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ALKALOID SYNTHESIS

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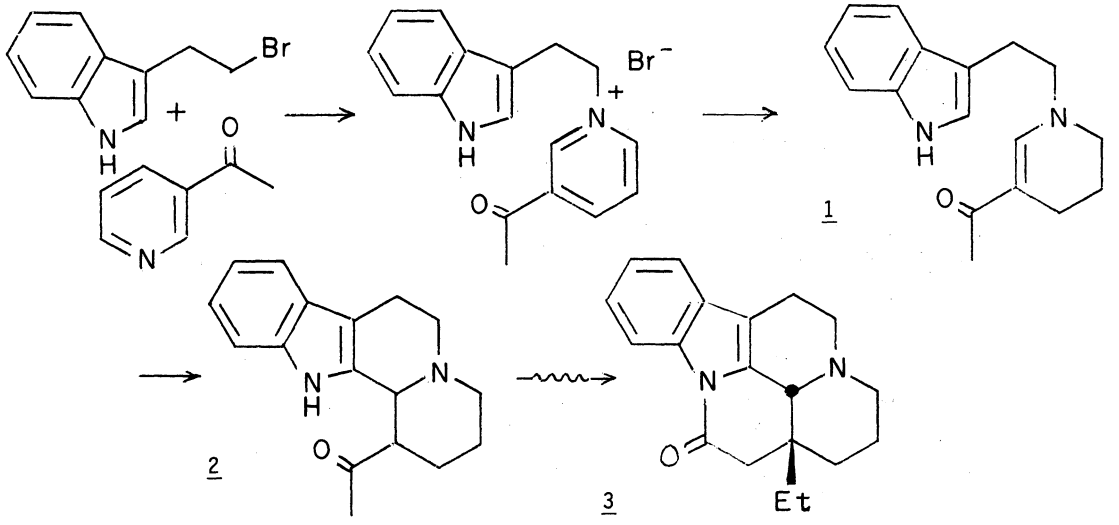
Abstract — Methods of short, stereospecific synthesis of indole alkaloids are described and the syntheses of deethylvincadifformine, hirsutine and geissoschizine emphasized.

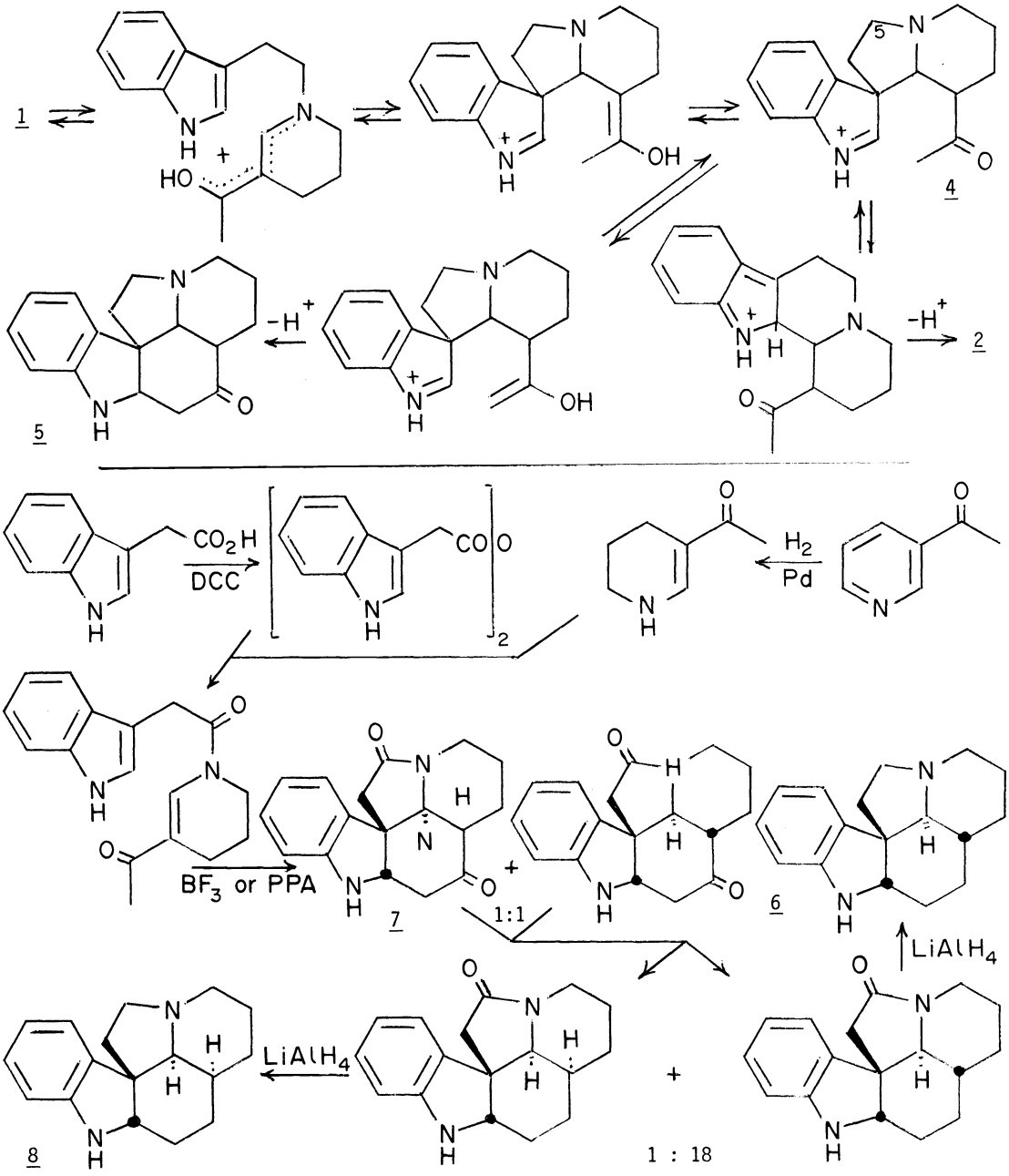
INTRODUCTION

For two decades the guiding concept for the research effort of my collaborators in the field of alkaloid synthesis has been a highly versatile, two-step hydrogenation-cyclization scheme of fused piperidine construction, which was based on an early discovery of the facile conversion of 1-alkyl-3-acylpyridinium salts into 1-alkyl-3-acyl-2-piperideines on palladium--catalyzed hydrogenation (1) and the easy acid-induced cyclization of nucleophilic centers at C(2) of the reduction products (2). The first application of this concept in the indole alkaloid area is illustrated by the following synthesis of eburnamonine (3) (3).



Whereas the two-step reaction scheme was involved in the synthesis of a large variety of alkaloid systems over the years (2), the eburnamonine synthesis left the legacy of a persevering, haunting thought of an unfinished story, i.e. the exciting idea of the possible utilization of its intermediates in the construction of the skeleton (e.g. 5) of the Aspidosperma or structurally related indoline alkaloids. As the following mechanistic pathway of the 1→2 transformation indicates, an intermediate (4), in principle, is also en route to Aspidosperma pentacycle 5. The lack of formation of the latter thus was the consequence of the cyclization taking place directly at the indole α-site or tetracycle 4 undergoing more rapid Wagner-Meerwein rearrangement than needed stereochemistry reorganization, ketone enolization and intramolecular Mannich condensation.

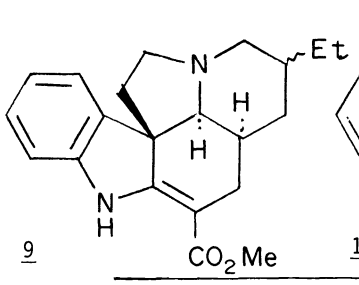
On the assumption of an intermediate γ-lactam (5-keto-4) having a higher likelihood of producing a pentacyclic structure like 5 due to its thermodynamic (the γ-lactam being more stable than its Wagner-Meerwein rearrangement product, a δ-lactam) and/or kinetic (5-keto-4 being more long-lived due to the reduction of the migratory aptitude of the migrating group) characteristics the N-acyl equivalent of 1 had to be prepared and its cyclization behavior tested. As the following outline of an improved version (4) of an earlier synthesis of deethylaspidospermidine (8) portrays (5), the concept was reducible to practice and the decade-old goal achieved.



SYNTHESES OF DEETHYLVINCADIFFORMINE

Pseudovincadifformine (9) and pandoline (10) represent one type of natural bases structurally akin to pentacycle 8 and related to the indole alkaloid portion of the medicinally important, indole-indoline alkaloid vincaleucoblastine (11) in a reduction--oxidation sense (6). Their synthesis by the above route requires the incorporation of ethyl and carbomethoxy groups. Four procedures for the easy introduction of the latter function have been developed (4).

Two carbomethoxylation methods involved photochemistry on the intact pentacyclic nucleus. Thus, for example, lead tetraacetate oxidation of amine 6 yielded its dehydro derivative 12, whose exposure to sodium hydride and methyl chlorocarbonate gave urethane 13. Irradiation of a methanol solution of the latter led to an isodeethylvincadifformine (14). Reduction of ketolactam 7 with lithium aluminum hydride and Oppenauer oxidation of the resultant alcohol afforded ketone 15, whose lead tetraacetate oxidation gave vinylogous amide 16a. Repetition of the two-step, 12→14 sequence on 16a yielded 16b, whose conversion into a thioketone with 2,4-bis-(p-anisyl-)2,4-dithiox-P,P-1,2,3,4-dithiadiphosphetane (7), followed by desulfurization with Raney nickel, led to deethylvincadifformine (17).



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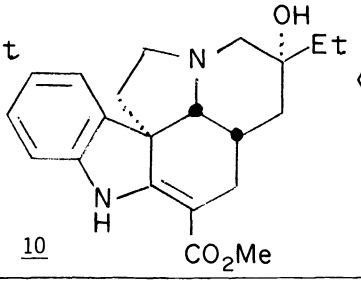

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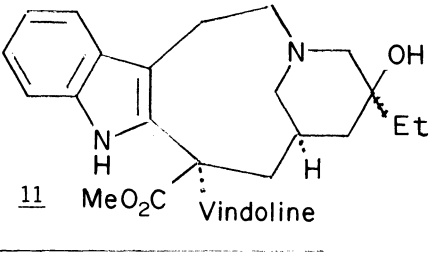

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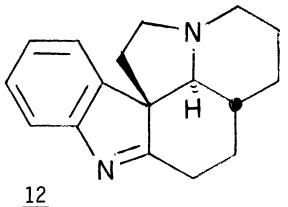

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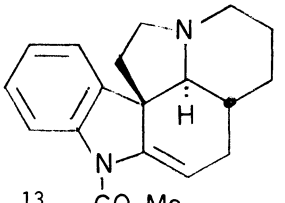

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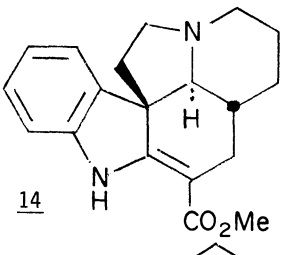

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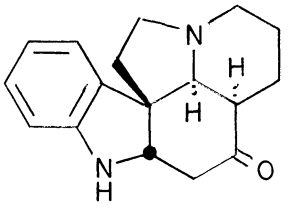

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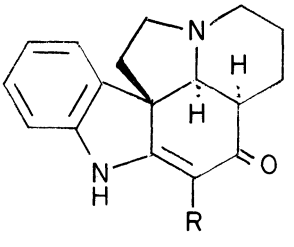
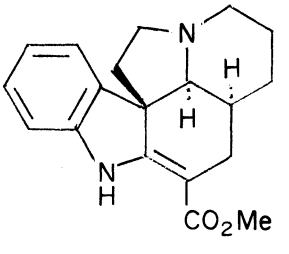


16a, R = H
b, R = CO_2Me



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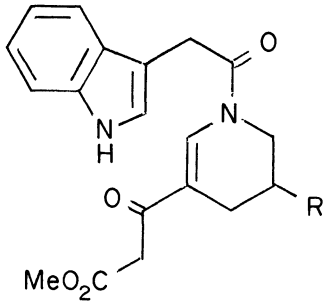
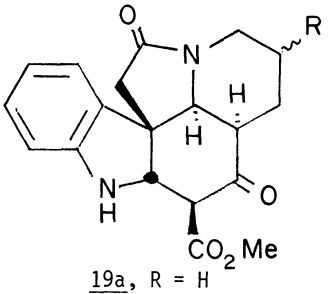
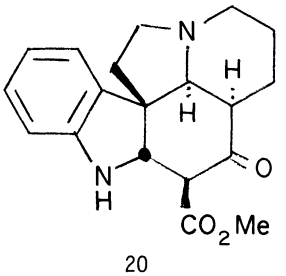
Two procedures involved the introduction of the carbomethoxy group at the outset of the synthesis. Hydrogenation of methyl nicotinylacetate over palladium produced the tetrahydropyridine derivative (1), whose N-acylation with indoleacetic anhydride in the presence of sodium hydride afforded diacylated piperideine 18a. Treatment of the latter with polyphosphoric acid yielded pentacycle 19a, whose lactam carbonyl group could be reduced with diborane after protection of the β-ketoester moiety as the enol-trifluoroborane complex. Oxidation of the product (20) with lead tetraacetate gave 16b, a compound described above as precursor to deethylvincadifformine (17). Alternatively, sequential reduction of the ketone function of 19a with sodium borohydride, dehydration of the resultant alcohol with polyphosphoric acid, hydrogenation of the conjugated, olefinic ester over palladium, diborane reduction of the lactam carbonyl group and oxidation of the aminoester led to deethylvincadifformine (17).



18a, R = H
b, R = Et



19a, R = H
b, R = Et



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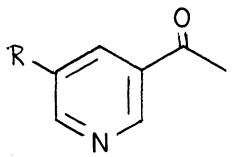
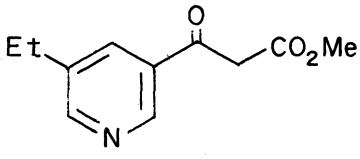
The various schemes of synthesis of deethylvincadifformine (17) assured the success of a projected synthesis of pseudovincadifformine (9), the first phase of which, i.e. the construction of pentacycle 19b, has been completed. 3-Acetyl-5-bromopyridine (21a) was converted into its ethylene ketal, whose successive treatments with n-butyllithium, ethyl iodide and aqueous acid led to 3-acetyl-5-ethylpyridine (21b). Interaction of the latter with sodium hydride and dimethyl carbonate yielded ketoester 22, whose hydrogenation over palladium gave the tetrahydropyridine 23. Treatment of the latter with sodium hydride and indoleacetic anhydride afforded 18b, whose cyclization, induced by polyphosphoric acid, led to 19b.



21a, R = Br
b, R = Et



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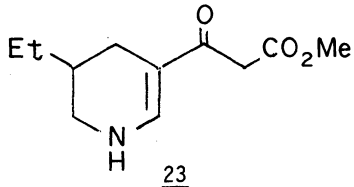

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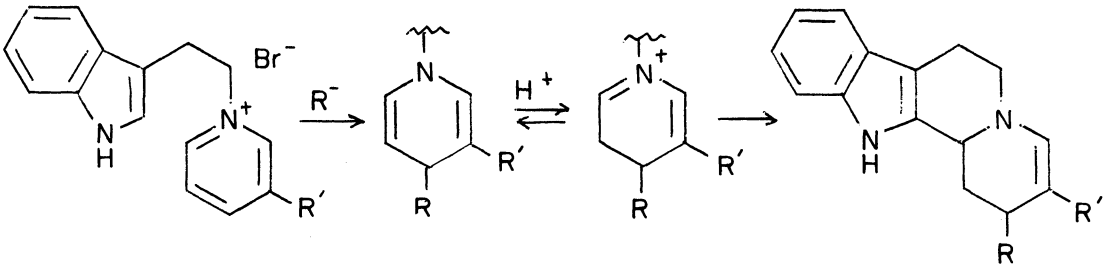
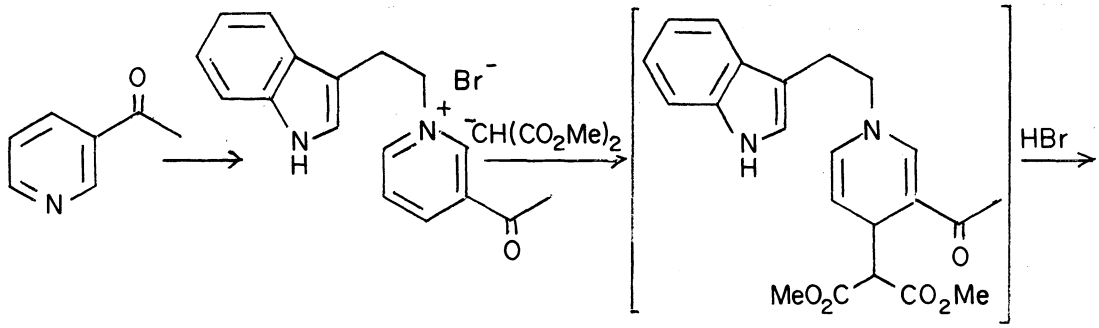
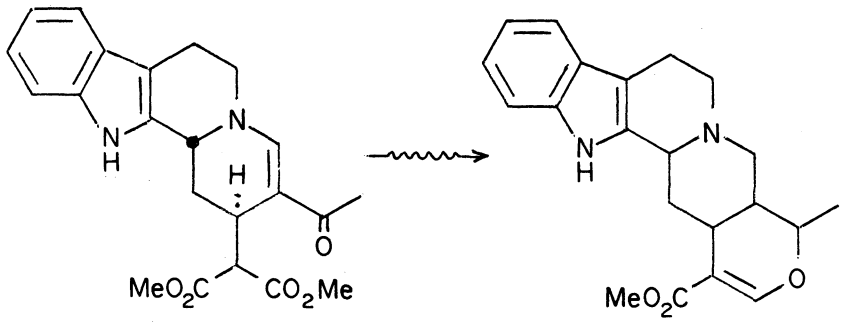
INTRODUCTION

As over the years the ideas initially adopted for the eburnamonine synthesis (vide supra) were applied to the synthesis of various indole alkaloid systems, it became obvious that the most time-consuming and intellectually least interesting task was the production of 4-alkyl or 4,5-disubstituted nicotinic esters prior to their use in the crucial, two-step, general alkaloid synthesis scheme (2). It thus became necessary to devise an alternate route of synthesis, which would permit the use of simple pyridines as starting compounds and the flexibility of introduction of needed substituents as part of a short reaction sequence. Based on the following theoretical model, a new two-step scheme, involving a condensation--cyclization sequence in lieu of the earlier hydrogenation-cyclization operation but still emanating from 1-alkyl-3-acylpyridinium salts, was adopted.



The novel reaction scheme opened a path for short, stereospecific syntheses of heteroyohimboid (25) and yohimboid (27) alkaloids (vide infra) (8,9).





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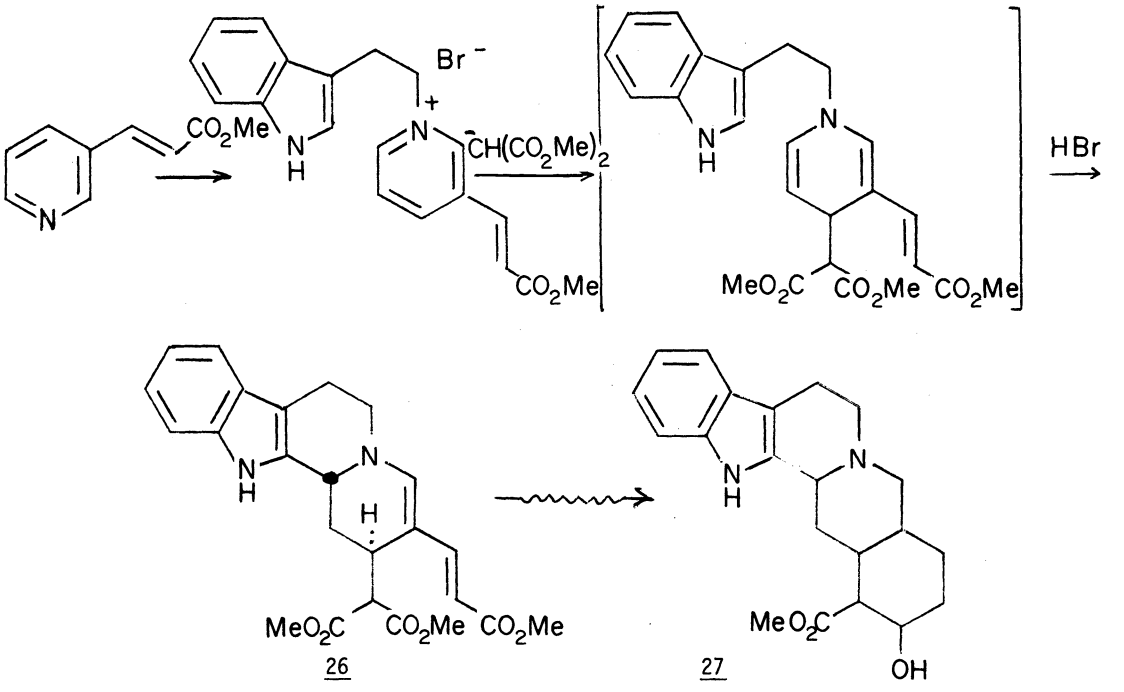
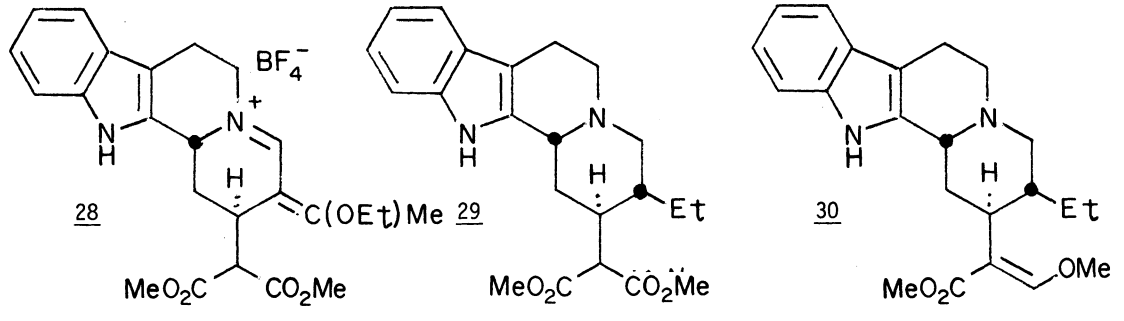


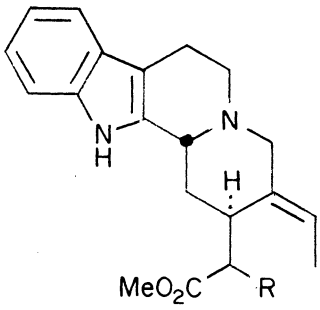
A SYNTHESIS OF HIRSUTINE

Only the corynantheioid bases remained among structurally related indole alkaloids to be submitted to the test of the new reaction sequence. The following syntheses of two representatives of this alkaloid family, hirsutine and geissoschizine, illustrate the power of the method. Exposure of vinylogous amide 24 to triethyloxonium tetrafluoroborate yielded salt 28, whose hydrogenation over palladium gave ester 29. Reduction of the latter with diisobutylaluminum hydride and treatment of the resultant aldehydoester with methanolic acid produced racemic hirsutine (30) (10).

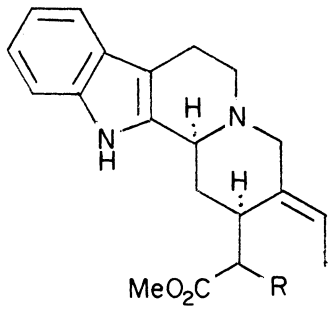


SYNTHESES OF GEISSOSCHIZINE

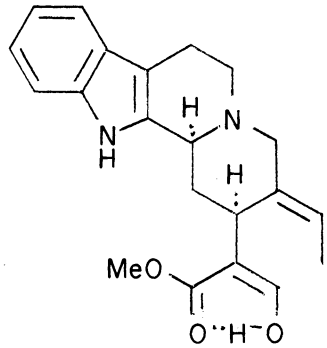
Two reaction sequences, starting with intermediates of the heteroyohimboid and yohimboid alkaloid syntheses, led to a tie-up with an earlier synthesis of racemic geissoschizine (33) (11). Reduction of salt 28 with sodium borohydride in methanol yielded an enol ether (i.e. the 1,2-reduction product), olefinic diester 31a and the latter's double bond stereoisomer (in minor amount). Alkaline hydrolysis, acid-induced decarboxylation and reesterification with methanolic acid converted 31a into ester 31b, a product obtained also from triester 26 on successive hydrolysis and didecarboxylation on refluxing an aqueous acid solution, reesterification with methanolic acid and reduction with methanolic sodium borohydride. An oxidation-reduction sequence (N_b-oxidation with m-chloroperbenzoic acid, dehydration with trifluoroacetic anhydride, and reduction with sodium borohydride in tetrahydrofuran) transformed ester 31b into its isomer 32a (10), whose earlier formylation (11) had yielded racemic geissoschizine (33).



31a, R = CO_2Me
b, R = H
c, R = $CH(OMe)_2$



32a, R = H
b, R = $CH(OMe)_2$



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An independent, third synthesis of geissoschizine avoids the loss of a carbomethoxy unit. Reduction of diester 31a with diisobutylaluminum hydride and treatment of the resultant aldehyde with methanolic acid yielded acetal 31c. The afore-mentioned oxidation-reduction sequence converted the latter into its isomer 32b, whose aqueous hydrolysis led to the racemic alkaloid (33) (10).

Acknowledgment. — The author expresses his heartfelt thanks to his collaborators, who are listed in the references, whose labors made this work possible and is indebted to the U.S. Public Health Service for constant support of the research.

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