Chapter One

The Nature and Definition of an Alkaloid

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1. INTRODUCTION

What is an alkaloid? After discussing this question with several alkaloid chemists, a colleague suggested that “an alkaloid is like my wife. I can recognize her when I see her, but I can’t define her.” Indeed, defining what the term alkaloid means today is no easy task [1, 13]. The reason is that over 5000 alkaloids of all structural types are known. No other class of natural products possesses such an enormous variety of structures. Steroids, for example, are all modeled on a few skeletal types. The same holds true for triterpenes, flavonoids, or polysaccharides. But alkaloids exhibit dozens of different skeletal types. This situation causes extraordinary difficulty in defining alkaloids so they may be readily recognized and differentiated from other classes of organic nitrogen-containing compounds.

This chapter treats the nature and definition of an alkaloid as the class of compounds is perceived by chemists and pharmacognosists. The term alkaloid was coined in 1819 by the pharmacist W. Messner and meant simply, alkalike (Middle English alkalie, from Medieval Latin alcalis, from Arabic al-kalkil = ashes of saltwort, from qalal, to fry). The first modern definition by WINTERSTEIN and Trier [14] described these substances in a broad sense as a mixture, nitrogen-containing compounds of either plant or animal origin. “True alkaloids” were defined as compounds meeting four additional qualifications:

1. The nitrogen atom is part of a heterocyclic system.
2. The compound has a complex molecular structure.
3. The compound manifests significant pharmacological activity.
4. The compound is restricted to the plant kingdom.

Alkaloids frequently occur as salts of plant acids such as malic, meconic, or...
1. Introduction

Quinic acid. Some alkaloids occur in plants combined with sugars (e.g., solanine from potato, Solanum tuberosum L., and tomato, Lycopersicon esculentum Mill.), whereas others are present as amides (e.g., piperine from black pepper, Piper nigrum L.) or as esters (e.g., cocaine from coca leaves, Erythroxylon coca L.) or as tertiary amine oxides. Compounds satisfying the definition of a "true alkaloid" are restricted to certain families and genera of the plant kingdom, rarely being distributed in larger groups of plants. Though about 40% of all plant families contain at least one alkaloid-bearing species, alkaloids have been reported in only 9% of over 10,000 plant genera. Among the angiosperms they occur abundantly in certain dicotyledons and particularly in the families Apocynaceae (dogbane, quebracho,
pereira bark, Asteraceae = Compositae (groundsel, ragwort), Berberidaceae (European barberry), Fabaceae = Leguminosae (broom, gorse, 'shrub', lupine, butterfly-shaped flowers), Lauraceae (rosewood tree), Loganiaceae (African jasmine, Strychnos species), Miconiaceae (moonseed), Papaveraceae (poppies, opium poppy), Papaver somniferum L.), the first pure alkaloid isolate (Sertter in 1805); strychnine (2, Strychnos nux-vomica L. and S. ignaci Berg.; quinine (3, Cinchona bark, various Cinchona species); and cocaine (4, poison hemlock, Conium maculatum L.). The latter three alkaloids were isolated by Pelletier and Caventou in 1817, 1820, and 1826, respectively. Cocaine is of special historical interest in that it was the compound responsible for the death of Socrates in 400 B.C., when he drank a cup of tea made from poison hemlock, and it was the first alkaloid to be synthesized (Ladenburg, 1886). An example of an alkaloid of modern vintage is reserpine (5, Rauvolfia serpentina (L.) Benth. ex. Kurz.), a compound widely used as an antihypertensive agent and as a tranquilizer.

2. PLANT BASES SOMETIMES EXCLUDED

Unfortunately there is no sharp distinction between alkaloids and certain other naturally occurring plant bases. Most chemists do not regard such simple and widely distributed plant bases as methylamine, trimethylamine, and other straight-chain amines as alkaloids. Many authorities also exclude the betaines (e.g., 6, choline; 7, and muscarine). By aperine, amanita muscaria L. ex. Fr. J[3]. Though these compounds are biosynthesized from amino acids and are basic, they are designated as biological amines[15], biogenic amines[16], or protocalkoaloids[16] because their nitrogen is not involved in a heterocyclic system. Aliphatic diamino, triamine, and tetratetramino compounds such as putrescine (9), spermidine (10), and spermine (11) are likewise excluded by most authorities, though macrocyclic derivatives of these polyamine bases are regarded as alkaloids (see Section 9.5). Some authorities even exclude the phenylalkylamines, such as o-phenetidylamine (12, miltier, Vicia album L.), hordenine (13, barley, Hordeum vulgare L.), dopamine (14, banana, Musa sapientum L.), (+)-epephedrine (15, "Ma Huang,") Ephedra sinica Stapf.), mesamine (16, "peyote," Lophophora williamsii (Lemaire) Coulter), and tryptamine (17, Asaica sop.][3]. In certain cases, the distinction between what is an alkaloid and what is not is arbitrary. For example, thiamine (vitamin B1, 18), though a heterocyclic nitrogenous base with profound physiological activity, is
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2. Plant Bases Sometimes Excluded

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\text{Spermidine (10)} & : \text{Spermine (11)} \\
\text{B-Phenylethylamine (12)} & : \text{Homodine (13)} \\
\text{Dopamine (14)} & \\
\text{\textit{L}-\textit{Epinephrine (15)}} & : \text{Muscine (16)} \\
\text{Tyramine (17)} & : \text{Theanine Hydrochloride (18)}
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\text{\textit{L}-\textit{Epinephrine (15)}} & : \text{Muscine (16)} \\
\text{Tyramine (17)} & : \text{Theanine Hydrochloride (18)}
\end{align*}
\]
The Nature and Extraction of an Alkaloid

Caffine (19)  Theophylline (20)  Theobromine (21)

\[ \begin{align*}
\text{Caffeine (19)} & : \quad \text{N} & & \text{N} \\
\text{Theophylline (20)} & : \quad \text{O} & & \text{N} \\
\text{Theobromine (21)} & : \quad \text{O} & & \text{N}
\end{align*} \]

Not classed by most writers as an alkaloid because it is almost universally distributed in living matter.

Other examples of compounds sometimes excluded are the purine bases caffeine (19, coffee bean, tea leaves, cocoa), theophylline (20, tea leaves), and theobromine (21, cocoa beans, Theobroma cacao L.). These plant bases contain heterocyclic nitrogen and possess physiological activity, but because they are unrelated biosynthetically to the amino acids, certain writers do not consider them alkaloids [3]. Heterocyclic nitrogen-containing compounds modeled on monoterpenoid (e.g., β-skytanine, 22. Skytanthus aceitus Meyer; and actinidine, 23. Actinidium polygama Franch.); sesquiterpenoid (e.g., α-deoxyxymphetidine, 24. Naphthapiguanum DC.); and sterpenoid skeleton (e.g., acocinine, 25. Acocinum species) are regarded by most chemists as alkaloids, but are considered by some chemotaxonomists as pseudoalkaloids because these compounds are not related biogenetically to the amino acids [3]. Two further examples illustrating the extreme position that a few authors embrace are ricinine (26, castor bean, Ricinus communis L.) and gentianine (27) [12, 17]. Because ricinine is the only alkaloid in R. communis, and because the only alkaloid the majority of the species of Gentianaceae contain is gentianine, these compounds are elated as pseudoalkaloids! The guiding principle invoked is that a true alkaloid-bearing plant must contain more than one alkaloid, the main component being accompanied by smaller amounts of a number of biogenetically related compounds [12, 17].
4. Terrestrial-Animal-Derived Alkaloids

3. NEUTRAL COMPOUNDS AS ALKALOIDS

Because the word alkaloid means alkalikke, basicity might be regarded as the hallmark of an alkaloid. Arbitrary conventions, however, have gained a secure foothold for many neutral compounds now are classified as alkaloids. A prime example is colchicine (28), a minor constituent of Colchicum autumnale L. (Eur.), an essentially neutral compound (pKa 12.55) in which the nitrogen is involved in an amide group. The only factors justifying inclusion as an alkaloid are its valuable medicinal properties and its restricted botanical distribution. Otherwise it does not fit the classical definition of an alkaloid. Another amide-type alkaloid is piperine (29) from black pepper (Piper nigrum L.). Other examples of neutral or weakly basic compounds that are usually classified by chemists as alkaloids are lactams, such as nicotine (26), mentioned above; certain N-oxides, such as the tightly active antitumor agent vinblastine N-oxide (30), Heliotropium indicum L.), and the di-N-oxide triquinine (31, Lupinus albus L. and L. luteus Rydb.); betaines [e.g., tachrydine (32), alfalfa, Medicago sativa L., and Chinese artichoke, Stachyurus polystachion L.] and trigonelline (33, garden peas, oats, peanuts, coffee beans, hemp)]; and certain quaternary nitrogen salts such as the aporphine alkaloid lastrifoline chloride (34, Cocculus lastrifolius DC); some authorities even accept certain nitro compounds, e.g., the aristolochic acid (35 and 56, Aristolochia species) [18-22].

4. TERRESTRIAL-ANIMAL-DERIVED ALKALOIDS

Alkaloids originally were considered basic compounds derived from plant sources. Certain purists still insist that alkaloids are found only in plants! Until
recently, compounds with alkaloid-type structures were found only rarely in animals. Today the situation has changed, with dozens of compounds with classical alkaloid-type structures having been isolated from animal sources. A brief survey of some of these compounds will illustrate the rich variety of alkaloidal structural types available from animals.

4.1. Salamander Alkaloids

The earliest authenticated example of the isolation of an alkaloid from animals is that of "salamandrine" from the skin glands of the European fire salamander (Salamandra maculosa Laurenti) [23, 24]. "Salamandrine" later turned out to be a mixture, from which the alkaloids samandarine (35) and samandaron (36) were isolated [25–27]. Subsequent work led to the isolation of other interesting structural variants: samandridine (39), cycloneosamandaridine (40), and cyclo-
4. Terrestrial-Amlal-Derived Alkaloids

Neoammandrolone (41) [28-30]. These compounds are basic, form salts, and manifest the usual properties of alkaloids. To insist that because these compounds were not isolated from a plant they are not alkaloids is irrational.

4.2. Anuran Alkaloids

Toxic steroidal alkaloids occur not only in salamanders but also in certain anurans (frogs, toads, and tree frogs) [31, 32]. The skin of the brightly colored Colombian arrow-poison frog, *Phyllobates auroaenea*, contains a highly lethal venom from which two major toxins, a cardiotoxin and a neurotoxin, both of which are steroidal alkaloids, have been isolated: batrachotoxin (42); LD₅₀ 2 µg/kg (mouse) and homobatrachotoxin (43); LD₅₀ 3 µg/kg) [33]. The skin extracts of another Colombian frog, *Dendrobates histromicus* Berland, yields several unusual acetylenic alkaloids, among which are histronotoxin (44), dihydrohistronotoxin (45) and gephyrotoxin (46) [34, 35]. The cyclohexadecasquamine alkaloids pumilotoxin C (47) has been isolated from the Panamanian frog *D. pumilio* [35, 36]. Subsequent studies on the companion alkaloids pumilotoxin A and pumilotoxin B have shown them to have the indolizidine structure 48 and 49, respectively [37].

The parotid gland of the common European toad, *Bufo bufo bufo* (B. vulgaris L.), yields a number of cryptentine-type alkaloids, among which are bufotenin (50), O-methylbufotenin (51), and dehydrobufotenin (52). This toad also elaborates bufotxin (53) a conjugate of a bufotxin with somatostatin.
Of interest is the occurrence of bufotenin (58) and O-methylbufotenin (59) in several plant species used by Indian tribes of South America and the Caribbean Islands as a ceremonial narcotic snuff called cohoba (e.g., in Piper aduncum Benth, P. colubrina, P. excelsa, P. marocarpa) [36-41], as well as in the fungus Amanita mappa Batsch. [42, 43], and in human urine [44].

4.3. Mammalian Alkaloids

A few alkaloids have been isolated from mammals. Thus (−)-doxystrophanthin (24) and (+)-castanosmine (54) have been obtained from the Canadian beaver (Castor canadensis) [45], and the interesting ames type pyridine structure muscophyridine (55) has been isolated from the scent gland of the musk deer (Moschus moschiferus) [46].

4.4. Arthropod Alkaloids [47]

4.4.1. Ant Alkaloids. The fire ant, Solenopsis invicta (= saevissima) F. O. Smith, secretes a powerful venom from which several 2,6-dialkylpyperidines (e.g., 56-
60) have been isolated [48, 49]. These compounds are structurally related to cassine (61), an alkaloid isolated from the tropical shrub Cassia excellos Shrad.

The large neotropical ant Odontomachus baueri (Fabricius) discharges a chocolate-flavored secretion from which the dialkylpyrazine (62) has been isolated. The related species O. brumneus (Patton) furnishes the trialkylpyrazines 63-66 [50]. These pyrazines are potent stimulators of alarm behavior for...
The Nature and Definition of an Alkaloid

Odonomachus workers and probably tubular are used also as defensive substances. The volatile fraction of the Argentine ant *Tridemnomyrmex humilis* (Mayr) contains piper constituents that have been identified as 2,5-dimethyl-3-isopropylpyrazine (62), and (E)-2,5-dimethyl-3-arylpiprazine (67). [51, 52]

The Texas leaf-cutting ant *Atta texana* elaborates a trail pheromone that has been shown to be methyl 4-methylpyrrole-2-carboxylate (68). [53] This alkaloid is also the major trail-active compound of the ant *Atta cephalotes* as well as several other ant species of the tribe Attini.

Pharaoh's ant, *Monomorium pharaonis*, produces a trail pheromone from which the all-cis indolizidine alkaloid (69) has been isolated. [54, 55]

4.4.2. Millipede Alkaloids (Diplopoda). Provocation of the European millipede *Glycerinus marginata* causes discharge from the dorsal glands of a defensive
4. Territorial-Animal-Derived Alkaloids

Gomerin (70) R=CH$_3$ Polyzonamine (72) Nitropolyzonamine (73)
Homogomerin (71) R=CH$_3$CH$_2$

secretion containing the quinazolines gomerin (70) and homogomerin (71), compounds that the millipede synthesizes using anthranilic acid as a precursor [56-58]. The defensive secretion of the millipede Polyzoonium roseolatum contains polyzonamine (72), as well as nitropolyzonamine (73) [59, 60].

4.4.3. Ladybug Alkaloids (Coccinellidae). Ladybugs (Coccinellidae), when molested, secrete hemolymph droplets of reflex bleeding at their joints. This

Coccineline (74) Precoccineline (75) Convergins (76)

Hepodonine (77) Myscinine (78) Propylene (79)

Adamsine (80) Purethamine (81)
bitter-tasting secretion affords an efficient protection against predators. The hemolymph of the European ladybug (Coccinella septempunctata) has been shown to contain the cis, trans, cis-N-oxide coccineline (74) and its free base, precocine (75 [61, 62]). Araphesine alkaloids corresponding to each of the other two ring systems have been isolated from different species of ladybugs. Thus, *Hippodamia convergens* affords the cis, cis, trans isomer, convergent (76), and its free base, hippodamine (77) [63], whereas *Myrtha oevus* contains the trans, trans, cis isomer, myrthine (78) [64]. This alkaloid has also been isolated from the soil snail, *Achatina fulica* [65].

The ladybug *Propylea quatuordecimpunctata* produces the alkaloid propyline (79) [66] and *Adalia bipunctata* elaborates the homotropine alkaloid adaline (80) [67].

Since coccineline (74) and its base (75) have been found in the eggs and larva of *C. septempunctata* but not in the adults upon which the ladybugs feed, these alkaloids, most probably, are synthesized by the insect itself [64, 68]. These araphesine alkaloids are not limited to ladybugs. Thus, panatherine (81) and closely related compounds have been isolated from the woody shrub *Panathera coriambosa* Brag. [69].

4.4.4. Water Beetle Alkaloids (Dytiscidae). The prothoracic-defensive gland of the water beetle *Bybius fenestratus* affords methy-8-hydroxyquinoline-2-carboxylate (82) [70]. This alkaloid manifests powerful antiseptic activity and is apparently used by the beetle to prevent penetration by microorganisms.

4.4.5. Beetle Alkaloids (Sphaphyllinae). Several species of beetles of the genus *Pseud-vis* elaborate a powerful cytotoxic and vesicant, pederin (83), which can be isolated from the hemolymph of the insect [71, 72]. The beetle *P. fascipes* contains in addition to pederin the closely related compounds pseudoepidopepin (84) and pederone (85) [73, 74]. Incorporation of (1,3-Cl and 2,3-C)acetate into pederin, followed by appropriate degradation schemes, suggest that pederin and its analogs are biosynthesized via a polyketide pathway.

4.4.6. Butterfly Alkaloids (Lepidoptera). All the arthropod alkaloids mentioned above are of endogenous origin. Certain species of arthropods elaborate pheromones derived from exogenous pyrrolizidine alkaloid precursors. The male Danaeine butterflies disperse pyrrolizidine-derived pheromones during courtship. The pyrrolizidinone alkaloid 86 has been identified in the hair-pencil secretions of *Lycia cerae cerae* and *Euploea pilipus bosvica*, where it elicits olfactory receptors in response to the female antennae and serves as the chemical messenger that induces mating behavior in the female. The related pyrrolizidinone alkaloids 87, 88, and 89 have been detected in several Danaeine butterflies [77].

Some butterflies of the family Pieridae are known to utilize pyrrolizidine-containing plants as larval host plants. Alkaloid 87 is present in the scent organ of *Uchiza pilosillodes* and *U. orris*, and alkaloid 88 is also present in *U. orris* [78].
5. Marine Alkaloids

Recently, alkaloidal structures have been isolated from several marine organisms, both plant and animal. A few of the compounds encountered to date will be summarized to illustrate the variety of alkaloidal structural types available from marine sources.

5.1 Dinoflagellate Alkaloids

The so-called red tides consist of high concentrations of toxic dinoflagellates, particularly *Gymnodinium catenatum* in the north Atlantic and *G. catenella* in the south Atlantic. Filter feeders, such as shellfish, concentrate the toxic constituents of the red tide and when consumed by organisms higher on the food chain, such as man, can lead to severe and sometimes fatal poisoning. The toxic principles...
isolated include the alkaloids saxitoxin (90, LD₅₀ 5–10 μg/kg in mouse), gonyautoxin-II (91), and gonyautoxin-III (92) (79–81). Saxitoxin has also been isolated from Alaskan halibut clams (Saxidomus giganteus), California mussels (Mytilus californianus), and oyster clams (M. arenaria).

### 5.2. Blue-Green Algae Alkaloids

The shallow-water variety of *Lyngbya majuscula* Gomont elaborates lyngbytoxin A (93), a potent inflammatory and vesicatory agent [82]. Lyngbytoxin A is the first indole alkaloid from a marine plant and has a structure similar to that of telodiol B (94), produced by certain Streptomyces strains.

From Hawaiian *Lyngbya majuscula* Gomont, Mariner and co-workers [23] have isolated two amide alkaloids, maunselamides A (95) and B (96). From this same alga, Moore *et al.* have isolated the amide alkaloid 97 [84].

6. Club M

A *vulpinus* is not a similar species. The structure of these plants is not related to each other.

### 5.3. Tetrapod

The ovine *Acantholoma nitidum* is the most toxic of the food fish species. It is a common species of elegantly shaped and slow-moving fish.
6. Club Moss Alkaloids

A supralittoral variety of the blue-green alga *Hydella caespitosa* produces two unusual carbazole alkaloids, hyellazole (98) and 6-chlorohyellazole (99) [85]. These structures are different from carbazole alkaloids isolated from terrestrial plants.

5.3. Tetrodotoxin

The ovaries and liver of the puffer fish (swellfish; Japanese: *fugu*), *Spheroideidae rubripes*, *S. vescicularis*, etc., contain the alkaloid tetrodotoxin (100), one of the most toxic low-molecular-weight poisons known [86]. Poisoning from this toxin has long been a serious problem in Japan, where the puffer fish is highly prized as a food item. Tetrodotoxin has also been isolated from the goby fish, *Gobiodes criniger*, from Taiwan [87] and from the California newt *Taricha torosa* (formerly *Trisanus torosa*), as well as several other newts such as *T. sierrae* and *T. rivularis* [88]. It has also been isolated from the skins of frogs of the genus *Ateles* from Costa Rica [89].

6. CLUB MOSS ALKALOIDS

Alkaloids are rarely found in cryptogamia. The club mosses, which are among the lowest forms of plant life, are an important exception, for the genus
Lycopodium is a prolific producer of alkaloids. With over 100 alkaloids now known, a few of the structural types are illustrated by annotinine (101, L. annotinum L.), lycopodine (102, L. complanatum L.), cernuine (103, L. cernuum L.) and lycoctone (104, L. annotinum L.) [90-92].

7. FUNGAL ALKALOIDS

Alkaloids of a variety of structural types have been isolated from fungal sources. Perhaps best known are those produced by ergot, the dried sclerotium of the fungus Claviceps purpurea (Fries) Tulssae, which grows parasitically on rye and certain other gramineous crop plants.

Examples of a few of the structural types elaborated by C. purpurea include chanoclavine-I (105), agroclavine (106), ergonovine (ergometrine) (107), and the peptide alkaloid ergo-crinine (108) [93, 94]. Aspergillus fumigatus furnishes agroclavine and chanoclavine-I in addition to edelmaclovine (109). Penicillium convolvulaceum produces alkaloids of a different structural type, rugulovasines A (110) and B (111). Penicillium roquefortii elaborates isofumigaclavine A (112), as well as the diketopiperazine alkaloid roquefortine (113) [95].

Several of these ergot alkaloids are also produced by higher plants of the family Convulvaceae; the genera Ipomoea, Argyreia, Rivina, and Stichocarca.
1. Fungal Alkaloids

Chromoclavine-I (105)

Agroclavine (106) R=OH

Elymoclavine (109) R=OCH3

Ergonovine (107)

Ergocristine (108)

Regelovasine A (110) R=H

Regelovasine B (111) R=H

Isotropanovacine A (112)

Roquefortine (113)
are particularly good sources. Thus chanoclavine-I (1105), ergonovine (107), and
eymoclavine (109) are produced by certain Ipomoea species.

The diterpene alkaloid gliotoxin (114), which is an inhibitor of viral
RNA synthesis, is elaborated by the fungi *Trichoderma viride*, *Penicillium*
terribilis, and *Aspergillus fumigatus* (96). Other related alkaloids are arantoin
piperazone alkaloid is mycelianamide (111, *Penicillium geesefulvum*) (99).

Green peanuts furnish a fungus, *penicillium versicolosum* Peyssonel, that
elevator a toxic metabolite, versicolosulin (119). This alkaloid represents the
first naturally occurring example of the octahydro-2H-pyrindo[1,2-a]pyrazine
system (99). Recently the fungal strain *Penicillium herquei* Fig. 372, has been
shown to produce herqueine (120), an alkaloid that inhibits platelet aggregation
induced by adenosine diphosphate, but shows no antimicrobial activities (101).

Gliotoxin (114)  Arantoin (115)

Echinulin (116)  Sporidesmin A (117)

Mycelianamide (118)  Verigostrigotoxin (119)

Marcuelin (120)

8. BACTEII

Very few alk.
inducing exc.
certain other
soybeans, oat.
The bact.
alkaloid, pyo

9. FACTOII

9.1. Source

Does the sou.
ary bearing c.
the same cor.
actidine (2).
species of an
*Phloxazus posterum* an
(58) occurs in
fungus *Aman* 
Piriodespius sp.
led is not at
ceased to be
source of a c.
compound is

9.2. Bioenerg

Nettoenergy
vectors, pers.
chemists and
biogenetical-
8. BACTERIAL ALKALOIDS

Very few alkaloids have been reported from bacterial cultures. The chlororxin-producing exotoxin tabtoxin (121) is produced by Pseudomonas habat and certain other phytopathogenic Pseudomonas species. It is toxic to tobacco, soybean, oat, and timothy [102].

The bacterium Pseudomonas aeruginosa elaborates a deep-blue-colored alkaloid, pyocyanine (122) [103].

9. FACTORS INFLUENCING CLASSIFICATION AS AN ALKALOID

9.1. Source

Does the source of a compound (i.e., plant, animal, fungus, or bacterium) have any bearing on its being classified as an alkaloid? I believe not. In certain cases the same compound has been isolated from both plants and animals. Thus actinidine (23) occurs in the plant Actinidia polygama, in two Conusmera species of ants [104], and in two species of beetles, Hesperus semipus and Philetus pallidus [105]. (3)-Deoxynuxphuridine (24) occurs in the plant Nuphar japonicum and in the scent gland of the Canadian beaver. Similarly, bulotin is found in several species of Psilotenia, in the toad Bufo bufo bufo, in the fungus Amanita mappa, and also in human urine. Is a sample of bulotin from Psilotenia species an alkaloid, whereas a sample of the same compound from the toad is not an alkaloid? Obviously an alkaloid derived from a plant does not cease to be an alkaloid because it also occurs in an animal. As a consequence, the source of a compound is not significant in determining whether a particular compound is an alkaloid.

9.2. Biogenesis

Heterocyclic nitrogen-containing compounds modeled on monoterpeneoid, sesquiterpeneoid, and diterpeneoid skeletons are not classed as alkaloids by some chemists and chemotaxonomists because these compounds are not related biogenetically to the amino acids. The concept of characterizing alkaloids by
their mode of biosynthesis led Hegnauer to propose the following definition for the purposes of plant taxonomy:

"Alkaloids are more or less toxic substances which act primarily on the central nervous system. They have a basic character, contain heterocyclic nitrogen, and are synthesized in plants from amino acids or their immediate derivatives. In most cases they are of limited distribution in the plant kingdom." [3]

In the arbitrary classification scheme followed by such writers, "true alkaloids" are those compounds in which decarboxylated amino acids are condensed with a non-nitrogenous structural moiety. These primary precursors amino acids are ornithine, lysine, anthranilic acid, phenylalanine/tyrosine, tryptophan, and histidine. The alkaloids formed from these precursors are regarded as by-products of protein metabolism that are metabolized on either amino nitrogen or hydroxy groups. In those cases in which "ammoniaca" is incorporated into isoprenoid or polyketide carbon skeletons, the resulting isoprenoid amines and polyketide amines are named as "pseudoalkaloids" or "alkaloida imperfecta" [106]. The series of compounds relegated by some authors to this class includes not only those derived from sterterpenes, sesquiterpenes, and diterpenes (e.g., β-lysanthine, 22, deoxyxymphetidine, 24, and cocaine, 25, respectively), but those from C7 and C10, steroidal (e.g., solandrine, 125, and holophyllamine, 124, respectively), from purines (e.g., caffeine, 19), and from nicotinic acid (e.g., nicotine, 26, and trigonelline, 33).

9.3. "True Alkaloids" Versus "Pseudoalkaloids"

This classification of nitrogenous compounds into "true alkaloids" and "pseudoalkaloids" based on biosynthesis is very arbitrary and needlessly complicates the already-difficult task of deciding what are and what are not alkaloids. This writer feels that the structure, and not the biogenetic pathway followed, should determine whether a compound is an alkaloid. To do otherwise means it is not possible to classify a compound of a new structural type as an alkaloid until one is reasonably certain of the biogenesis of the compound. Moreover, the term alkaloid serves functions for the chemist and pharmacognostist that are well beyond those necessary for the plant taxonomist. For these reasons I recommend that the term alkaloid be defined on the basis of structure and not on the basis of
Influence of an Alkaloid

Factors Influencing Classification As An Alkaloid

As a corollary, the term "pseudoalkaloid" should be abandoned, and appropriate nitrogenous compounds derived from terpenes, steroids, putrescine, and iminosine acid should be classified as genuine alkaloids.

4. Antibiotics

Should antibiotics of appropriate structure be classified as alkaloids? Though some authors automatically exclude antibiotics, I believe this practice is not justified. The term antibiotic is generally defined as "a chemical substance produced by a microorganism that has the capacity, in low concentration, to inhibit selectively or even to destroy bacteria and other microorganisms through an unspecific mechanism" [107]. This definition has been expanded to include higher plants as the source and tumors as a site of action [107]. The term antibiotic thus has reference to a function the compound performs, not to its chemical structure. Therefore, following the concept that the structure of a compound determines classification as an alkaloid, one should accept antibiotics of appropriate structure into the alkaloid class. Examples of antibiotics that, on the basis of structure, can be classified as alkaloids are gliotoxin [114], pycnophylline [121], cycloheximide [125], mitomycin C [126], and the macrocyclic maytansinoids such as maytansine [127].
9.5. Polyamines

The polyamines putrescine (9), spermidine (10), and spermine (11) are considered by most authorities as biogenic amines (i.e., alkaloid building blocks) rather than genuine alkaloids [19-22]. I concur in this view, for these compounds are simple, straight-chain amines that are widely distributed in animals, microorganisms, and higher plants. For example, among plants used for foods, they have been detected in:

- Oncine (12)
- Inosadine-12-one (13)
- Palustrine (130)
- Lusatrine (131)
- Chaenorhine (132)
- Homeline (133)

Recent studies have shown that the spermine and spermidine in these plants are derived from Chaenorhine, a natural product.

10. DEF

That the cis-1,4-dimethylpyridine is naturally occurring in plants is well known.

10.1. Baseline

Though there are many reports of the presence of this compound in plants, it is important to note the following:

- Although the cis-1,4-dimethylpyridine is well known to be present in many plants, it is not commonly used as a natural product.

10.2. Nitric Oxide

Although the presence of nitric oxide in plants is well documented, its role in the complex processes of plant physiology is not yet fully understood.

10.3. Conclusion

Complexes of nitric oxide are perceived to play an important role in the physiology of higher plants. Further research is needed to fully understand their role in the physiology of these plants.
of an Alkaloid

detected in apple, cabbage, spinach, tomato, and in the leaves of wheat, maize, pea, black currant, and tobacco. Spermidine and spermine are also found in substantial concentrations in human semen [108].

Recently, a group of structurally complex derivatives of spermidine and spermine that are genuine alkaloids have been isolated. There are several dozen of these interesting macrocyclic alkaloids of which a few representative examples follow: 1,2,5-oxadiazole (128, Ocinomita nitida), steroidal di-12-one (129, Ocinomita monacensis), palustrine (130, Eutrema species), and lunarine (131, Eutrema arvensis) are all derived from spermidine (10). The alkaloids chaconine (132, Chaconia angustifolia) and homaline (133, Homalium prostratum) are derived from spermine (11) and two cinnamic acid units [109].

10. DEFINITION OF AN ALKALOID

That the classical definition of an alkaloid is no longer serviceable should be clear from the previous discussion. There are many examples of compounds that are universally accepted as alkaloids and that violate one or more of the cardinal requirements of definitions of the Winterstein–Trier [14] type. A brief summary of the inappropriateness of certain of these requirements in a modern definition follows.

10.1. Basicity

Though the term alkaloid originally meant alkalië, we have seen that basicity can no longer be regarded as a necessary property of an alkaloid. Such glaring exceptions as colchicine (28), piperine (29), amine oxides (e.g., 30), and important quaternary salts such as laurilamine chloride (34) require that basicity no longer be included in a definition.

10.2. Nitrogen as Part of a Heterocyclic System

Although most early classified alkaloids contained nitrogen in a heterocyclic system, there are now too many exceptions for this condition to be mandatory. If it is to be part of a definition, one must exclude colchicine (28) as well as all of the familiar $\beta$-phenethylamines such as hordeine (43) and mesocline (44). Common sense dictates that rather than exclude these compounds, the definition must be modified.

10.3. Complexity of Molecular Structure

Complexity of structure is too vague a concept to include as a requirement. What is perceived as a complex molecule by one chemist may be considered simple by another. Thus this requirement has no place in a modern definition of an alkaloid.
10.4. Pharmacological Activity

Though most alkaloids manifest pharmacological activity, I believe it inappro-
priate to make such activity a requirement for classification as an alkaloid.
Otherwise a newly isolated structural type must be submitted for pharmacolo-
gical screening before classification. Also, just what is meant by pharmacolo-
gical activity? Almost any compound if administered in large enough dosage
will have a physiological effect on a living organism. A concentration level would
have to be specified if pharmacological activity were to be made a part of the
definition of an alkaloid.

10.5. Restriction to Plant Kingdom

We have already seen that dozens of compounds possessing classical alka-
loid-type structures have been isolated from animal, fungal, and bacterial sources.
One cannot on any rational basis exclude such compounds because they happen
to occur in living tissue rather than plants. A plant-derived requirement no longer
has validity in a functional definition.

10.6. A Modern Definition

An appropriate definition must be workable in the sense of accommodating
most, if not all, of the compounds regarded as alkaloids by most chemists and
pharmacognosists. This means compounds such as caffeine (28), nicotine (29),
quaternary-salt alkaloids (34), certain amine oxides (30 and 31), and the
phenylethylamines must be included. The various structural types of alkaloids
discussed in the chapter may suggest that alkaloids should be defined simply as
naturally occurring nitrogenous compounds. For practical considerations the
definition must be more restrictive. By common consent most authorities would
agree that the members of the following classes of compounds are not alkaloids:
simple low-molecular-weight derivatives of ammonia e.g., methylamine, tri-
ethylamine, and other acyclic alkylamines; choline (7), acyclic betaines such as
6, amino acids, amino sugars, peptides (exception: peptides alkaloids such as
ergocristine, 108), proteins, nucleosides, peroxides, porphyrins, and
vitamins.

After much soul-searching and discussion with colleagues, I suggest the
following simple definition for an alkaloid:

An alkaloid is a cyclic organic compound containing nitrogen in a negative
oxidation state which is of limited distribution among living organisms.

The requirement for a cyclic structure in some part of the molecule excludes
simple low-molecular-weight derivatives of ammonia as listed above, as well as
acetic polyamines such as putrescine (9), spermidine (10) and spermine (11). Also
acetylated are such acyclic amides as 134 and 135, recently isolated from the green
algae Caulerpa racemosa [110] and the red algae Laurencia midifica [114],
respectively, and incorrectly classified as alkaloids [111]. The requirement of
nitrogen in a negative oxidation state includes amines (−3), amine oxides (−1),
amines (−3), and quaternary ammonium salts (−3), but excludes nitro (−3) and
nitroso (−1) compounds. Thus by this definition the aristolochic acids 35 and 36
are not classified as alkaloids, nor should they be! The requirement for a limited
distribution among living organisms seems essential for practical considerations.
Otherwise one must classify almost all naturally occurring nitrogenous com-
pounds as alkaloids. By imposing the requirement of restricted occurrence among
the various genera of plants, animals, and other living organisms, one
excludes the almost ubiquitous compounds such as amino acids, amino sugars,
peptides, proteins, nucleic acids, nucleotides, porphyrins, and vitamins. This
definition has the advantage of including most of the compounds that are
exceptions to the classical-type alkaloid definitions, viz., colchicine (28), piperine
(29), the β-phenylethylamines, ricinine (26), gentiannine (27), bufotoxin (55), and
bolinine (83). It also includes as alkaloids the purine bases caffeine (19),
theophylline (20), and theobromine (21).

I welcome comments from others as to the suitability of this definition.

REFERENCES

The Nature and Definition of an Alkali

References

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References


