

**Molecular Biology
Biochemistry
and Biophysics**

3

Trevor Robinson

The Biochemistry of Alkaloids

Second Edition



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Second Edition

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Preface

The alkaloids were of great importance to mankind for centuries, long before they were recognized as a chemical class. The influence they have had on literature is hinted at by some of the quotations I have used as chapter headings. Their influence on folklore and on medicine has been even greater. The scientific study of alkaloids may be said to have begun with the isolation of morphine by Sertürner in 1804. Since that time they have remained of great interest to chemists, and now in any month there appear dozens of publications dealing with the isolation of new alkaloids or the determination of the structures of previously known ones. The area of alkaloid biochemistry, in comparison, has received little attention and today is much less developed.

There is a certain amount of personal arbitrariness in defining "biochemistry", as there is in defining "alkaloid", and this arbitrariness is doubtless compounded by the combination. Nevertheless, it seems to me that in any consideration of the biochemistry of a group of compounds three aspects are always worthy of attention—pathways of biosynthesis, function or activity, and pathways of degradation. For the alkaloids, treatment of these three aspects is necessarily lopsided. Much has been learned about routes of biosynthesis, but information on the other aspects is very scanty. It would be possible to enter into some speculation regarding the biosynthesis of all the more than 4,000 known alkaloids. I have for the most part limited consideration to those alkaloids for which there is experimental information. In a few cases, however, rigid adherence to this principle would have resulted in the exclusion of important

compounds that seemed worthy of mention even if only in a purely speculative way.

In the 13 years since the first edition of this book was published, knowledge of biosynthetic pathways has expanded mostly in the sense that details have been filled in rather than that any surprising new pathways have emerged. There is also a body of work with cell-free systems and even a few highly purified enzymes that had barely begun 13 years ago. The next likely advance will come as regulatory mechanisms are discovered using these isolated systems.

The alkaloids are best known for their pharmacological effects, but most of these effects are only slightly interpretable in terms of biochemistry. However, this is the fastest growing area represented here. The number of literature citations in the area of biochemical pharmacology of alkaloids has increased almost tenfold since the first edition, and Chap. 15 threatens to become a book in its own right.

I thank all those who helped in the preparation of this book—some who helped with their criticism and positive suggestions, others who helped with their forbearance in putting up with my withdrawal from many other endeavors.

The literature has been reviewed through June 1980, with a few later references. I shall appreciate having any errors or omissions called to my attention.

Trevor Robinson

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Chapter 1

Introduction

Glory to God for dappled things—
All things counter, original, spare, strange;
Whatever is fickle, freckled (who knows how?)
With swift, slow; sweet, sour; adazzle, dim;
He fathers forth whose beauty is past change:
Praise Him.

Pied Beauty, GERARD MANLEY HOPKINS¹

The alkaloids are a group of naturally occurring organic compounds containing nitrogen. Their name, meaning "alkali-like," was given them because most of them are basic in nature and form salts with acids. Basicity is a common characteristic of organic nitrogen compounds, which can be regarded as derived from ammonia by the substitution of organic radicals for hydrogen. The simple amines are considered a class apart from the alkaloids, although with increasing complexity of structure the dividing line between amine and alkaloid tends to become indistinct. According to one definition, alkaloids contain nitrogen in heterocyclic rings while the nitrogen of amines is aliphatic. Compounds such as colchicine and mescaline would be excluded from the alkaloids by such a definition, but the exclusion seems inadvisable on the basis of historical usage. Introduction of the term "protoalkaloid" for a group of borderline compounds leaves very few compounds unclassified. A few otherwise impeccable alkaloids, such as rutaecarpine and ricinine, that have electron-withdrawing functional groups either adjacent to or conjugated with their nitrogen atoms, do not show the characteristic of basicity.

The chemical classification of alkaloids is based on their carbon-nitrogen skeletons. Some of the commonest skeletons are shown in Fig. 1-1. The chemistry of alkaloids is outside the scope of this book. Many textbooks of organic chemistry and heterocyclic chemistry offer an adequate introduction to the general chemical properties of alkaloids. Except for some increase in complexity, alkaloids show no striking peculiarities to set them

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apart from simpler compounds with the same functional groups. Readers interested in the proof of structure and synthesis of alkaloids are referred to the comprehensive treatise of Manske et al. [28] or the books of Pelletier [47] and Dalton [8]. The last book, in particular, is organized according to metabolic pathways of biosynthesis. The Chemical Society (London) publishes annual Specialist Reports reviewing the literature on alkaloids; and two encyclopedic works are valuable for finding information on both structures and occurrence of alkaloids [12,48].

Physically, most alkaloids are colorless, crystalline solids slightly soluble in neutral or alkaline aqueous solution but readily soluble in acid or in organic solvents such as ether, chloroform, or ethanol. Although most alkaloids are basic, a few N-oxides and some that have carbonyl groups adjacent or conjugated with nitrogen are neutral and can be missed in the customary isolation procedures. A few alkaloids (e.g., nicotine and coniine) are liquid at room temperature, and some (e.g., berberine and sanguinarine) are colored.

Many alkaloids are optically active, and the fact that they rarely occur as racemic mixtures is taken as evidence that they are synthesized at least partially by enzymatic catalysis. In some cases both enantiomorphs are known to be naturally occurring, but each from a different source. Because of their polar, basic nature, most alkaloids occur dissolved in plant saps as cations which, on evaporation of the sap, form salts with the organic acids that are also present. Just as some plants are noted for containing certain alkaloids, they may be noted for containing a preponderance of certain

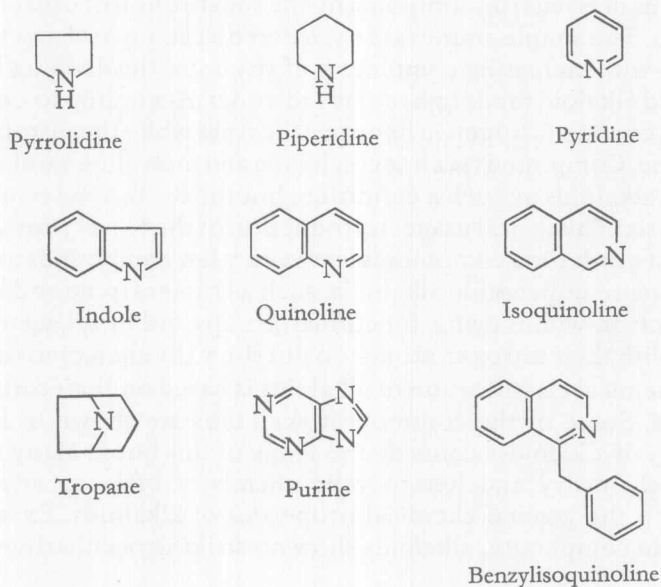


Fig. 1-1. Some common alkaloid ring skeletons

acids; therefore, a particular alkaloid may occur most often as the salt of a particular acid. However, there appears to be no necessary correlation between the biosynthesis of the alkaloid and of its accompanying acid.

The distribution of alkaloids in nature, while not completely random, cannot be described in any simple and unambiguous way. Higher plants are the chief source of alkaloids, yet alkaloids are also known from club mosses (*Lycopodium* spp.), horsetails (*Equisetum* spp.), and fungi [53]. Surveys of ferns and bryophytes have revealed that alkaloids are lacking or extremely rare [46,59]. Results suggestive of the presence of alkaloids are given by bacteria, but none have actually been identified [29]. Certain nitrogenous compounds occurring in animals are sometimes referred to as animal alkaloids, but many of them are relatively simple bases such as histamine, noradrenaline, and spermine. However, a few compounds with more typical alkaloid structures have been found in animals. Some of these may simply be derived with slight structural modification from plants eaten by the animal, but the possibility that some are synthesized in the animal body from simple precursors cannot be ruled out. The best examples of animal alkaloids are the salamander compounds (see Chap. 13) and the quinazolones excreted as a repellent by certain millipedes. Arthropod alkaloids are reviewed in [56,63]. Marine worms and bryozoans have also produced some peculiar alkaloids [5,19]. The extremely powerful toxins of puffer fish and certain toads could also be classed as alkaloids [2,72]. Among the seed plants a greater variety of alkaloids has been found in dicotyledons than in monocotyledons or gymnosperms. It has been estimated that about 20%–30% of all plants contain alkaloids, but the accuracy of any such estimate is limited by the sensitivity of the analytical methods used. Among the dicotyledons there are also considerable differences between taxa. Not a single alkaloid has been found among the thousands of plants in the orders Pandanales, Salicales, and Fagales [21]. In the family Solanaceae about two-thirds of the species have alkaloids [57]. A famous alkaloidal family, the Apocynaceae, has produced nearly 900 different alkaloids [21]. A convenient listing of plants and alkaloids isolated from them is found in [70,71].

Three times as many alkaloid-producing plant families are found in the tropics as in temperate zones, but this only reflects the greater number of tropical plants generally, since the ratio of tropical alkaloid families to total tropical families is the same as the ratio for temperate families [34]. Although some alkaloids are taxonomically quite restricted in occurrence, others are found widely in unrelated plants. A statistical analysis of 3600 alkaloid plants showed caffeine occurring in the largest number of families, lycorine in the largest number of genera, and berberine in the largest number of species [69]. Some conflicting ideas on the geographical distribution of alkaloid-bearing plants can be found in [23,24] and [32].

When the same alkaloid has been found in several different plant species, it is tempting to assume an evolutionary relationship between the plants and therefore to describe the occurrences as “homologous.” However, decisions about homology must depend more on knowledge of biosynthetic pathways

and mechanisms than on knowledge of end products. Far too little is known to make any generalization that the same alkaloid is always produced in the same way. If different pathways or mechanisms are found in different plants to lead to the same alkaloid, the occurrences must be described as "analogous," and they then can offer no information regarding phylogenetic relationships. A striking example of what must be an analogous occurrence is the presence of the same hallucinogenic indole alkaloids in ergot and morning glory (cf. Chap. 10). Mothes has stressed the important point that the presence of an alkaloid in a plant shows not only that the biosynthetic pathway is present but also that the plant can tolerate the alkaloid. The absence of an alkaloid does not mean necessarily that the biosynthetic pathway is absent; it may mean that an active degradative pathway is also present [36]. The foregoing considerations show that taxonomy can be based only approximately on accumulated products of metabolism. For the most part, classical taxonomy has taken little account of alkaloid distribution. If the same type of alkaloid is observed in two plants already thought to be related, its presence is used as evidence to support the relationship; its occurrence in two plants thought to be unrelated is cited as an example of independent evolution. The appearance of two apparently quite different structural types of alkaloid in supposedly closely related species cannot be taken as grounds for questioning the closeness of relationship, since it is not difficult to visualize a single-gene mutation setting off an entirely different biosynthetic pathway—for instance, using many of the type reactions of the original pathway but in a different order or with a different starting material (see Chap. 2). Still, alkaloids of similar structure are often found within plants of a given taxonomic grouping, and the lower the grouping in the taxonomic hierarchy, the greater the similarities in structure. Practically, this generalization is useful in locating plant material for the study of alkaloid biochemistry. Theoretically, it probably does argue for similar biosynthetic pathways in plants that are otherwise similar.

The occurrence of "chemical races" has been frequently observed among alkaloid plants. A chemical race is an intraspecific variety distinguished from other plants of the same species only by its composition. The intensive breeding of medicinal plants for high content of some active constituent has produced some of these races, but others appear to have arisen naturally and to have persisted in geographical isolation. Some examples of chemical races are tabulated as follows:

Species	Distinguishing features
<i>Duboisia myoporoides</i>	Hyoscyamine or hyoscyne or norhyoscyamine
<i>Sedum acre</i>	Sedamine and nicotine, or sedridine
<i>Hordeum vulgare</i>	Ordenine or N-methyltryamine
<i>Papaver somniferum</i>	Narcotine or absence of narcotine
<i>Claviceps purpurea</i>	Ergotamine or ergocristine

Many examples can be found in [60]. Extensive breeding of the oil poppy [44] and forage lupines [14] for low alkaloid content has not succeeded in producing plants that are completely alkaloid-free. In a few cases thorough genetic analysis of alkaloidal plants has been carried out, and some such studies have been useful in delineating biosynthetic pathways [67]. Differences in ploidy have sometimes resulted in differences in composition. It has been consistently found among *Datura* and *Atropa* spp. that tetraploid plants have a higher alkaloid content than diploid plants. [54].

The formation of alkaloids varies notably from tissue to tissue within the same plant and also changes during the course of ontogeny. This kind of variability as well as the occurrence of chemical races can account for disagreements over the presence or absence of a particular alkaloid in a given plant [38]. In general, alkaloids tend to accumulate in:

1. Very active tissues
2. Epidermal and hypodermal tissue
3. Vascular sheaths
4. Latex vessels

Many examples of alkaloid localization are cited by James [17] and Mothes [35]. It must be emphasized that the sites of accumulation are not necessarily the sites of synthesis. Nicotine, for example, is synthesized in the roots but is translocated and accumulates in the leaves. In other cases the complete synthesis may require cooperation of different plant tissues. Thus, those species of tobacco that have nornicotine in their leaves make nicotine in the root, translocate it to the leaves, and then demethylate it (see Chap. 4). Tropane alkaloids first made in the roots of *Datura* spp. are extensively modified in the leaves [35]. Although prominent in very actively growing tissues, alkaloids are found not in the youngest cells of these tissues but in somewhat older cells which are becoming vacuolated. The presence of alkaloids in vacuoles rather than the surrounding cytoplasm was amply shown in early studies and has more recently been demonstrated using modern techniques such as electron microscopy [7,30,41]. Vacuoles isolated from *Chelidonium majus* take up sanguinarine from the surrounding medium, and it has been suggested that vacuoles act as traps for alkaloids because phenols in the vacuolar sap form complexes with alkaloids [30]. Besides in vacuoles, alkaloids have been observed attached to cell walls and to thickenings in xylem vessels [66,41]. In some plants, alkaloids are confined to special cell types [20,40,74]. In the opium poppy there are alkaloidal vesicles in laticifer cells, and these vesicles appear to form by a dilation in the endoplasmic reticulum [40]. An overall theory to account for the way alkaloids are distributed in a plant has been proposed by McKey [33], based on the assumption that alkaloids are protective substances and that specialized locations are adaptive. As a result of translocation and of different steps taking place in different tissues, it may be quite difficult to determine the real site of alkaloid synthesis. Grafting experiments and culture of isolated plant parts have been the two techniques giving the

greatest amount of useful information, but difficulties exist with both approaches. The chief problem is that negative findings may not necessarily mean that the cultured or grafted organ has no synthetic ability, but only that alkaloid synthesis requires contributions from other parts of the plant. Interspecific grafts have been known to result in the appearance of alkaloids that are absent from either graft partner growing singly [26,67]. The same phenomenon also occurs in tissue cultures [1,15]. Experiments where labeled alkaloids were fed to plants have shown that alkaloids native to the particular plant migrate and become localized where they are normally found, but foreign alkaloids may become immobilized at the site of application [43,65]. There are certainly exceptions to this observation, though, because on the one hand alkaloids do cross interspecific graft unions, and on the other hand, alkaloids applied externally can be toxic to plants that normally contain them internally [37].

Ontogenetic changes in alkaloid content of plants have been known for many years and are the basis for various empirical rules about the proper time for harvesting plants whose alkaloids have commercial value. The most general principle of ontogenetic change is that alkaloid content increases rapidly at the time of cell enlargement and vacuolization, the increase being followed by a slow decline in concentration during senescence. This pattern has been observed in several tissues of different plants, although leaves have been most often studied. The time of maximum alkaloid content will differ according to whether concentration or total amount is stated, with the concentration maximum coming earlier. Several other circumstances may have striking effects on the overall ontogenetic pattern. The initiation of flowering may stop or inhibit alkaloid formation [35] or stimulate it [39]. A young leaf on an old plant may reflect in its alkaloid content the plant's stage of development rather than its own [17], but in some perennial, woody plants leaves follow a pattern of declining concentration through the growing season [50,75]—even to containing no detectable alkaloid in the fall [50]. There is no consistent pattern for the ontogeny of alkaloids in developing seeds and germinating seedlings, although unfertilized ovules of alkaloid plants normally have alkaloids. In some species the alkaloid concentration may decrease after fertilization, giving mature seeds with little or no free alkaloid (e.g., *Nicotiana*, *Papaver*, *Hordeum*, *Datura*, and *Erythroxylum* spp.). The word “free” is included in the previous sentence because some seeds that have been traditionally regarded as not containing alkaloids do, in fact, contain bound forms of them [13,68]. Seeds of other species may contain high concentrations of alkaloid (e.g., *Lupinus* and *Physostigma* spp.). During germination, alkaloid synthesis may begin within a few days (*Hordeum*) or only after several weeks (*Datura*). The alkaloid content of alkaloid-rich seeds may actually decline in the early stages of germination—both in concentration and, more significantly, in total amount per plant. A striking example of ontogenetic change is offered by *Catharanthus roseus*, which contains virtually no alkaloid in its seed, then develops alkaloids until at 3 weeks after germination they are present throughout the

plant. They then disappear almost completely and reappear at 8 weeks [38]. Besides changes over longer periods, there have also been observed cyclic diurnal variations in alkaloid content, with certain alkaloids more than doubling or halving their concentration within a few hours [51].

Several external factors have been found to influence alkaloid content, but direct biochemical explanations for these influences are mostly lacking. Light is, of course, essential for growth of higher plants, so that its beneficial influence on total alkaloid content is expected. However, chlorophyll formation and alkaloid formation are not always influenced in the same way by light [16]. For the most part the influence of light is probably indirect; however, more specific light effects have also been observed. Etiolation increases both concentration and total amount of ricinine in *Ricinus communis*. In the light *Catharanthus roseus* has vindoline as its predominant alkaloid, but in the dark this alkaloid is absent [38]. The effect of photoperiod on alkaloid content are obviously related to the effects of photoperiod on initiation of flowering. *Lycopersicon glandulosum*, a short-day plant, if grown under long days contains five times as much tomatine as under short days. Species less dependent on day length for flowering show a lesser response of tomatine content to photoperiod [55]. Such findings raise the possibility that tomatine serves specifically as an inhibitor of flowering and acts as a chemical mediator of photoperiodic flower induction. Another interpretation would be that decomposition of tomatine gives rise to other steroids related to pregnenolone which serve as flowering hormones (see Chap. 13). With tobacco, long days favor alkaloid production; this is largely a phytochrome response rather than due to increased photosynthesis [62].

Effects of nutrition and plant growth substances on alkaloid content have received some attention, with the rather commonplace conclusion that factors favoring growth generally favor alkaloid formation [51,67]. It does appear that nitrogen supplied to plants in the form of ammonium salts is somewhat better than nitrates for increasing alkaloid formation [17]. This result suggests a rather direct use of ammonia in alkaloid synthesis, while nitrate acts more indirectly by increasing overall growth. A potassium-calcium antagonism has also been observed. A high K/Ca ratio favors protein synthesis, but a low ratio favors alkaloid synthesis [17]. Effects of more unusual ions such as lithium [10] and manganese [11] have also been observed. Such growth factors as kinetin, gibberellins, and auxins have been investigated. Several of these growth regulators increase the alkaloid content of lupine embryos in sterile culture [27]. Auxins depress the nicotine content of tobacco [73]. Gibberellins have diverse effects, depending on the plant and the experimental conditions [51].

Tissue cultures and cell-suspension cultures derived from alkaloid plants are being used more and more as a convenient tool for studying alkaloid biosynthesis, but also with the hope that they can be used in production of some commercially valuable alkaloids. So far it must be concluded that alkaloids are especially difficult to produce in this way [3,6,58]. Some cultures grow well but produce little or no alkaloid. Sometimes supple-

mentation of the medium with necessary substrates or growth factors has been able to increase alkaloid production. Sometimes alkaloids are accumulated only if dedifferentiation occurs because specialized cells are required for alkaloid synthesis or storage [42]. At the theoretical level many fascinating findings have resulted, but industrial exploitation still seems far off.

Any discussion of the function of alkaloids in plants runs the danger of becoming teleological, but the matter has been of too much interest to too many people to ignore it altogether. Most often alkaloids have been called nitrogenous "waste products" analogous to urea and uric acid in animals. Their occurrence in vacuoles rather than the living parts of protoplasm supports such a view. However, nitrogen is often scarce for plants, and its reutilization is more often the rule in plant metabolism. The metabolic activity of some alkaloids also puts them in a class apart from ordinary waste products. Fluctuations in concentration and frequently rapid conversion to other products have been observed [51]. Knowledge of alkaloid catabolism is still scanty, so that generalizations are not possible. However, there is evidence that some of the pyridine alkaloids can serve as precursors of nicotinic acid and thus can be reservoirs of this vitamin (see Chap. 4). A possible role of alkaloids in protecting plants against herbivores has been frequently proposed, and a few examples can be given in support of such an idea [17,25,52], but there are many more examples of plants whose high content of alkaloids confers no protection against their major enemies. Defense against microbial pathogens is another proposed function; the generalization has been put forward that most resistance to herbivores is constitutive but most resistance to microorganisms and nematodes is induced [22]. Although alkaloids are constitutive, some do have activity against fungi [22], bacteria [61,64], nematodes [4], and even viruses [61,69]. The role of alkaloids as detoxication products appears plausible in some instances, as in the case of alkaloids that may remove such active molecules as indole-3-acetic acid or nicotinic acid from sites where they could unbalance metabolism. Because of the great diversity among alkaloids, it seems likely that theories which give plausible functions to several of them cannot be universally applicable. Furthermore, it is impossible to state what kind of evidence is acceptable for proving the function of an alkaloid. Complete removal of an alkaloid from a plant, where experimental manipulation has made this possible, usually has no effect on the plant; of course, 70%–80% of all plants never contain alkaloids. However, alkaloids do have effects on plant growth—usually inhibiting such processes as elongation or seed germination [9,31,49]. Some of these inhibitions could be significant in the competition between plants [45].

It is evident that biosynthesis of alkaloid molecules often must require energy and in some instances the presence of highly specific enzymes. The perpetuation of such a low entropy system through the course of evolution seems to call for an explanation in terms of useful function, but no generally adequate explanation has been forthcoming.

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