The Source of Indole Alkaloids

Tryptophan and a monoterpenoid moiety are biogenetic precursors of the complex indole alkaloids

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The word *alkaloid* was first used to describe all organic bases, including the alkali-like substances which occur in plants. At the time this name was introduced, few of these latter substances were known, and these few all exhibited physiological activity in addition to being basic. These two characteristics, in conjunction with their complex structure, led to the opinion that the plant bases formed a well-differentiated group of chemical compounds, and the plant bases, along with other naturally occurring nonbasic nitrogen compounds, were grouped together in organic-chemistry texts under the heading alkaloids, a custom which is still practiced today (*1*). It turned out, however, that there was little obvious structural uniformity among alkaloids except those from phylogenetically related plants, and the work leading to the recognition of this fact has played an important part in the development of organic chemistry.

As a result of the comparative ease with which alkaloids can be isolated, we now recognize several thousand, most of whose structures are also known (*2*). We can see relationships between alkaloids and other plant extractives such as amino acids, amides, nitro derivatives, steroids, and nitrogen heterocycles, as well as certain exotic products from animals. But in spite of this understanding, and although the effects of alkaloids in animals can be spectacular, we remain ignorant as to their place in plant metabolism. (Because crude alkaloids have proved easy to obtain we know a great deal more about them than we do about some other, less readily isolable metabolites whose presence may be much more pertinent.)

From their structural formulae, it can be seen that alkaloids are the products of either the reaction of ammonia or amino acids with polyacetate- or polymevalonate-derived systems or the complex fusion of two or more amino acids, especially the aromatic ones (*3*). In this connection the indole alkaloids are especially interesting because nature has contrived a wide variety of heterocycles out of similar building blocks. Some 600 indole alkaloids have been isolated, most of them in the last 10 years, from about 300 plants, in the family Apocynaceae, and some also from members of the Asclepiadaceae, Loganiaceae, and Rubiaceae (*2*).

The indole alkaloids can be classified into two broad groups in which a 3-β-aminoethylindole residue is either (i) modified slightly by alkylation, ring closure, or fusion to an acetate, a mevalonate, or an *o*-aminobenzaldehyde residue, or (ii) combined with a 10-carbon system, which in the case of yohimbine (Fig. 1) has the pattern of the yohimbine moiety illustrated in Fig. 2. Some bases of the second group lack either carbon No. 17′ or No. 21 or the three-carbon unit Nos. 16, 17, and 17′, and these cases have to be fitted into any biogenetic scheme (*4*).

Not unexpectedly, it was shown that tryptophan can function as a source of at least the carbon atoms of the 3-β-aminoethylindole residue (5), but it has only just been established that the 10-carbon residue of the complex bases is monoterpenoid.

Early Theories

The mevalonate origin for the 10-carbon system could not easily have been predicted 15 years ago when yohimbine and strychnine were the only complex indole alkaloids whose structures had been well established. These alkaloids, by analogy with the classical hypothesis, so well borne out by the benzylisoquinoline bases, were assumed to originate from amino acids (*6*). It was conceivable that the pentacyclic system of yohimbine could be made from tryptophan, tyrosine, and formaldehyde, or their equivalents (*7*). Up to the formation of the pentacyclic system the chemical steps were plausible, but there was never a serious discussion as to how the tyrosine equivalent was reduced to generate the hydroaromatic ring E of yohimbine. A mechanism for the insertion of the carbomethoxyl group was also a problem. Both these difficulties were ingeniously circumvented by a later postulation that instead of tyrosine, its hydroaromatic precursor, prephenic acid (Fig. 1) could be the source of the 10-carbon system (*8*).

For the biogenesis of strychnine, whether from a phenylalanine or one of its hydroaromatic precursors, a ring fission had to take place in order to allow the formation of a 7-membered cyclic ether. It was originally suggested that the precursor of strychnine was 3,4-dihydroxyphenylalanine or its equivalent (*9*). The concept of ring fission also proved useful in explaining the origins of other, apparently unrelated bases, such as the isoquinoline, emetine (*10*), and cinchona bases (*11*). As the structures of more and more complex indole alkaloids were unraveled, it became apparent that only yohimbine and its isomers had the intact 6-membered carbocyclic ring which was the principal basis for the aromatic amino acid hypothesis; all the remaining bases were dissectable into 3-β-aminoethylindole units and carbon patterns identical to, or reminiscent of, the one cut out of strychnine.

Although there are now a large number of known alkaloids, each incorporates one of the three carbon patterns, the yohimbine, the iboga, and the aspidosperma moieties, illustrated in Fig. 2. If the aromatic amino acid hypothesis was correct, the appropriate phenylalanine would have not only to split but also to undergo further rearrangements. It seemed much simpler to assume that the precursor of the hydroaromatic portion of the indole alkaloids was a linear 6-carbon unit plus one carbon (carbons 3, 14, 15, 20, 19, 18, and 21) to which a 3-carbon unit (carbons 17, 16, and 17′) could be attached in at least three ways, as indicated in Fig. 2 (*12*). On this as-

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sumption the carbocyclic ring E of the yohimbine must have resulted from a ring closure.

It has been proposed (*13*) that the 6C + 1C + 3C moiety is specifically derived from 3 acetates + 1 formate + 1 malonate, but subsequent feeding experiments have eliminated this hypothesis (*14*). After a great deal of hard work, substituted phenylalanines, as well as their hydroaromatic precursors, shikimic and prephenic acid (*5, 15*), have also been finally eliminated as precursors.

In 1961 Thomas showed that there was a remarkable resemblance between the complex indole alkaloids and the carbon skeleton of a newly recognized group of natural products, the cyclopentano glycosides and alkaloids, which have the carbon skeleton shown in Fig. 2. He pointed out that if a cleavage between carbons 3 and 19 took place, then the carbon pattern formed would be identical with the yohimbine moiety (*16*). From the point of view of plant biochemistry, this suggestion emphasized for the first time that these alkaloids were also monoterpene derivatives.

Four years later, and after some mistrials, the validity of the mevalonate hypothesis has been confirmed almost simultaneously by several groups (*17*). Their results are summarized in Fig. 2, where the carbon atoms in the systems depicted are given the same numbers as their equivalents in yohimbine and strychnine (Fig. 1). It should be noted that the No. 2 and No. 6 positions of mevalonic acid are equivalent along the biosynthetic pathway since radioactivity of the mevalonic acid $-2-{}^{14}C$ is evenly distributed between carbons 17 and 17′ in the alkaloids. The dots are used to illustrate the location and relative amounts of radioactivity in the mevalonic acid and the end products.

Although the suspected close relationship between the yohimbine, iboga, and aspidosperma systems has now been proved, we know neither how nor when the 3-carbon unit (carbons 17, 16, and 17′) migrates from its original point of attachment at carbon No. 15 to No. 14 and No. 20 in the three isomeric types. Nor do we know what factors are responsible for bases which lack carbon No. 21, No. 17, or the 3-carbon unit itself. This problem can now be examined rationally and reasons sought also for the well-known invariance of the absolute stereochemistry at carbon No. 15 of the yohimbine group and the isolation of d-, l-, and racemic isomers of many of the aspidosperma bases. The occurrence of optical antipodes in the aspidosperma group may be due to equivalence of the two propyl groups in the aspidosperma moiety.

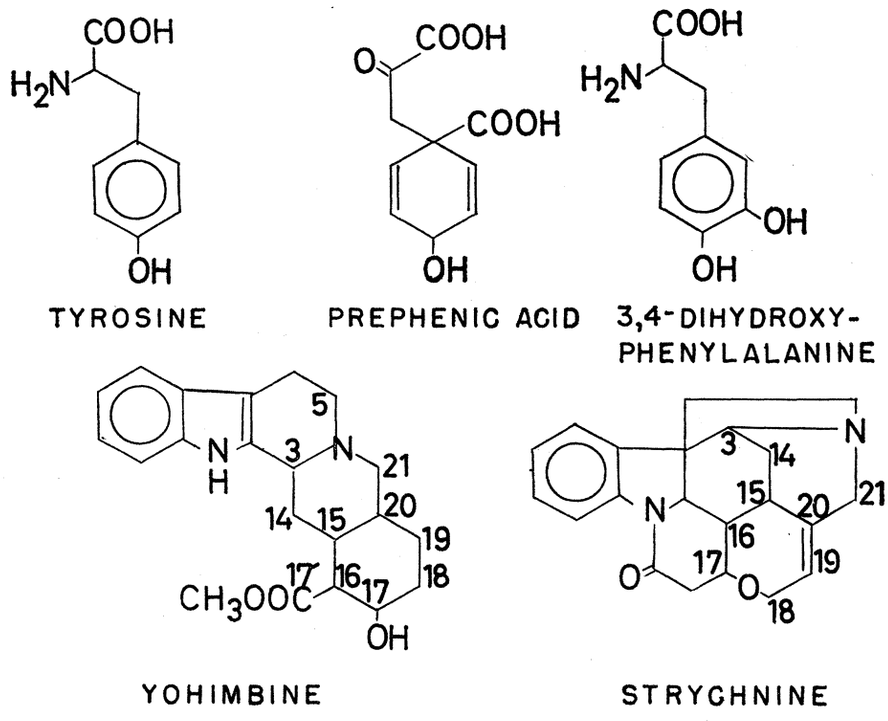

Fig. 1. Possible aromatic and hydroaromatic precursors of yohimbine and strychnine.

In the development of the chemistry of natural products, a startling variety of chemicals have been isolated, characterized, degraded, and synthesized. As information has accumulated, repetitive structural elements have been recognized, many of which were equivalent to simple cell constituents. It is upon this foundation that attempts have been made to mimic synthesis of natural products or models which would be possible in living cells by carrying out reactions in water at *p*H's near 7 (*18*). Although the recorded successes do not by themselves prove anything, they do provide a basis for preliminary biochemical work. This is an area of increasing interest to the organic chemist now that his classical challenges have been considerably lightened by advances in methodology, principally in isolation procedures and the extensive use of spectrophotometry as a tool for

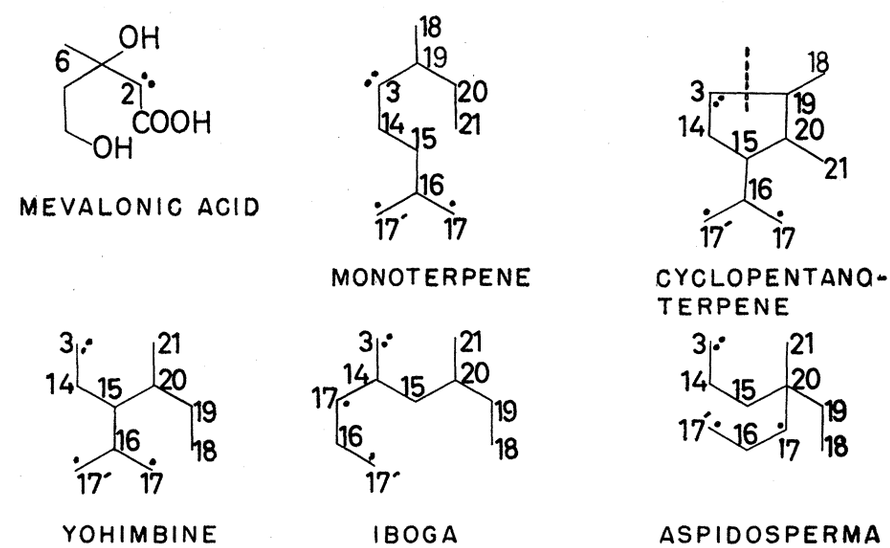

Fig. 2. Relationships between mevalonic acid, the monoterpene, and the indole alkaloid moieties.

characterization and elucidation of chemical structures. One of the most powerful methods is x-ray diffraction analysis, by which complex structures (including absolute stereochemistry) have been obtained, the chemist's contribution being the provision of the suitable single crystals. The chemist now has the time to enlarge his experience by directing more of his inquiry into the relationship between his isolates and the living plant.

Most of our knowledge concerning indole alkaloids, and most alkaloids, for that matter, is based on the analysis of large amounts of dried plant tissue. The number and kinds of bases may be somewhat different in the living plant. Moreover, they may well differ from one individual to another, for such genetic differences may not show up in the morphology of the plants. There is also evidence that some indole alkaloids may be modified during conventional isolation procedures. Chemical transformations may be produced by the solvents and chemicals used, as well as by the inevitable changes in *p*H (*19*). The most fundamental way to solve such problems is to study synthesis in plant tissue culture or tissue homogenates as a preliminary step toward the final enzymatic experiments in the test tube.

It is the basic nature of the indole alkaloids which makes them, and alkaloids in general, easy to isolate even when present in minute amounts. If neutral equivalents (lactams) of the indole alkaloids are of general occurrence in similarly small amounts, they are escaping detection, except when some factor facilitates their detection and isolation. A few lactams of the aspidosperma group are known (*20*) and other examples will be found if they are looked for. The predicted position for the lactam carbonyl is No. 5 in yohimbine (see Fig. 1). In our own work we have not found any lactams, but our important analytical tool has been pharmacological activity; such lactams, if present in the plants that we have looked at in detail, have no striking effects on small animals.

Perhaps the tracing out of the participation of mevalonic acid in the biosynthesis of indole alkaloids will help to put this fascinating group of compounds into proper perspective with regard to plant metabolism as well as revealing non-basic congeners.

After many years of speculation, it is now certain that the complex indole alkaloids are monoterpenoid derivatives. This discovery marks the first major step towards an understanding of the function of indole alkaloids in plants.

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Quality versus Quantity in American Medical Education

The Flexner doctrine is dead. As sickness increases, we need quantity production of high-quality physicians.

Greer Williams

Most, though not all, American health and medical authorities agree that there is a doctor shortage. After 15 years of debate, that is progress.

The American Medical Association itself has intelligently backed off from its earlier position that there is no shortage—that there are merely fewer doctors in some places than in others. Opposition to the training of more physicians has been beaten down, and the annual crop of new M.D.'s has gradually increased. A half dozen new medical schools opened in the last decade; a dozen or more are in the making. In 1963, Congress for the first time provided federal aid to education in the health professions, and in 1965 it greatly increased such aid.

Efforts to date have met about one-third of the annual need for new doctors forecast by *Physicians for a Growing America*, a study published by the Public Health Service in 1959 (*1*). This so-called Bane Report became medical liberals' bible of medical manpower needs. According to its predictions, medical schools will have to increase the present 275,000 physicians to 330,000 by 1975 simply to keep up with the population growth. Inasmuch as American medical schools are now graduating physicians at the rate of nearly 75,000 every 10 years, it would appear that Frank Bane's objective is being met (*2*).

Where, then, is the generally agreed upon doctor shortage? Many accept its existence, but few attempt to demonstrate it. For example, the latest study of medical education, *Planning for Medical Progress Through Education*, published by the Association of American Medical Colleges (*3*), also assumes

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