The Origin of Indole Alkaloids[1]

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It has long been the practice of the organic chemist to attempt to discern common denominators among classes of natural products by a process which can best be regarded as a visual dissection of the structural formulae. The most well-known example of such an exercise has been the recognition of repeating branched chain five carbon units in terpenes and the use of this observation in reverse in order to predict structures which could then be checked against the experimental results (10). The origin of the indole alkaloids in particular have been the subject of much speculation and precursors as diverse as aromatic amino acids (9), prephenic-shikimic acids (16), mevalonic acids (13), and others (11) have been proposed. In this essay the respective merits of the above ideas will not be discussed but rather attention will be focussed on whether certain indole alkaloids might not be artifacts formed, *inter alia*, in the isolation process [cf. benzylisoquinoline alkaloids (3)].

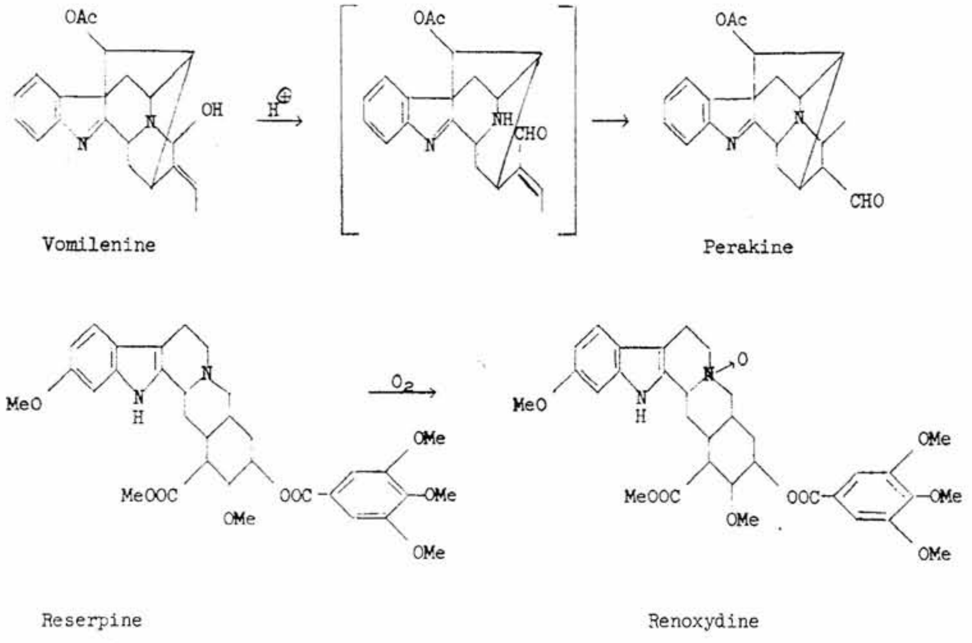

FIG. 1. *Relationships between some Rauwolfia alkaloids.*

The noun alkaloid was first coined at the dawn of experimental organic chemistry as a generic name for organic bases isolated from plants and it is not our purpose here to change this definition but rather to encourage a more critical appraisal of current isolation methodology viz. are we isolating what is there or

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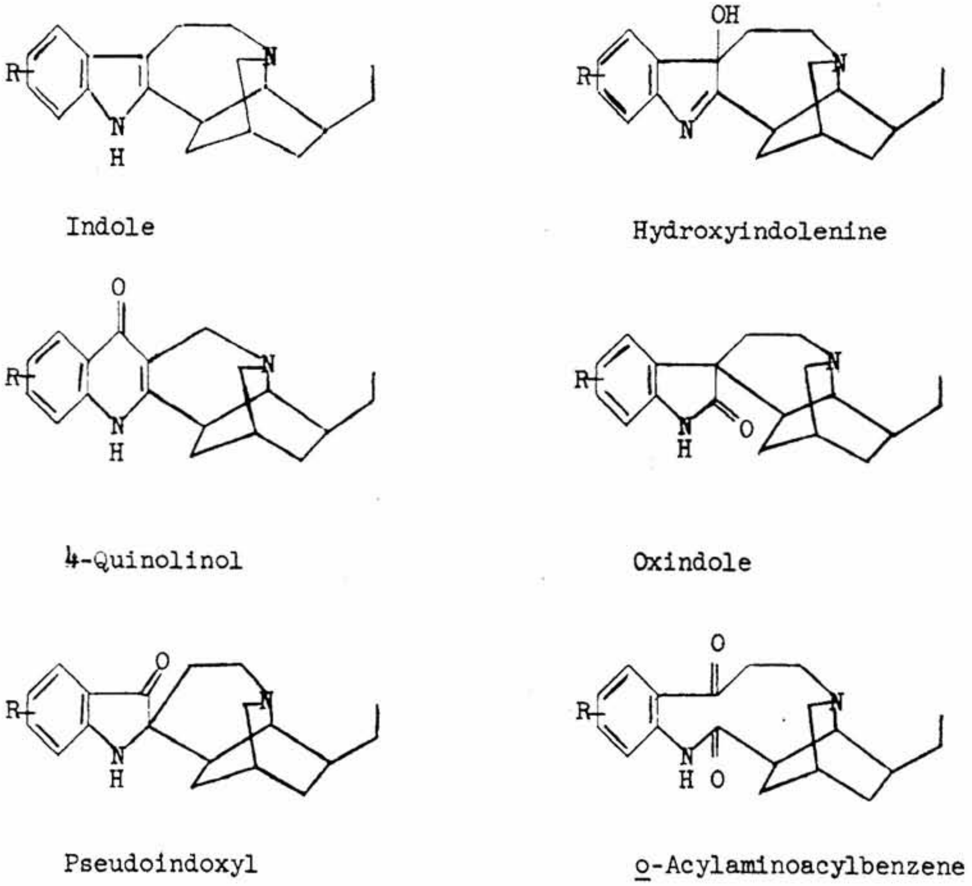
are we in addition manufacturing artifacts? It is also as well to inquire into the apparent alkaloid content of absolutely fresh plants. In many cases the plant material has been collected and dried many months before being worked up and may in addition be subjected to many changes of temperature and humidity before reaching the chemist's bench. Even with fresh plant material we may face the problem that the plant's biosynthetic machinery may have deposited in say, the bark, a primary product(s) which slowly and non-enzymatically is gradually converted into other substances which are later to be isolated and characterized by the chemist. One such example of this process might well be the formation of the dimeric curare alkaloids from a Wieland-Gumlich aldehyde-like precursor (2).



Indole

Hydroxyindolenine

4-Quinolinol

Oxindole

Pseudoindoxyl

o-Acylaminoacylbenzene

FIG. 2. *Different types of Tabernanthe iboga alkaloids.*

If artifacts are being formed during the isolation process, a clue to this is often obtained by comparing the results from different laboratories and for the purposes of illustration examples shall be cited from studies carried out at the CIBA laboratories over the last ten years.

From the manufacturing mother liquors of the isolation of reserpine from the root bark of *Rauvolfia vomitoria*, two alkaloids, perakine (15), and renoxydine (14) have been obtained. These bases have only rarely been detected by other workers (5, 7, 18) and an inspection of fig. 1 will show that both alkaloids are closely related to two other bases of *R. vomitoria*, viz., vomilenine and reserpine. The fact that vomilenine can be transformed into perakine in a weakly acid medium (12) and that one of the products of the aerial oxidation[2] of reserpine is its N-oxide, renoxydine, may mean that the two bases in question are not plant-made but man-made.

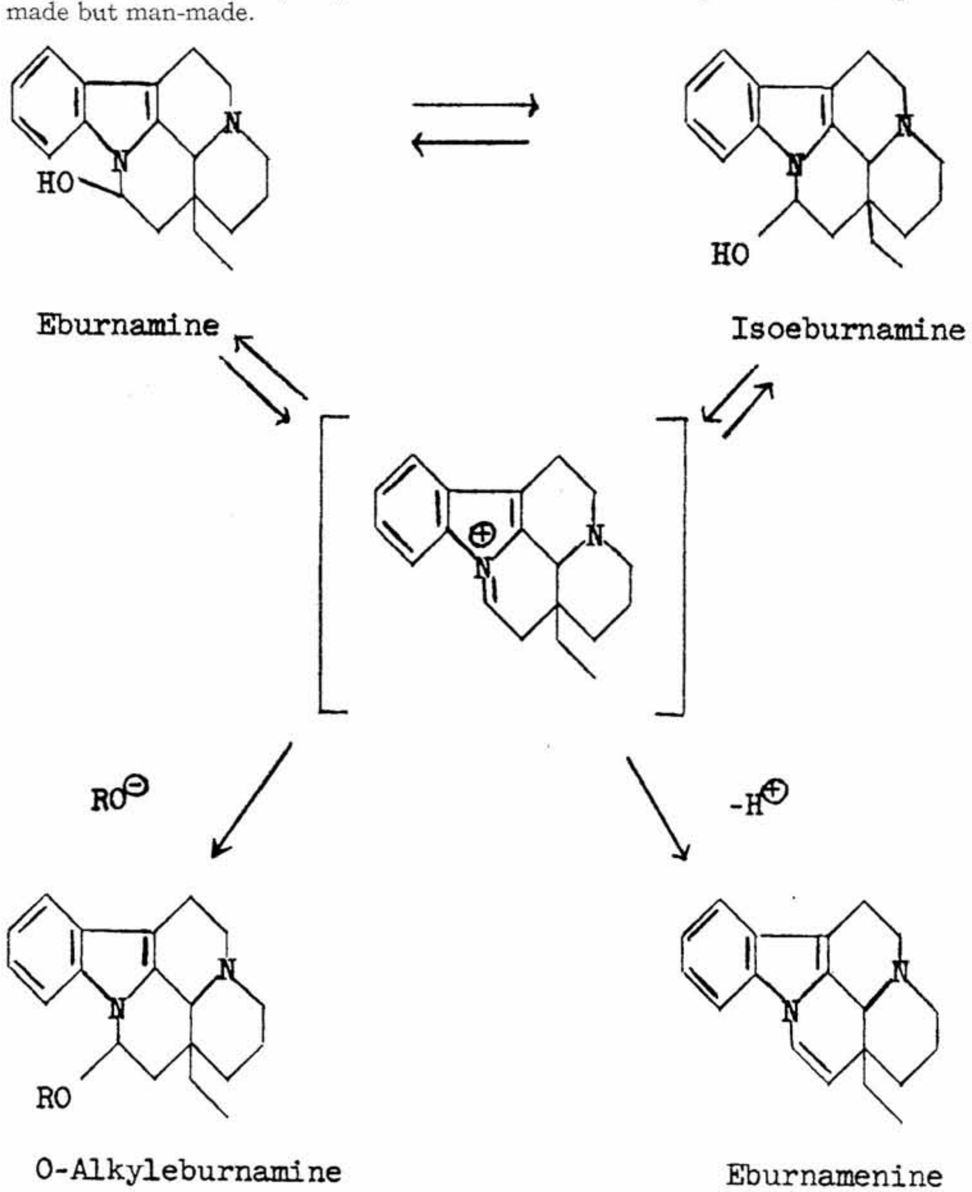


FIG. 3. *Transformations of the eburnamine group of alkaloids.*

In another study, we had examined the alkaloids of *Tabernanthe iboga* and had isolated several alkaloids (fig. 2) along with a number of derived bases which could have formed by autöoxidation followed by subsequent rearrangement (4).

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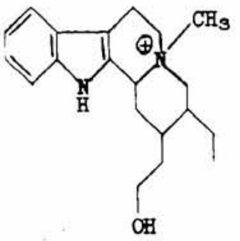
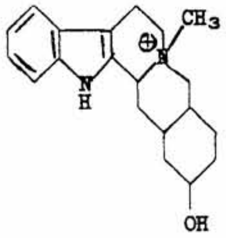
[2] P. R. Ulshafer, personal communication.

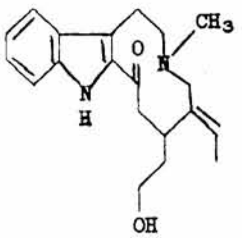
Other workers have reported similar results but since our work up was carried out on a large scale we were able to characterize more of these minor products. Even if it be argued that all these alkaloids are plant products, we cannot pass one of those tests laid down earlier, namely, in contrast to another investigator (8) we never isolated ibogaline (10, 11-dimethyoxyibogamine) but only its oxidative transformation products. The formation of these compounds, *viz.* ibogaline oxindole (gabonine) and kisantine (a dimer derived from ibogaline *o*-acylaminoacylbenzene) have their analogies in the extensive work carried out on more readily available indoles (17).



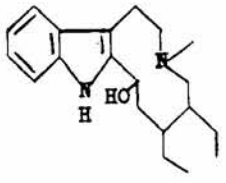
Dihydrocorynantheol methosalt



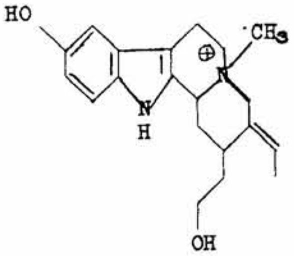
Yohimbol methosalt



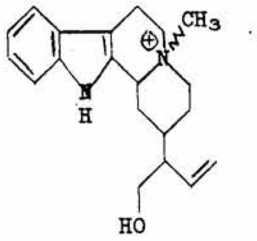
Burnamicine



Hypothetical Precursor



Huntrabrine Metho salt



Hunterburnine α and β metho salts

FIG. 4. *Some Hunteria alkaloids.*

A rather different problem is represented in the eburnamine group of *Hunteria eburnea* alkaloids (fig. 3) (1). In the presence of inorganic acid either one of the two carbinolamine alkaloids are rapidly converted into a mixture of about 9 parts eburnamine to 1 part isoeburnamine. Upon warming such an acidic solution the enamine, eburnamenine is first formed which in turn polymerises if the heating is continued. Under other conditions, e.g. in methanolic picric acid, both the above carbinolamines give rise to the same methyl ether. In the case of these alkaloids, then, it is difficult to be sure what the original alkaloid composition was.

As our knowledge of the Hunteria alkaloids became more extensive some ideas of possible biogenetic significance suggested themselves. From a perusal of fig. 4 it can see that burnamicine could have resulted from a ring opening of a yohimbinoid system, however, the reverse of this hypothesis has considerable merit. Thus, ring closure of appropriate ten membered precursors could have given rise to all the compounds in the figure, and if true were these very closures carried out in the plant or in the drug isolation process? These are questions which cannot as yet be answered but they carry the implication that perhaps substances such as yohimbine might be products of an analogous ring closure, natural or artifical. In the latter case the isolation of dimeric products would also have to be predicted, but if such derivatives are already reported they have not been recognized as such.

Great strides have been made in the last fifteen years in the detection, separation, characterization and structural elucidation of indole alkaloids. The application of techniques such as thin layer and gas-liquid chromatography coupled with high resolution mass spectroscopy bid fair to revolutionize the conduct of our work in that the amounts of material required become vanishingly small. This will make it possible to study the alkaloid composition of parts of a single plant rather than our current practice of working up a mixture of hundreds or thousands of individuals which although morphologically identical differ in many ways assumed to be trivial, such as age, location, type of soil. It is to be hoped that attention will also turn to a more thorough analysis of the total plant extractives of which alkaloids if present at all make up a very small part. We as chemists seem to have taken the easy path of taking advantage of the basicity of an alkaloid for its isolation and in not grappling with the remaining marc. There is good reason to believe that many of the neutral constituents of the plant may be as interesting chemically and perhaps even more useful to the phytochemist.

The indole alkaloids seem to be formed via a number of Mannich condensations (9) and if it be imagined that an oxidative pathway is also present lactams would result which presently escape our isolation procedure. The obtention of such lactams in the Aspidosperma field (isolated by taking advantage of the remaining weakly basic indoline nitrogen) provide support for this suggestion (6).

From the above remarks it can be seen that we can still ask many more questions than we can answer. There is still a vast amount to be discovered and discover it we shall.

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