenation permitted entry into the pseudo (3) and epiallo (4) class of compounds, the former of which led to pseudoyohimbine (5)[6] and the latter to a 3-epi-α-yohimbine derivative (6).[7] Since a drawback of the pseudoyohimbine synthesis had been the lack of regioselectivity in the Dieckmann condensation of intermediate diester 3, it was decided to undertake a second synthesis of the alkaloid by a route designed to block the undesired Dieckmann condensation path.

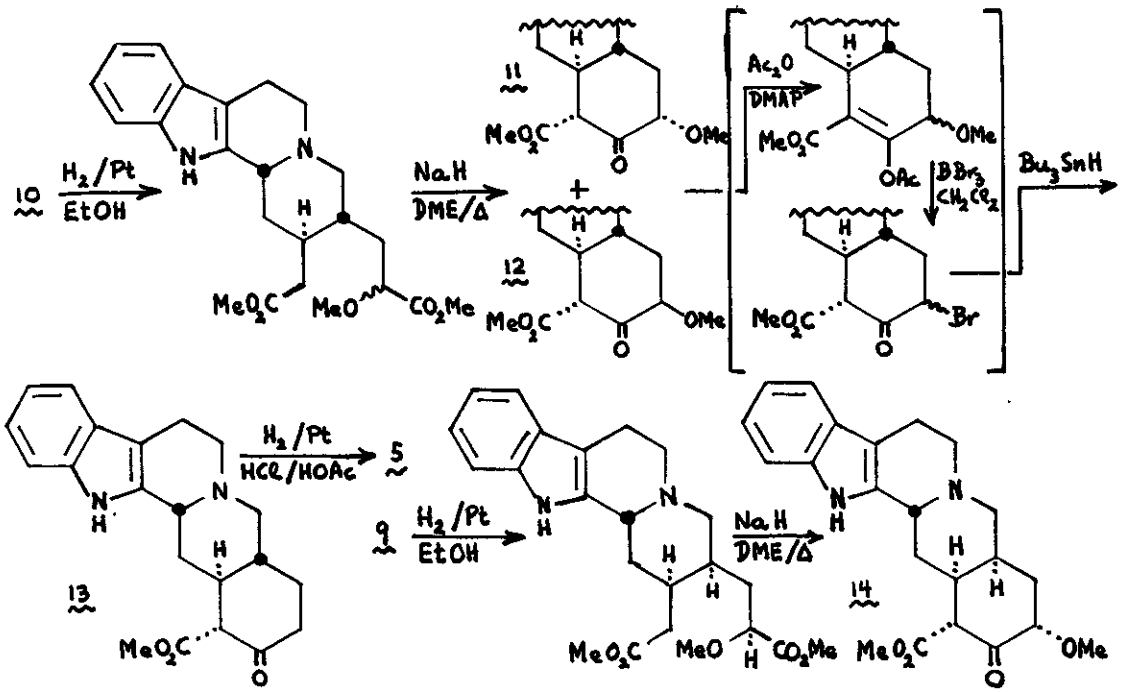




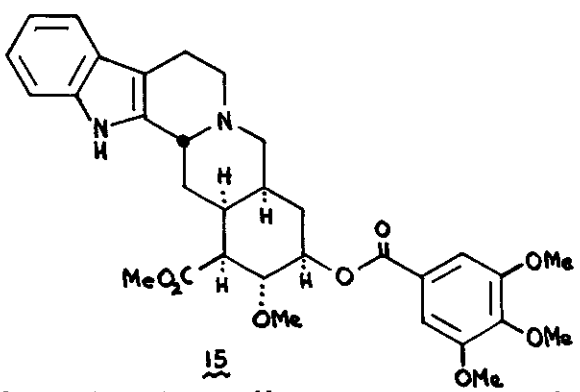
Base-induced condensation of nicotinaldehyde with methyl methoxyacetate yielded methyl α-methoxy-β-(β-pyridyl-)acrylate, whose N-alkylation with tryptophyl bromide gave a pyridinium salt. Exposure of the latter to dimethyl sodiomalonate, followed by treatment of the adduct with hydrogen bromide, afforded tetracycle 7, whose lithium iodide-induced decarbomethoxylation produced doubly vinylogous urethane 8. Both esters 7 and 8 underwent ready cyanoborohydride reduction, leading to epiallo and pseudo isomer mixtures of triesters and diesters, respectively (*diesters 9 and 10 having been formed in ca. 2:1 ratio*).



Catalytic hydrogenation of the pseudo diester (10) and Dieckmann condensation of the dihydro products yielded 18-epimers of 18-methoxypseudoyohimbinone (11 and 12). Treatment of the latter with acetic anhydride and γ-dimethylaminopyridine, followed by exposure of the resultant enol acetate to boron tribromide and subsequently to tributyltin hydride, afforded pseudoyohimbinone (13), which had been transformed earlier[6] into pseudoyohimbine (5).



The presence of the methoxy group on the acrylic ester sidechain of the starting pyridine compound not only had served the purpose of making available a unidirectional route of synthesis of pseudoyohimbine (5), but, more importantly, it also had been designed to offer ready access to the indole alkaloids of the reserpine family. Hence the thus far unused intermediate, epiallo diester 9, became an important compound for the construction of natural bases of the latter type. Hydrogenation of acrylic ester 9 yielded a dihydro derivative, whose Dieckmann condensation led to ketoester 14. The latter substance possesses the pentacyclic nucleus, the required, relative configuration of its bridgeheads, and ring E substituents of such nature as needed for alkaloids as, for example, deserpidine (15). Substituent manipulation is now in progress.



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