ALKALOID SYNTHESIS[1]

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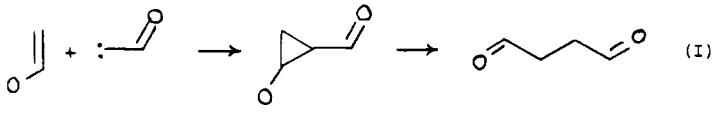
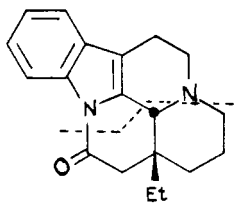
Dedicated to the memory of the late Professor Robert B. Woodward

The two-step construction of γ-dicarbonyl compounds by the copper-assisted cyclopropanation of enol derivatives with α-diazocarbonyl substances and acid-catalyzed ring opening of the resultant β-oxycyclopropylcarbonyl compounds, as illustrated in abbreviated form in equation I, has been the cornerstone of our synthesis of natural products, especially terpenes, for some time (1). It became of interest to exploit the simple reaction scheme in the realm of alkaloid synthesis, and the pentacyclic indole base eburnamonine (**1**) was chosen as the initial goal.



(I)



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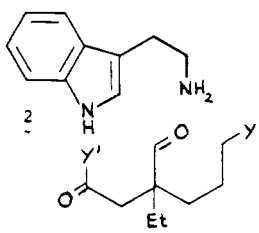
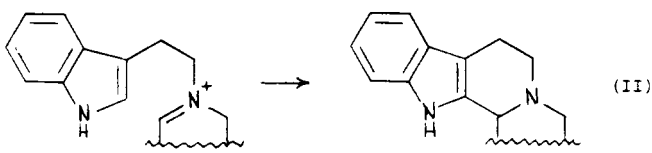


2

3

On the precondition of the eburnamonine skeleton's being constructed via one of the traditional routes of tetrahydrocarboline synthesis (equation II), the alkaloid structure could be envisaged in the shape of two halves (*cf.* dotted line in formula **1**) and, hence, its synthesis imagined in the form of a chemical combination of tryptamine (**2**) and the trifunctional intermediate **3**. In view of the latter's being a γ-diketo system, such eburnamonine synthesis appeared ideally suited as an early application of scheme I in the alkaloid field.



(II)

For the preparation of intermediate **3** along lines of scheme I, β-ethyldihydropyran (**4**) was needed as starting compound. This substance had been made earlier by a route related to scheme I (2).

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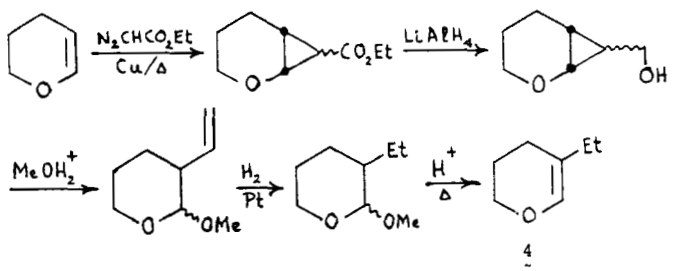
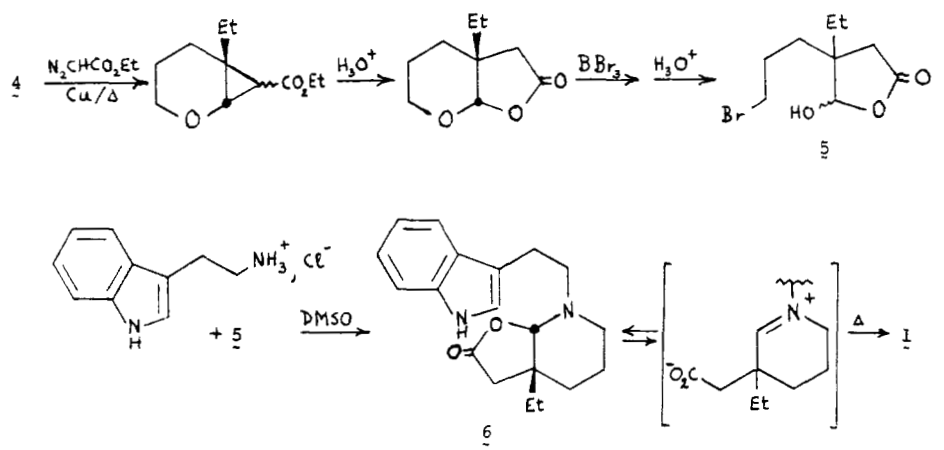
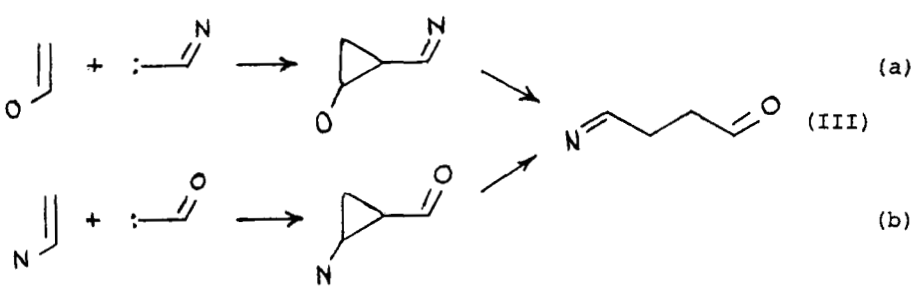


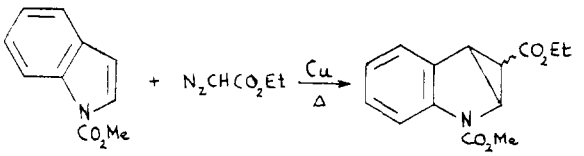
Copper-catalyzed thermolysis of ethyl diazoacetate in dihydropyran (**4**) gave a β-oxycyclopropylcarboxylate, whose acid-induced hydrolysis yielded a lactone ether. Activation of the latter by boron tribromide, followed by mild hydrolysis, led to bromolactol **5**, a masked form of the desired intermediate **3**. Exposure of **5** to tryptamine afforded the carbinolamine lactone **6**, whose heating produced (±)-eburnamonine (**1**) (3, 4).



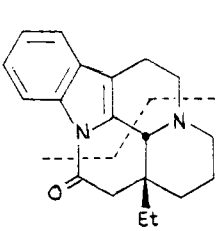
Since alkaloids are nitrogenous substances and the nitrogens become involved with the carbonyl group(s) of the γ-diketo system at some stage en route to the alkaloids, their early incorporation (or, in general, that of any heteroatom other than oxygen) into the procedure of preparation of the γ-dicarbonyl substances, e.g., via the formation of a γ-iminoketo system, assumed importance. This necessitated the modification of scheme I into scheme III.



Unfortunately, scheme III is fraught with difficulties. Thus scheme IIIa requires the use of diazoimines in the cyclopropanation step, an unattractive situation in view of diazoimines existing mostly in the form of triazoles and little being known about the thermochemistry of these heterocycles. Scheme IIIb suffers from an acid-base side reaction between enamines and diazomethyl carbonyl compounds in the cyclopropanation step, leading to β-amino-α-diazocarbonyl substances whose thermolysis yields undesired materials (5). However, as the following chemistry of a *N*-acylindole illustrates, the replacement of an enamine by an enamide overcomes the difficulty of the cyclopropanation step (6).



Dissection of the eburnamonine structure (**1**) in such a way as to exclude nitrogen-b from the indole-bearing part (*vide infra*) leads to tryptophyl halide (or arenesulfonate, etc.) (**7**) and a γ-iminocarbonyl moiety (**8**), a chemical combination of which along reaction path II could be expected to yield yet another synthesis of the alkaloid. In order to test this γ-iminoketo route of alkaloid construction, a *N*-acylpiperideine equivalent of dihydropyran **4** was needed as starting material, and its conversion into lactone **6** by reactions related to the **4**→**6** path required exploration.



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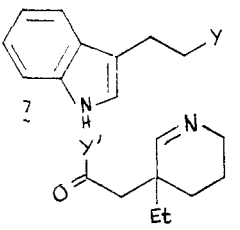
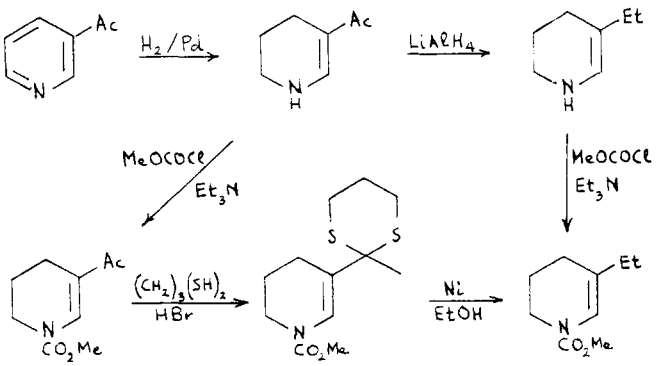


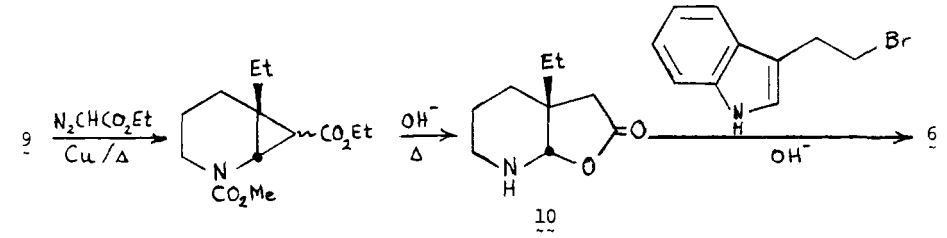
7 **8**

Hydrogenation of β-acetylpyridine yielded a tetrahydro derivative (**7**), which was transformed into methyl 3-ethy-2-piperideine-1-carboxylate (**9**) by the following two different reaction sequences.

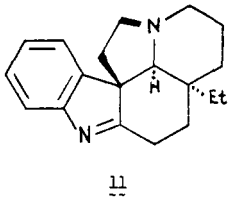


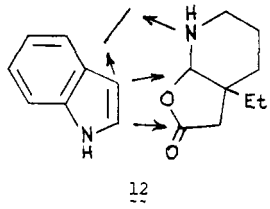
9

Copper-assisted, thermal decomposition of ethyl diazoacetate in piperideine **9** produced a β-amidocyclopropylcarboxylate, whose saponification gave carbinolamine lactone **10**. N-Alkylation of the latter with tryptophyl bromide led to **6** and hence to (±)-eburnamonine (**1**) (3, 4).

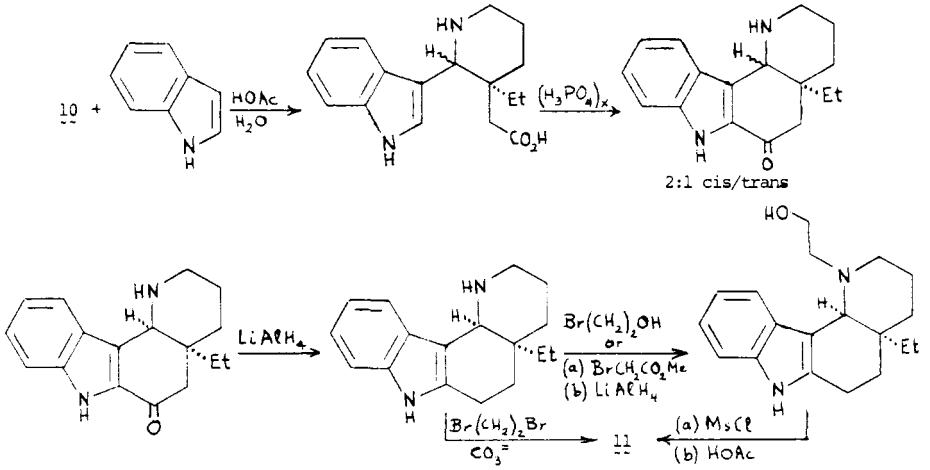


Since the eburnamonine structure (**1**) represents a rearranged Aspidosperma alkaloid skeleton, i.e., the non-tryptamine portion being attached to the indole nucleus at the latter's α-carbon and nitrogen in lieu of the β- and α-carbon sites, respectively, as, for example, in dehydroaspidospermidine (**11**), several of the intermediates in the eburnamonine syntheses seemed likely candidates for exploitation in syntheses of the Aspidosperma bases. Formula set **12** illustrates the use of carbinolamine lactone **10**, in conjunction with indole and a two-carbon dielectrophile, in such an endeavor.

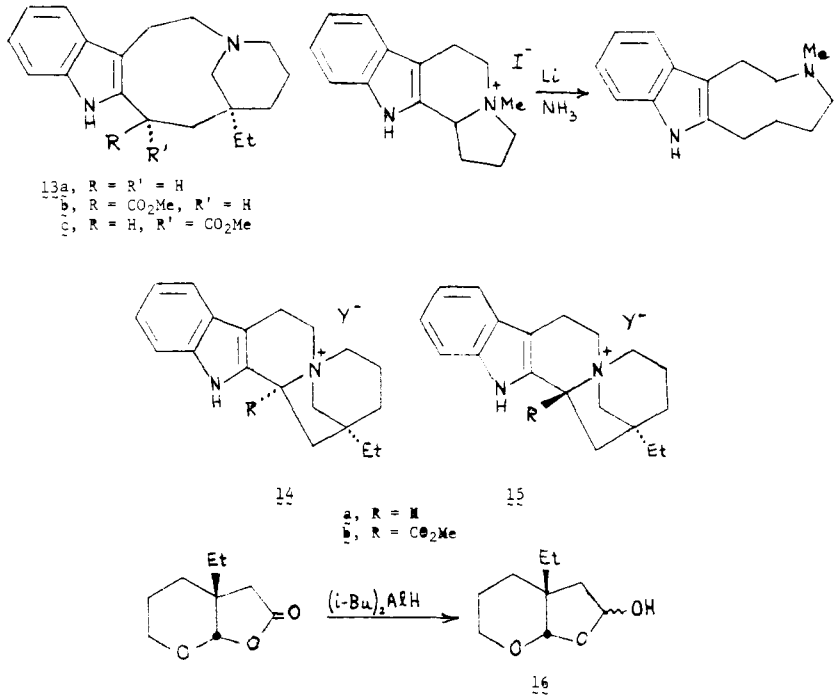




The following reaction sequence delineates the synthesis of (±)-dehydroaspidospermidine (**11**) according to this concept (8).

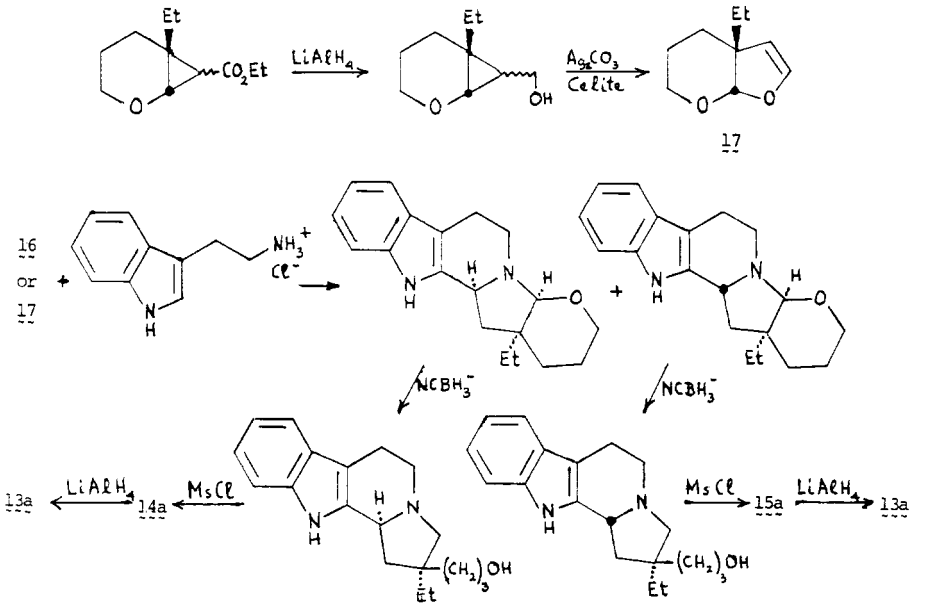


Quebrachamine (**13a**), a structurally simpler Aspidosperma alkaloid, possesses a nine-membered heterocycle as the sole challenge in any synthesis of the natural base. The facile formation of an indoloazacyclononane by the reduction of an indoloindolizidinium salt (*vide infra*) had yielded a ready response to the challenge some time ago (9) and had suggested salts **14a** or **15a** as a penultimate stage in a quebrachamine synthesis (10). Whereas the construction of the salts could be envisioned to proceed along various lines of traditional organic synthesis, the γ-diketo route of natural product synthesis now offered a new approach to the problem by permitting the use of intermediates emanating from dihydropyran **4** as starting materials.



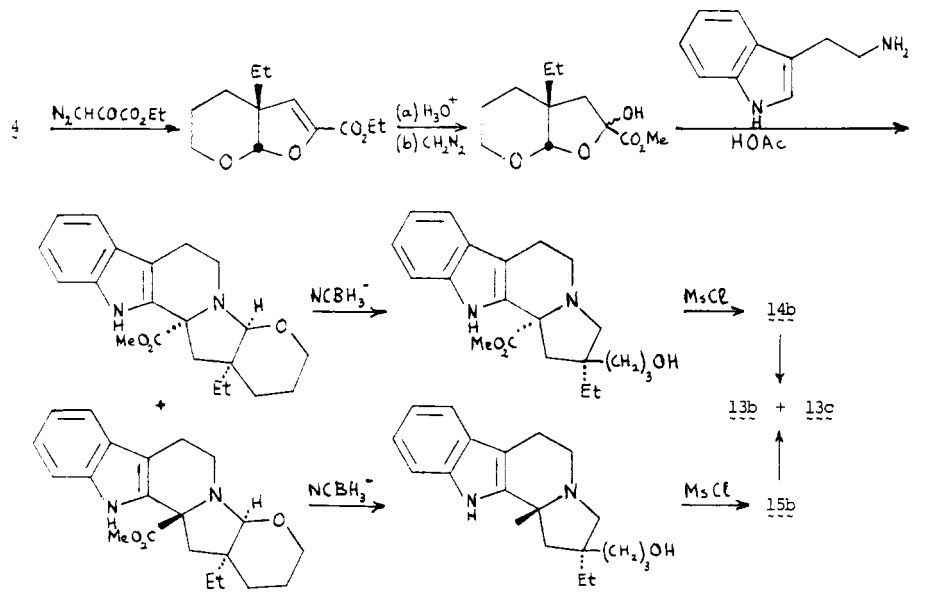
Partial reduction of the tetrahydropyran lactone and reduction-oxidation of its precursor yielded masked dialdehydes **16** and **17**, respectively. Condensation of either substance with tryptamine and reduction of the resultant carbinolamine ethers gave aminoalcohols, whose O-mesylation led to the salts **14a** and **15a** (Y = mesylate) (10). Lithium aluminum hydride reduction of the salts (10, 11) afforded (±)-quebrachamine (**13a**) (12, 13).

In view of the known, qualitatively comparable reactivity of aldehydes and α-ketoacid derivatives as electrophiles, it could be anticipated that placement of a carboalkoxy group on the reactive, masked aldehyde carbon would afford compounds capable of interacting with tryptamine and of being transformed along the above reaction path into alkaloids functionally more complex than quebrachamine (**13a**). This concept could be exploited in the following short syntheses of (±)-vincadine (**13b**) and (±)-epivincadine (**13c**) (13) as a consequence of the availability of dihydropyran **4** and the recently discovered, one-step preparation



of alkyl 5-alkoxy-4,5-dihydrofuran-2-carboxylates from enol ethers and diazopyruvic esters (14).

The experiences described in this review bear witness to the power of the γ-diketo and γ-iminoketo routes in alkaloid synthesis and constitute a good omen for their successful future applications in other natural products syntheses.



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