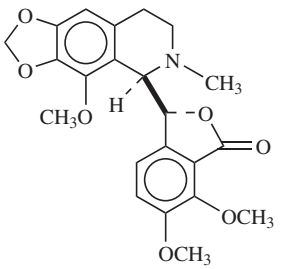
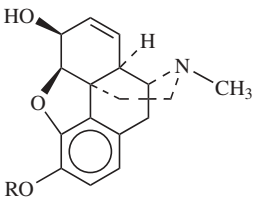
ALKALOIDS

1. Introduction

Crude preparations of the naturally occurring materials now known as alkaloids were probably utilized by the early Egyptians and/or Sumarians (1). However, the beginnings of recorded, reproducible isolation from plants of substances with certain composition first took place in the early nineteenth century. Then in close succession, narcotine [128-62-1] (**1**, now called noscopine, $C_{22}H_{23}NO_7$) (2) and morphine [57-27-2] (**2**, R = H) (3) (both from the opium poppy, *Papaver somniferum* L.) were obtained.



(**1**)

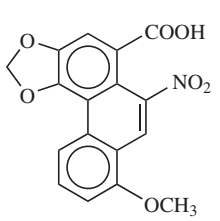


(**2**)

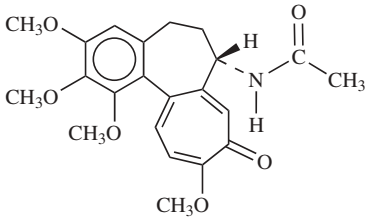
Although their presently accepted structures were unknown, they were characterized with the tools available at the time. Because morphine (2, R = H), $C_{17}H_{19}NO_3$, was shown to have properties similar to the basic soluble salts obtained from the ashes of plants (alkali) it was categorized as a vegetable alkali or *alkaloid*, and it is generally accepted that it was for this case that the word was coined.

However, there is currently no simple definition of what is meant by alkaloid. Most practicing chemists working in the field would agree that most alkaloids, in addition to being products of secondary metabolism, are organic nitrogen-containing bases of complex structure, occurring for the most part in seed-bearing plants and having some physiological activity. A 1961 compendium

(4) carefully avoids simple amine bases known to be present in some plants, but does list a variety of compounds such as aristolochic acid I [313-67-7] (**3**) (from *Aristolochia indica* L., the Dutchman's Pipe) and colchicine [64-86-8] (**4**) (from *Colchicum autumnala* L., the autumn crocus), neither of which is basic, but both of which are physiologically active. In a later (1975) reference (5), the list of materials called alkaloids had grown and more structures had been elucidated, but the definition was essentially unchanged. Subsequently, a much more sophisticated definition was proposed (6) which, while meritorious, has apparently been found unworkable. The most recent catalog (7), listing nearly 10,000 alkaloids, contains compounds generally fitting within the categories that were used in 1960, but widened still further to include not only nonbasic nitrogen-containing materials from plants, but also substances occurring in animals. Other compounds, the physiological activity of which has not been measured, are also reported (8). Nonetheless, because of their widespread distribution across all forms of life, alkaloids are intimately interwoven into the fabric of existence. Both our understanding of the roles these substances play in their respective sources and the possibility of genomic modification to adjust alkaloid production are being pursued as the twenty-first century dawns.



(**3**)



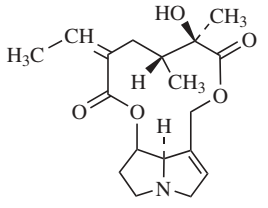
(**4**)

2. History

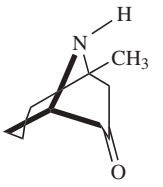
From today's perspective, the history of alkaloid chemistry can be divided into four parts. The first part, which doubtlessly developed over aeons prior to the appearance of present-day flora and fauna and about which, with genomic mapping a little is now known, deals with the role alkaloids may really play (as divorced from anthropocentric imaginings) in animal and plant defense, reproduction, etc. Second, in the era prior to ~1800, human use was apparently limited to apothecaries' crude mixtures and folk medicinals that were administered as palliatives, poisons, and potions. Knowledge of this is based on individual or group records or memory. In the third period, ~1800–1950, early analytical and isolation technologies were introduced. Good records were kept and techniques honed, so that the wrenching out of specific materials, in truly minute quantities, from the cellular matrices in which they are held could be reproducibly effected. This time period also saw the beginnings of correlation of the specific structures of those hard-won materials with their properties. Finally, the current era has seen a flowering of structure elucidation as a

consequence of the maturation of some analytical techniques, a renaissance in synthetic methods, the introduction of biosynthetic probes, and the application of molecular genetics to biosynthesis (9). The most recent developments build on the newest analytical techniques and the ability to correlate huge quantities of information at high speed.

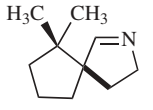
During the first era some insects developed relationships with the plants on which they fed, which allowed them to incorporate intact alkaloids for storage and subsequent use. This type of relationship apparently continues to exist. Thus in 1892 there was a report (10) that pharmacophagus swallowtail butterflies (*Papilios*) obtain and store poisonous substances from their food plants, and some 75 years later an investigation (11) showed that the warningly colored and potently odoriferous Aristolochia-feeding swallowtail butterfly (*Pachlioptera aristolochiae* Fabr.) is even less acceptable than the unpalatable Danainae to bird predators. Both the plant on which the swallowtail feeds (eg, *Aristolchia indica* L.) and the swallowtail itself contain aristolochic acid I (3), $C_{17}H_{11}NO_7$, and related materials. These materials are presumably ingested as larvae feed on the plant, stored during the pupal stage, and carried into the adult butterfly. With regard to the *Danainae*, the larvae of the butterflies *Danaus plexippus* L. and *Danaus chrysippus* L. feed on *Senecio* spp. which contain, among other compounds, the pyrrolizidine alkaloid senecionine (5) (12). Metabolites of this and other related alkaloids apparently serve in courtship and mating, with the more alkaloid-rich individuals having an advantage (13).



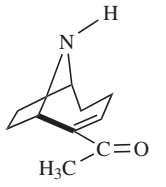
(**5**)



(**6**)



(**7**)



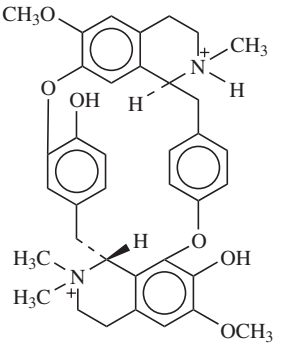
(**8**)

There are many other examples of insect use of alkaloids, such as the homotropane alkaloid euphococcinine [15486-23-4] (6), $C_9H_{15}NO$, which has been noted as a defensive alkaloid in the blood of the Mexican bean beetle (*Epilachna varivestis*) (14) and the azaspiroalkene polyzonimine [55811-47-7] (7), $C_{10}H_{17}N$, an insect repellent produced by the milliped *Polyzonium rosalbum* (15).

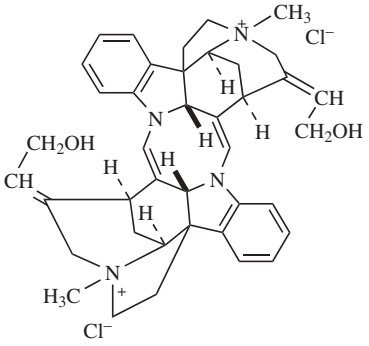
The "very fast death factor" (VFDF), anatoxin-a [64285-06-9] (**8**), $C_{10}H_{15}NO$, a fish poison, has been isolated from a toxic strain of microalgae *Anabaena flos-aquae* (16). For (**6**), (**7**), and (**8**), little is yet known about the formation (or genesis) of the alkaloid material.

The period prior to ~1800 includes the history of the crude exudate from unripe poppy pods, which, it is now known, contains narcotine (1, noscopine), $C_{22}H_{23}NO_7$, and morphine (**2**, R = H) along with other closely related materials. Also during this time natives of the Upper Amazon basin were making use of crude alkaloid-containing preparations as arrow poisons. To help their hunting,

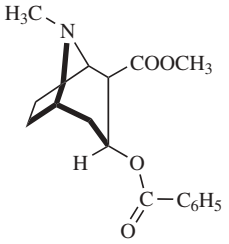
some tribes developed the red resinous mixture called tubocurare, containing, among others, the alkaloid tubocurarine [57-95-4] (9), $C_{37}H_{41}N_2O_6$, obtained primarily from plants of the *Chondrodendron*; others developed Calabash curare, containing, among others, the alkaloid C-toxiferine [6696-58-8] (10), $C_{40}H_{46}N_4O_2 \cdot 2Cl$, from plants belonging to *Strychnos* spp.



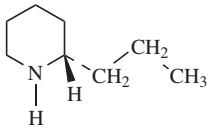
(**9**)



(**10**)



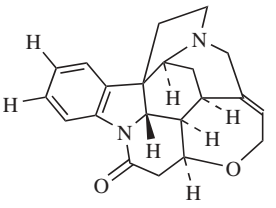
(**11**)



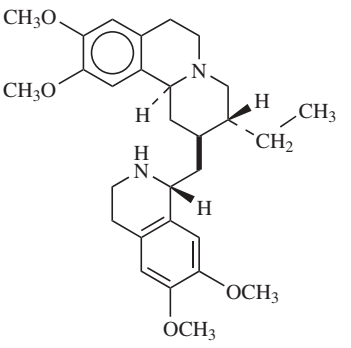
(**12**)

The natives of Peru were learning to ease their physical pains by chewing the leaves of coca shrub (*Erythroxylon truxillence*, Rusby), which contain, among others, the alkaloid cocaine [50-36-2] (**11**), and European citizens were recognizing other poisons such as coniine [458-88-8] (**12**), from the poison hemlock (*Conium maculatum* L.).

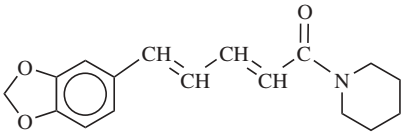
With the introduction of improved analytical techniques, starting ~1817, the evaluation of drugs began and, over a span of ~10 years, strychnine [57-24-9] (**13**, R = H), emetine [283-18-1] (**14**), brucine [357-57-3] (**13**, R = OCH_3), piperine [94-62-2] (**15**), caffeine [58-08-2] (**16**), quinine [130-95-0] (**17**, R = OCH_3), colchicine (**4**), cinchonidine [118-10-5] (**17**, R = H), and coniine (**12**) were isolated (17). But, because the science was young and the materials complex, it was not until 1870 that the structure of the relatively simple base coniine (**12**) was established (18) and not until 1886 that the racemic material was synthesized (19). The correct structure for strychnine (**13**, R = H) was not confirmed by X-ray crystallography until 1956 (20) and the synthesis was completed in 1963 (21).



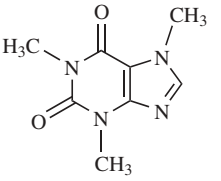
(**13**)



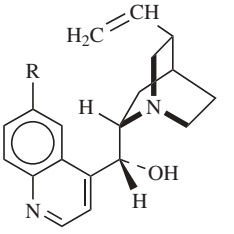
(**14**)



(**15**)



(**16**)



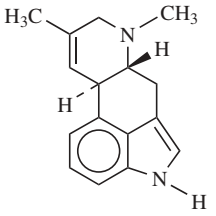
(**17**)

3. Occurrence, Detection, and Isolation

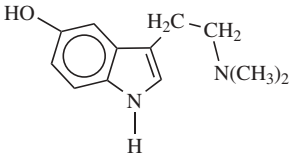
Given the massive volume of material available, the following discussion is necessarily incomplete and the interested reader is directed to the materials in (7) and (8), in particular, for more detailed information.

The most recent compendium (7) of alkaloids indicates that most alkaloids so far detected occur in flowering plants and it is probably true that the highest concentrations of alkaloids are to be found there. However, as detection methods improve it is almost certain that some concentration of alkaloids will be found almost everywhere. In the higher plant orders, somewhat more than one-half contain alkaloids in easily detected concentrations. Major alkaloid bearing orders are *Campanulales, Centrospermae, Gentianales, Geraniales, Liliflorae, Ranales, Rhoedales, Rosales, Rubiales, Sapindales*, and *Tubiflorae*, and within these orders most alkaloids have been isolated from the families *Amaryllidaceae, Apocynaceae, Euphorbiaceae, Lauraceae, Leguminoseae, Liliaceae, Loganiaceae, Menispermaceae, Papveraceae, Ranuculaceae, Rubiaceae, Rutaceae*, and *Solanaceae*. Alkaloids have also been found in butterflies, beetles, millipedes, and algae and are known to be present in fungi, eg, agroclavine [548-42-5] (**18**) from the fungus *Claviceps purpurea*, which grows as a parasite on rye and has been implicated, with its congeners, in causing convulsive ergotism (22). They are found in toads (*Bufo vulgaris*, Laur.), eg, bufotenine [487-93-4] (19), an established hallucinogen in humans (23); in frogs (*Epipedobates tricolor*) eg, epibatidine [140111-52-0] (20), and in the musk deer [family *Moschidae* and three species *Moschus*

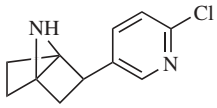
moschiferus, M.berezovskii, and M. chrysogaster.], muscopyridine [501-08-6] (21), $C_{16}H_{25}N$. Even in humans morphine (**2**, R = H) is a naturally occurring component of cerebrospinal fluid (24).



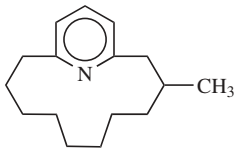
(**18**)



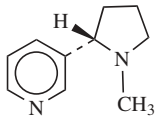
(**19**)



(**20**)



(**21**)



(**22**)

The concentration of alkaloids, as well as the specific area of occurrence or localization within the plant or animal, can vary enormously. Thus the amount of nicotine [54-11-5] (**22**), $C_{10}H_{14}N_2$, apparently synthesized in the roots of various species of *Nicotiana* and subsequently translocated to the leaves varies with soil conditions, moisture, extent of cultivation, season of harvest, as well as other factors that may not yet have been evaluated and may be as high as 8% of the dry leaf, whereas the amount of morphine (**2**, R = H) in cerebrospinal fluid is of the order of 2–339 fmol/mL (24).

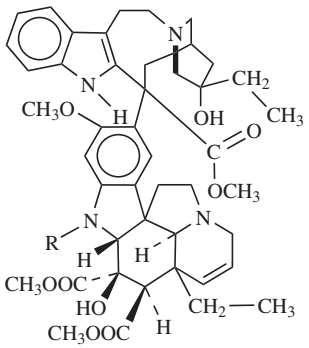
Initially, the search for alkaloids in plant material depended largely on reports of specific plant use for definite purposes or observations of the effect specific plants have on indigenous animals among native populations. Historically, tests on plant material have relied on metal-containing reagents such as that of Dragendorff (25), which contains bismuth salts, or Mayer (26), which contains mercury salts. These metal cations readily complex with amines and the halide ions present in their prepared solutions, yielding brightly colored products. Despite false positive and negative responses (27), field testing continues to make use of these solutions. However, it is now clear that newer methods, such as kinetic energy mass spectrometry (MIKE) on whole plant material (28), have the potential to replace these spot tests.

After detection of a presumed alkaloid, large quantities of the specific plant material are collected, dried, and defatted by petroleum ether extraction if seed or leaf is investigated. This process usually leaves polar alkaloidal material behind but removes neutrals. The residue, in aqueous alcohol, is extracted with dilute acid and filtered, and the acidic solution is made basic. Crystallization can occasionally be effected by adjustment of the pH. If such relatively simple purification fails, crude mixtures may be used or, more recently, very

sophisticated separation techniques have been employed. Once alkaloidal material has been found, taxonomically related plant material is also examined.

Until separation techniques such as chromatography (29,30) and countercurrent extraction had advanced sufficiently to be of widespread use, the principal alkaloids were isolated from plant extracts and the minor constituents were either discarded or remained uninvestigated. With the advent of, first, column, then preparative thin layer, and now high pressure liquid chromatography (hplc), even very low concentrations of materials of physiological significance can be obtained in commercial quantities. The alkaloid leurocristine [57-22-7] (vincristine, **23**, R = CHO), one of the >90 alkaloids found in *Catharanthus roseus* G. Don, from which it is isolated and then used in chemotherapy, occurs in concentrations of ~2 mg/100 kg of plant material.

Most recently, with the advent of enzyme assay and genomic manipulation, the possiblity of utilization of callous or root tissue or even isolated enzymes along with genetic engineering techniques can be employed to enhance or modify production of specific alkaloids (31–36)



(**23**)

4. Properties

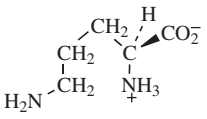
Most alkaloids are basic and they are thus generally separated from accompanying neutrals and acids by dilute mineral acid extraction. The physical properties of most alkaloids, once purified, are similar. Thus they tend to be colorless, crystalline, with definite melting points, and chiral; only one enantiomer is isolated. However, among >10,000 individual compounds, these descriptions are over generalizations and some alkaloids are not basic, some are liquid, some brightly colored, some achiral, and in a few cases both enantiomers have been isolated in equal amounts, ie, the material as derived from the plant is racemic (or racemization has occurred during isolation).

5. Organization

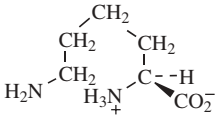
Early investigators grouped alkaloids according to the plant families in which they are found, the structural types based on their carbon framework, or their

principal heterocyclic nuclei. However, as it became clear that the alkaloids, as secondary metabolites (37–40), were derived from compounds of primary metabolism (eg, amino acids or carbohydrates), biogenetic hypotheses evolved to link the more elaborate skeletons of alkaloids with their simpler proposed progenitors (41). These hypotheses continue to serve as valuable organizational tools (7,42,43) and in many cases, enzyme catalyzed processes affirming them have been found (36).

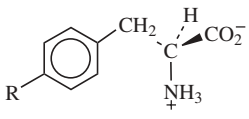
The building blocks of primary metabolism, from which biosynthetic studies have shown the large majority of alkaloids to be built, are few and include the common amino acids ornithine (**24**), lysine (**25**), phenylalanine (**26**, R = H), tyrosine (**26**, R = OH, and tryptophan (**27**). Others are nicotinic acid (**28**), anthranilic acid (**29**), and histidine (**30**), and the nonnitrogenous acetate-derived fragment mevalonic acid (**31**). Mevalonic acid (**31**) is the progenitor of isopentenyl pyrophosphate (**32**) and its isomer 3,3-dimethylallyl pyrophosphate (**33**), later referred to as the C_5 fragment. A dimeric C_5 fragment (the C_{10} fragment), ie, geranyl pyrophosphate (**34**), gives rise to the iridoid loganin [18524-94-2] (**35**), and the trimer farnesyl pyrophosphate (**36**). The C_{15} fragment is also considered the precursor to the C_{30} steroid, ie, $2 \times C_{15} = C_{30}$.



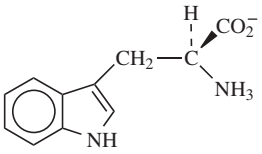
(**24**)



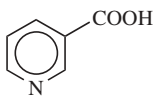
(**25**)



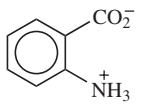
(**26**)



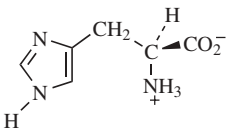
(**27**)



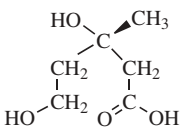
(**28**)



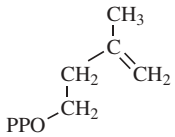
(**29**)



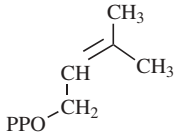
(**30**)



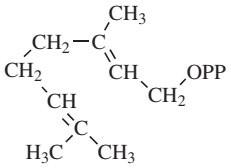
(**31**)



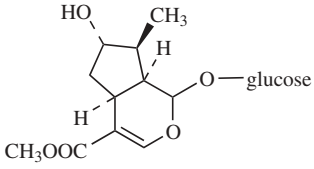
(**32**)



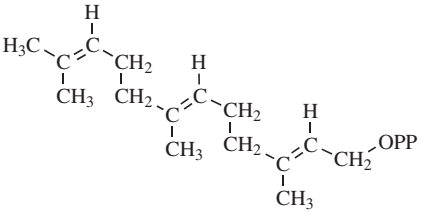
(**33**)



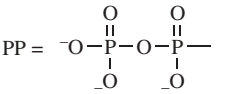
(**34**)



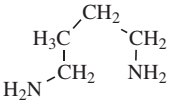
(**35**)



(**36**)

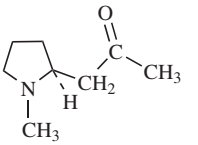


5.1. Ornithine-Derived Alkaloids (44). Ornithine (24) undergoes biological reductive decarboxylcation to generate either putrescine [110-60-1] (37), $C_4H_{12}N_2$, or its biological equivalent, and subsequent oxidation and cyclization gives rise to the pyrroline [5724-81-2], (38), C_4H_7N.



(**37**)

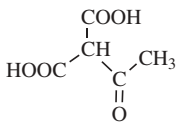
(**38**)



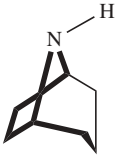
(**39**)

The details have been confirmed by suitable labeling (^{14}C and ^{15}N) and it is fairly certain that either (**38**) or something very similar to it is available to react with either acetoacetic acid or its biological equivalent to generate the alkaloid hygrine (**39**). Hygrine is an oily, distillable base found, along with cocaine (**11**), in the leaves of the Peruvian coca shrub (*Erythroxylon truxillense* Rusby).

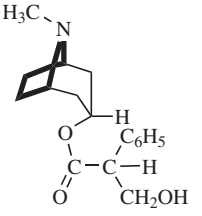
If, instead of an acetoacetate equivalent, a malonyl derivative such as (**40**) were involved (45), appropriate condensation reactions would lead to the tropane [280-05-7] skeleton (**41**), $C_7H_{13}N$.



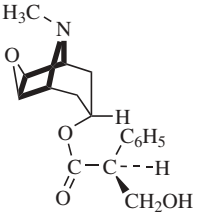
(**40**)



(**41**)



(**42**)



(**43**)

The physiologically and commercially important alkaloids of this group of compounds, occurring widely in the *Solanaceae* and *Convolulaceae* as well as the *Erythroxylaceae*, include not only cocaine (**11**) but also atropine (**42**) and scopolamine (**43**) (33).

Atropine (**42**), isolated from the deadly nightshade (*Atropa belladonna* L.) is the racemic form, as isolated, of (−)-hyoscyamine [which is not isolated, of course, from the same plant but is typically found in *Solanaceous* plants such as henbane (*Hyoscyamus niger* L.)]. Atropine (**42**) is used to dilate the pupil of the eye in ocular inflammations and is available both as a parasympatholytic agent for relaxation of the intestinal tract and to suppress secretions of the salivary,

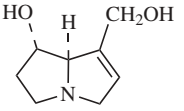
gastric, and respiratory tracts. In conjunction with other agents, it is used as part of an antidote mixture for organophosphorus poisons (see CHEMICALS IN WAR).

Scopolamine (**43**), an optically active, viscous liquid, also isolated from *Solanaceae*, eg, *Datura metel* L., decomposes on standing and is thus usually both used and stored as its hydrobromide salt. The salt is employed as a sedative or, less commonly, as a prophylactic for motion sickness. It also has some history of use in conjunction with narcotics as it appears to enhance their analgesic effects. Biogenetically, scopolamine is clearly an oxidation product of atropine, or, more precisely, because it is optically active, of (−)-hyoscyamine.

Cocaine (**11**) had apparently been used by the natives of Peru prior to the European exploration of South America. Stories provided by early explorers suggested that the leaves of, for example, *Erythroxylon coca* Lam. were chewed without apparent addiction by the indigenous peoples and with only mild numbing of the lips and tongue in return for increased endurance. Indeed, the recognition of the anesthetic properties possessed by the leaves and the (unwarranted) assumption that addiction was avoidable led to creation of plantations in Bolivia, Brazil, and Java to ensure a continued supply of this valuable material for medicinal purposes. Although it appears that native populations continue the practice of leaf chewing, the purified base obtained by simple extraction of the leaves has become a substance of abuse in the more civilized world. It is now recognized that the alkaloid (**11**) itself is too toxic to be used as an anesthetic by injection.

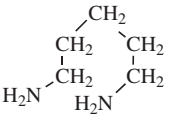
Condensation of a pyrroline system (38) with a second equivalent of ornithine-derived precursor is presumably an alternative to condensation with acetoacetate- or malonate-derived fragments. Indeed, early feeding experiments with, eg, *Senecio istideus* showed that two equivalents of ornithine (24) could be accounted for in the structure of the necine, ie, the 1-azabicyclo[3.3.0]heptane or pyrrolizidine portion of the alkaloids, eg, heliotridine (44), containing that ring system (46). Generally, the pyrrolizidine alkaloids are found esterified with low molecular weight carboxylic acids [or dicarboxylic acids, as in senecionine, (5)] at either or both of the hydroxyl groups of the necine. The acids themselves, called necic acids, are generally not found elsewhere in alkaloids, and, although for some time they were believed to arise from acetate or mevalonate, it is now clear that, at least for the few that have been carefully examined, they are themselves derived from simple amino acids.

In addition to the alkaloids in *Senecio* spp. (including asters and ragworts) commented on earlier, the adaptive use of which by butterflies was noted, members of this widely spread group of compounds are found in different genera (*Heliotropium, Trachelanthus*, and *Trichodesma*) within cosmopolitan families (eg, *Boraginaceae* and *Leguminoseae*). Most of these alkaloids are toxic, affecting the liver (an organ lacking in moths, butterflies, etc) and their ingestion is manifested in animals with the onset of symptoms associated with names such as "horse staggers" or "walking disease". The cell biology and metabolic engineering of some alkaloids discussed here have recently been reviewed (47,48).



(**44**)

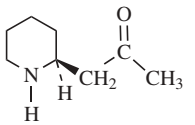
5.2. Lysine-Derived Alkaloids. Just as putrescine (**37**) derived from ornithine (**24**) is considered the progenitor of the nucleus found in pyrrolidine-containing alkaloids, so cadaverine [462-94-2] (**45**), $C_5H_{14}N_2$, derived from lysine (**25**) is the idealized progenitor of the 1-dehydropiperidine [28299-36-7] nucleus (**46**), C_5H_9N, found in the pomegranate, *Sedum, Lobelia, Lupin*, and *Lycopodium* alkaloids (49).



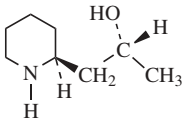
(**45**)

(**46**)

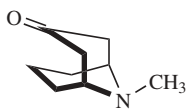
As was the case for the alkaloids derived from ornithine (**34**), if either (**46**), its biological equivalent, or something closely resembling it reacts with acetoacetate or its biological equivalent, the pomegranate alkaloid pelletierine (**47**) can arise; note the resemblence to hygrine (**39**). Simple reduction of the carbonyl, with stereospecificity common to enzyme-mediated reactions, can be accommodated and the Sedum alkaloid sedridine (**48**) results; cyclization and N-methylation produce pseudopelletierine (**49**). There are somewhat more than 600 annual, biennial, or perennial succulents belonging to the *Sedum* genus of the family *Crassulaceae*, many of which are characterized by the ability to grow where little else can.



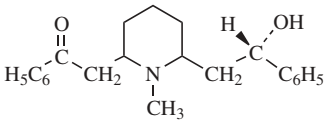
(**47**)



(**48**)



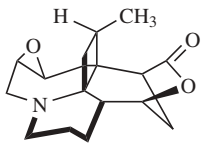
(**49**)



(**50**)

(**51**)

(**52**)



(**53**)

The pomegranate alkaloids, pelletierine (**47**) and pseudopelletierine (**49**) as well as minor accompanying bases, have a long history as salts of tannic acid as an anthelmintic mixture for intestinal pinworms. The alkaloids themselves (as the tannates) are obtained from pomegranate tree (*Punica granatum* L.)

root bark and are among the few bases named after an individual (P. J. Pelletier) rather than a plant.

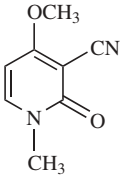
Isolates from Indian tobacco (*Lobelia inflata* L.), as a crude mixture of bases, have been recognized as expectorants. The same (or similar) fractions were also used both in the treatment of asthma and as emetics. The principal alkaloid in L. inflata is lobeline (**50**), an optically active tertiary amine which, unusual among alkaloids, is reported to readily undergo mutarotation, a process normally associated with sugars. Interestingly, it appears that the aryl-bearing side chains in (**50**) are derived from phenylalanine (**26**, R = H) (50).

Feeding experiments utilizing ^{13}C-, ^{15}N-, and ^{2}H-labeled cadaverine (**45**) and lysine (**25**) in *Lupinus augustifolius*, a source of the lupine alkaloids (−)-sparteine (**51**, R = H,H) and (+)-lupanine (**51**, R = O), have been reported that lend dramatic credence to the entire biosynthetic sequence for these and the related compounds discussed above (51). That is, the derivation of these bases is in concert with the expected cyclization from the favored all-trans stereoisomer of the trimer expected on self-condensation of the 1-dehydropiperidine (**46**).

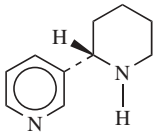
The spores of *Lycopodium clavatum* L. (a club moss), sometimes called vegetable sulfur, have been used medicinally as an absorbent dusting powder; other uses as diverse as additives to gunpowder and suppository coatings have also been recorded. Although for some years the alkaloids common to a number of *Lycopodium* spp., lycopodine (**52**) and annotinine (**53**), were thought to have arisen from suitably folded polyketide chains, it is now accepted that two pelletierine (47) or pelletierine-like fragments would suffice. The details of feeding experiments with pelletierine and its precursors appear to indicate, however, that only one pelletierine and, separately, a second acetoacetate and a second 1-dehydropiperidine (46), which could otherwise be combined to a second pelletierine, are used to generate both of these alkaloids.

5.3. Tobacco Alkaloids. The relatively small number of alkaloids derived from nicotinic acid (**28**) (the tobacco alkaloids) are obtained from plants of significant commercial value and have been extensively studied. They are distinguished from the bases derived from ornithine (**24**) and, in particular, lysine (**25**), since the six-membered aromatic substituted pyridine nucleus common to these bases apparently is not derived from (**25**). Current work with isolated enzymes and plant genomic material (32,48,52) confirms and extends earlier work with less pure fractions (53) that led to the early hypotheses.

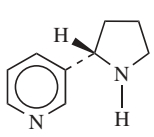
These alkaloids include the substituted pyridone ricinine [524-40-3] (**54**), $C_8H_8N_2O_2$, which is easily isolated in high yield as the only alkaloid from the castor bean (*Ricinus communis* L.). The castor bean is also the source of castor oil (qv), which is obtained by pressing the castor bean and, rich in fatty acids, has served as a gentle cathartic.



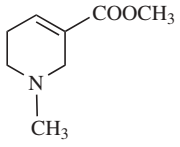
(**54**)



(**55**)



(**56**)



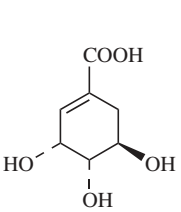
(**57**)

The highly toxic alkaloid *S*-(−)-nicotine (22) and related tobacco bases including such materials as (−)anabasine [494-52-0] (55), $C_{10}H_{14}N_2$, are obtained from commercially grown tobacco plants (eg, *Nicotiana tabacum* L.). Various tobaccos have differing amounts of these and other bases, as well as different flavoring constituents, some of which are apparently habituating to some individuals. Currently, the assay of the (−)-nicotine (22) content of tobacco, the annual world production of which is in excess of 7 million tons (see below), is desirable and in some countries mandatory, although the toxicity of the unassayed plant bases may be as high as or higher than that of (−)-nicotine (**22**). Interestingly, there appears to be some evidence that cultivation of tobacco increases the alkaloid content, from which it can be argued that increased alkaloid content has insured survival of a particular cultivar.

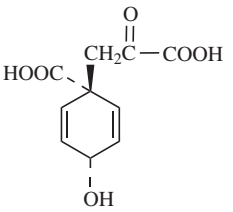
The pyrrolidine ring of nicotine is derived from ornithine (**24**), whereas the piperidine ring of anabasine (**55**) is derived from lysine (**25**) (54). Also, the carboxylic acid functionality of nicotinic acid (28) is lost (along with the C-6 proton) during the biosynthesis in the roots of the tobacco plants from which the bases are subsequently translocated to the leaves. Curiously, whereas nornicotine [494-97-3] (**56**), $C_9H_{12}N_2$, frequently accompanies nicotine, the former is apparently derived by demethylation of the latter rather than the latter undergoing methylation to the former. This is in contrast to what usually seems to occur; ie, methylation at nitrogen and oxygen is usually a late-stage process in alkaloid biosynthesis.

Finally, millions of people in the Far East are apparently addicted to chewing ground betel nut, the fruit of the palm tree Areca catechu L., which they mix with lime and wrap in betel leaf (Piper betle L.) for consumption. They are said to experience a feeling of well-being. Among the alkaloids found in betel nut is arecoline [63-75-2] (**57**), $C_8H_{13}NO_2$, an optically inactive, steam-volatile base that is used commercially as a vermifuge in dogs and is also a potent muscarinic agent. It is reasonable to assume (evidence lacking) that arecoline may be derived from nicotinic acid (**28**) by a (rare) reductive mechanism.

5.4. Phenylalanine- and Tyrosine-Derived Alkaloids. Carbohydrate metabolism leads via a seven-carbon sugar, ie, a heptulose, derivative to shikimic acid [138-59-0] (**58**), $C_7H_{10}O_5$, which leads in turn to prephenic acid [126-49-8] (**59**), $C_{10}H_{10}O_6$ (55).



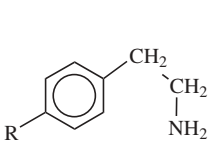
(**58**)



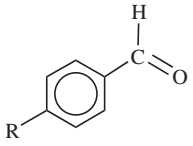
(**59**)

This is the branch-point differentiating phenylalanine (26, R = H) from tyrosine (**26**, R = OH). Both phenylalanine and tyrosine contain an aryl ring, a three-carbon side chain (a C_6–C_3 fragment), and a nitrogen. Decarboxylation yields a two-carbon side chain (a C_6–C_2 fragment), eg, 2-phenethylamine (**60**, R = H) from phenylalanine and tyramine (**60**, R = OH) from tyrosine, although

it is not certain that in all cases decarboxylation must precede use in alkaloid construction.



(**60**)

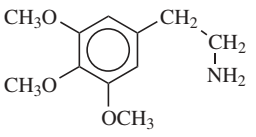


(**61**)

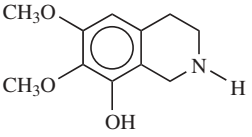
After the branching point at prephenic acid (**59**), phenylalanine (**26**, R = H) and tyrosine (**26**, R = OH), as well as the amines (**60**), are not interconvertible. Finally, deamination and oxidative cleavage of the presumed (and in some circumstances isolated) resulting alkenes yields the equivalent of benzaldehyde (**61**, R = H), C_7H_6O, and *p*-hydroxybenzaldehyde (**61**, R = OH), ie, aromatics with one aliphatic carbon attached C_6–C_1 fragments).

All of these pieces are used, in conjunction with some of the earlier fragments discussed, as building blocks for alkaloids containing an aromatic ring. In the cases discussed here, a link to either phenylalanine or tyrosine or, in some cases with two aromatic rings to both, has been established by suitable feeding experiments on growing plants.

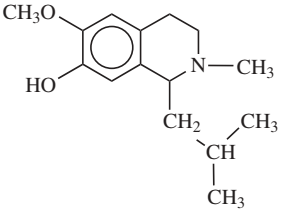
There is a relatively large number of alkaloids that may be considered as simple phenethylamine [64-04-0] (60, R = H), $C_8H_{11}N$, or tyramine [51-67-2] (**60**, R = OH), $C_8H_{11}NO$, derivatives. These include mescaline (**62**) from the small woolly peyotyl cactus *Lophophora williamsii* (Lemaire) Coult., anhalamine (**63**) and lophocerine (**64**) from other *Cactaceae*, and the important antamebic alkaloids (−)-protoemetine (**65**), (−)-ipecoside (**66**), and (−)-emetine (**67**) from the South American straggling bush *Cephaelis ipecacuanha* (Brotero) Rich. All of these bases are derived from tyrosine (**26**, R = OH) and not from phenylalanine (**26**, R = H).



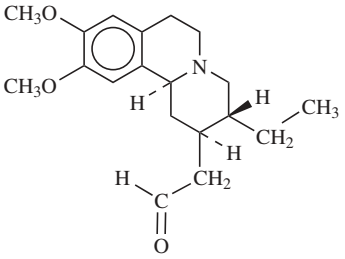
(**62**)



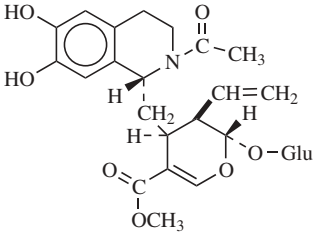
(**63**)



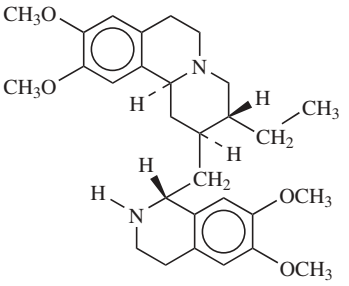
(**64**)



(**65**)



(**66**)



(**67**)

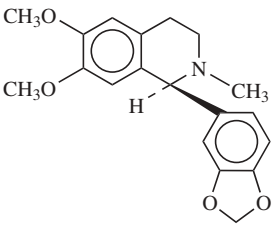
Crude preparations of mescaline (**62**) from peyote were first reported by the Spanish as they learned of its use from the natives of Mexico during the Spanish invasion of that country in the sixteenth century. The colorful history (56) of mescaline has drawn attention to its use as a hallucinogen and even today it is in use among natives of North and South America. Although in connection with drug abuse complaints, mescaline is considered dangerous, it has been reported (57) that it is not a narcotic nor is it habituating. It was also suggested that its sacramental use in the Native American Church of the United States be permitted since it appears to provoke only visual hallucination while the subject retains clear consciousness and awareness.

Both of the alkaloids anhalamine (**63**) from *Lophophora williamsii* and lophocerine (**64**) from *Lophocereus schotti* were isolated (after the properties of purified mescaline had been noted) in the search for materials of similar behavior. Interestingly, lophocerine (**64**), isolated as its methyl ether, after diazomethane treatment of the alkali-soluble fraction of total plant extract, is racemic. It is not known if the alkaloid in the plant is also racemic or if the isolation procedure causes racemization.

The iridoid loganin (**35**), $C_{17}H_{26}O_{10}$, has been shown to serve as a C_{10} progenitor and, here, C_{10} fragments are apparent in the alkaloids (−)-protoemetine (**65**), (−)-ipecoside (**66**), and (−)-emetine (**67**). It has been shown that loganin is specifically incorporated into each of these bases in *Cephaelis ipecacuanha* (Brot. A. Rich) and that they are apparently formed sequentially, that is, formation of (−)-ipecoside (**66**) precedes that of (−)-protoemetine (**65**) and (−)-emetine (**67**). The crude dried rhizome and roots from *C. ipecacuanha* which is sometimes known as Rio or Brazilian ipecac, contains all three, as well as other related bases, and has a long history based on native Indian reports of use as an emetic. Purification of the crude extract yields the individual bases, and, because it is relatively more stable and is also present in reasonable quantity, led to the use of emetine (**67**) as its hydrochloride salt in place of the crude plant extract. This use of the pure base rather than crude plant extract has allowed greater certainty in dosage, which is important because, although emetine is quite effective in combating acute amebic hepatitis and is claimed to have some effect against the present scourge of African schistosomiasis, its administration may be accompanied by a rapid drop in blood pressure, irregular heart function, and paralysis of skeletal muscle. The danger of inappropriately large doses, certain to cure the ailment but with the possible death of the patient, is clearly

greater with crude extract than with purified alkaloid. Long term, even appropriate dosage may be accompanied by dermatitis, diarrhea, and nausea.

There are only two groups of alkaloids that appear to be derived from tyrosine (**26**, R = OH) utilized as a C_6–C_2 fragment and a C_6–C_1 unit that comes from phenylalanine (**26**, R = H). The first is that small group found only in the *Orchidaceae*, exemplified by cryptostyline I [22324-79-4] (**68**, from *Cryptostylis fulva* Schltr.), $C_{19}H_{21}NO_4$.



(**68**)

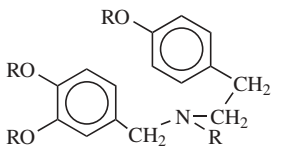
The second, a very large group of compounds, is the alkaloids of the *Amaryllidaceae*. This cosmopolitan family of related compounds includes >100 isolated and characterized members of known structure. In every case examined the C_6–C_2 unit is derived from tyrosine and the C_6–C_1 unit comes from phenylalanine, never from tyrosine. For this large number of compounds it is now believed (48) that a single progenitor derived from the original coupling of the C_6–C_2 unit and a C_6–C_1 unit, ie, norbelladine (69, R = H) accounts for all of the compounds isolated. This precursor (69, R = H) undergoes a variety of enzyme-catalyzed free-radical intramolecular cyclization reactions, followed by late-stage oxidations, eliminations, rearrangements, and O- and N-alkylations. Working from this generalization as an organizing principle, the majority of known Amaryllidaceae alkaloids can be divided into eight structural classes (59).

Alkaloids typical of the eight classes as shown below. The simple base ismine (**76**), isolated from, eg, *Sprekelia formosissima*, along with numerous other alkaloids, has long been considered a degradation product of other bases and is presumably generated in that way from a suitable member of the pyrrolo-[*de*]phenanthridine or [5,10b]ethanophenanthridine group.

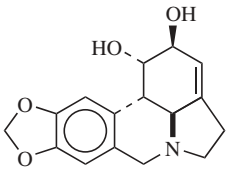
Lycorine (**70**) was recognized as a potent emetic and a moderately toxic base from the time of its initial isolation from *Narcissus pseudonarcissus* L. (in ~1877) (60). Since that time its isolation from many other *Amaryllidaceae*, eg, *Lycoris radiate* Herb., has served to establish it as the most cosmopolitan alkaloid of the family. Typically, as much as 1% of the dry weight of daffodil bulbs may consist of lycorine (**70**), which has been reported to crystallize as colorless prisms directly from aqueous acid extract of crude plant material after basification. A high yield synthesis of the racemic base has been reported (61). Galanthamine (**72**) was originally isolated from the Caucasian snowdrop, *Galanthus woronowii* Vel., and as its hydrobromide salt has been proposed for use in regeneration of sciatic nerve. Galanthamine (**72**) is currently sold as a paliative in the treatment of Alzheimer's disease. In addition to demonstration of powerful cholinergic

activity (62), it is reported to have analgesic activity comparable to morphine (**2**, R = H) (63).

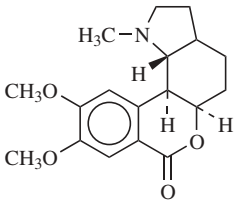
Tazettine (74) has gained some small notoriety since, subsequent to its isolation from *Sprekelia formosissima* or *Narcisus tazetta* and proof that it was generated *in vivo* from haemanthamine [466-75-1] (77), $C_{17}H_{19}NO_4$, in accord with biosynthetic dogma (64), more careful work (65), in which the strongly basic conditions usually employed in alkaloid isolation were avoided, showed that it is an artifact of isolation. Further, it is readily generated from its precursors during the work-up of the plant material. Manthine (**75**) occurs, along with several homologues, in South African *Haemanthus* species. Manthine is of interest because it appears that, like tazettine (**74**), it can be easily generated *in vitro* from a derivative of haemanthamine (**77**) (66).



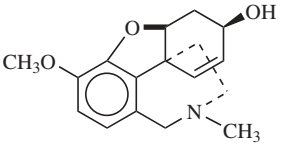
(**69**)



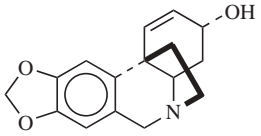
(**70**)



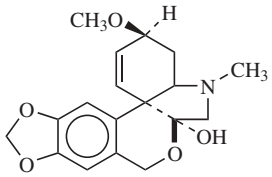
(**71**)



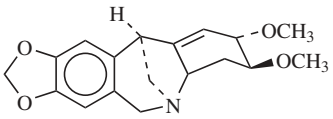
(**72**)



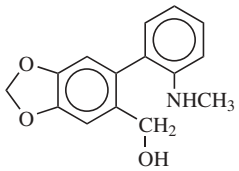
(**73**)



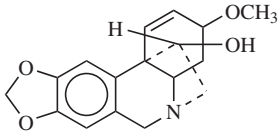
(**74**)



(**75**)



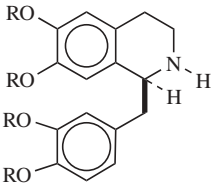
(**76**)



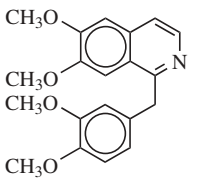
(**77**)

Just as norbelladine (**69**, R = H) can be considered as the precursor of C_6–C_2 + C_6–C_1 alkaloids, norlaudanosoline (**78**, R = H) seems to be the progenitor of the vast number of C_6–C_2 + C_6–C_2 alkaloids. Laudanosine (**78**, R = CH_3), isolated from *Papaver somniferum* L. [along with narcotine (**1**, noscopine), morphine (**2**, R = H), and numerous other alkaloids], has been shown to have tyrosine (**26**, R = OH) as a specific precursor. Labeling experiments with, eg, [2-^{14}C]tyrosine show that two equivalents of this amino acid are incorporated specifically but not to the same extent, implying that some partitioning has occurred prior to alkaloid formation. Papaverine (**79**), isolated in much greater

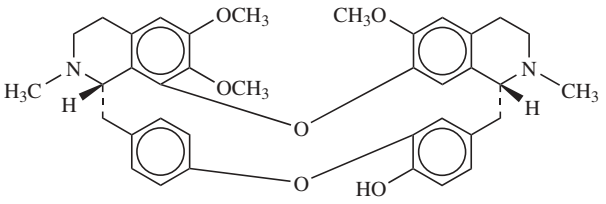
quantity from *P. somniferum* L. than its tetrahydro-derivative laudanosine (**78**, R = CH_3), has a long history of use as an antispasmodic for smooth muscle. It is used as its hydrochloride salt, a more stable material than the free base. It is said to be nonhabit-forming, although it is classified as a narcotic by the U.S. Federal Narcotic Laws. Large doses may produce drowsiness, constipation, and increased excitability; if it is given orally, gastric distress may occur.



(**78**)

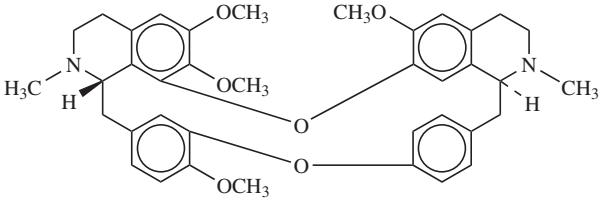


(**79**)

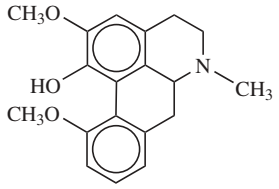


(**80**)

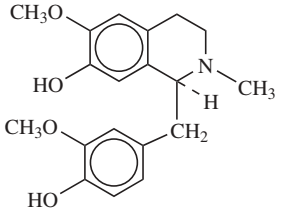
Phenolic intermolecular coupling (58) of two laudanosoline (**78**, R = H) fragments, which may be preceded or followed by partial O- or N-methylation, gives rise to the dimeric or bis(benzylisoquinoline) alkaloids such as oxyacanthine (**80**), obtained along with related materials from the roots of *Berberis vulgaris* L.



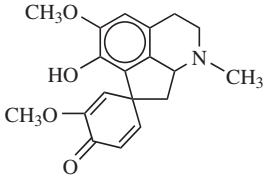
(**81**)



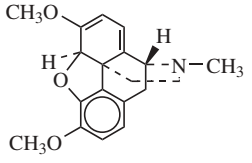
(**82**)



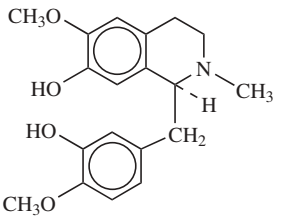
(**83**)



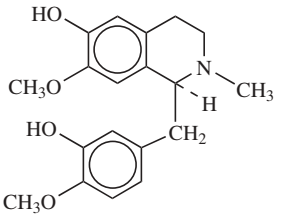
(**84**)



(**85**)



(**86**)



(**87**)

Many other bisbenzylisoquinoline alkaloids, such as tetrandrine (81), from *Cyclea peltata* Hook., are also known. Compound (**81**), although it causes hypotension and hepatotoxicity in mammals, possessed enough anticancer activity to be considered for preclinical evaluation (66). The arrow poison tubocurare prepared from *Chondrendendron* spp. also contains the bisbenzylisoquinoline alkaloid tubocurarine (**9**). In this vein it is noteworthy that specific enzymes required for the genesis of some bis(benzylisoquinoline) alkaloids have been isolated (48).

In an early attempt to understand the genesis of alkaloids from amino acids it was postulated (68) that intramolecular phenolic coupling should lead from benzylisoquinoline bases such as laudanosine (**78**, R = CH_3), before it was completely methylated, to aporphine bases such as isothebaine (82). For example, between a benzylisoquinoline derived from laudanosoline (**78**, R = H), such as orientaline (83), and an aporphine alkaloid such as isothebaine (82), there should be a proaporphine alkaloid such as orientalinone (**84**) (68). The isolation of **84** lent credence to the hypothesis. Indeed, the fragile nature of **84** (it readily undergoes the dienone–phenol rearrangement on acid treatment) required unusual skill in obtaining it from total plant extract.

Isothebaine (**82**), which may be derived from orientalinone (84) in the laboratory, is isolated from the roots of *Papaver orientale* after the period of active growth of the aerial parts and the production of thebaine (85) has ceased. The viscous milky exudate of the unripe seed pods of *P. orientale* as well as the opium poppy *Papaver somniferum* L. is opium. Opium cultivation appears to have spread from Asia Minor to China (via India) and it has been noted that the smoking of opium was common in China and elsewhere in the Far East when trade began in earnest as the eighteenth century closed. Active cultivation was encouraged by the revenues generated from addicts. Today, in the United States, although narcotine (1, noscopine) has some commercial value as a nonaddictive antitussive that occasionally leads to drowsiness, it is morphine (**2**, R = H), codeine (**2**, R = CH_3), and thebaine (**85**), the latter being converted to both of the former, which are of major commercial value.

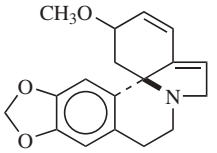
The importance of morphine (2, R = H) as an analgesic, despite danger of addiction and side effects that include depression of the central nervous system, slowing of respiration, nausea, and constipation, cannot be underestimated, and significant efforts have been expended to improve isolation techniques from crude dried opium extract. Depending on its source, the morphine content of poppy straw or dried exudate may be as high as ~20%. Although the details of current manufacturing processes are closely held secrets, early work (69) has probably not been modified extensively. Usually, the crude opium is extracted with water and filtered, and the aqueous extract concentrated, mixed with

ethanol, and made strongly basic with ammonium hydroxide. Morphine usually precipitates, while the other bases remain in solution, and is further purified by crystallization as its sulfate.

Codeine (**2**, R = CH_3) occurs in the opium poppy along with morphine (**2**, R = H) but usually in much lower concentration. Because it is less toxic than morphine (**2**, R = H) and, because its side effects (including depression, etc) are less marked, it has found widespread use in the treatment of minor pain. Much of the morphine (**2**, R = H) found in crude opium is converted to codeine (2, R = CH_3). The commercial conversion of morphine to codeine makes use of a variety of methylating agents, among which the most common are trimethylphenylammonium salts. In excess of 200 tons of codeine are consumed annually from production facilities scattered around the world (see below).

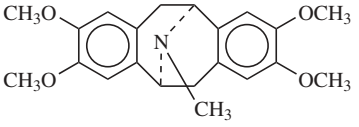
The first synthesis of morphine, and therefore also codeine, was completed in 1956 (70). Although an additional 15 or so syntheses have been reported since then, isolation of morphine remains more important than any synthetic process. However, synthetic endeavors continue. These efforts produce new synthetic tools and continue the search for modified analogues that retain the analgesic properties of morphine but are nonaddicting.

Whereas the particular methylated derivative of laudanasoline (**78**, R = H) called (−)-reticuline (**86**) (71) gives rise to thebaine (**85**), codeine (**2**, R = CH_3), and morphine (**2**, R = H), a different derivative of **78** (R = H), ie, (+)-*N*-norprotosinomenine (**87**), serves as the progenitor of erythraline (**88**), one of the bases found in *Erythrina crista galli* (72). The alkaloids found in all plant parts of *Erythrina* have been intensively studied because many of them produce smooth muscle paralysis, much like tubocurarine (**9**). A significant amount of work on the enzymes involved in the biosynthesis of the opium alkaloids has been summarized (33–36,48,73).

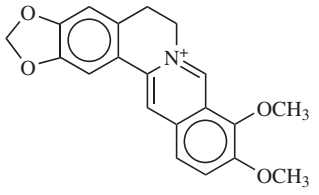


(**88**)

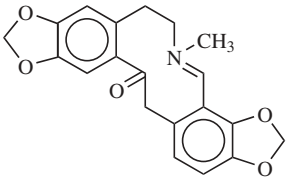
Additional oxidative coupling processes among the various methylated derivatives of laudanosoline yield many other families of bases, including the pavine argemonine (**89**) from *Argemone mexicana* L.; berberine (**90**) from *Hydrastis canadensis* L. which, despite its toxicity, has been used as an antimalarial; protopine (**91**) and chelidonine (**92**) from *Chelidonium majus* L.; rhoeadine (**93**); and the cephalotaxus ester harringtonine (**94**) from Japanese plum yews (*Cephalotaxus* spp.), which is a compound of some significance because it possesses potent antileukemic activity.



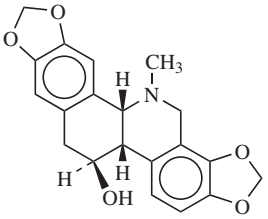
(**89**)



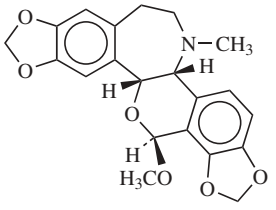
(**90**)



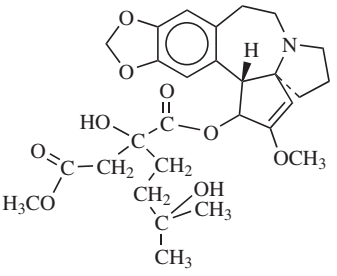
(**91**)



(**92**)

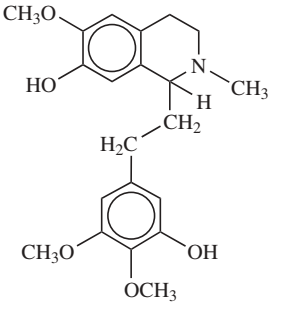


(**93**)

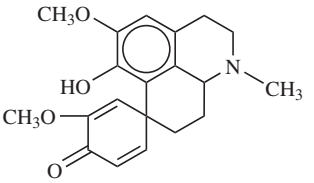


(**94**)

The last group of compounds from tyrosine and phenylalanine to be discussed here is the group derived from utilization of tyrosine (**26**, R = OH) as the C_6–C_2 fragment and phenylalanine (**26**, R = H) as a C_6–C_3 fragment. They include the 1-phenethyl-tetrahydroisoquinoline autumnaline (95), the homoproaporphine kreysiginone (**96**), which are typical of their kind. Both are isolated from *Colchicum cornigerum* (Schweinf.) and share a genesis similar to the toxic principle of the autumn crocus (*Colchicum autumnale*), colchicine (**4**). In crude form, extracts of *Colchicum* spp. were reportedly known to Dioscorides, a contemporary of Pliny, who served Nero as a physician and was the first to establish systematically the medicinal value of some 600 plants. The use of *Colchicum* spp. extracts in the treatment of gout appears to have begun in the sixteenth century, although it was not until much later that colchicine (**4**) was actually isolated (~1884). Recent interest in colchicine stems from its ability to bring cell division to an abrupt halt at a particular stage.

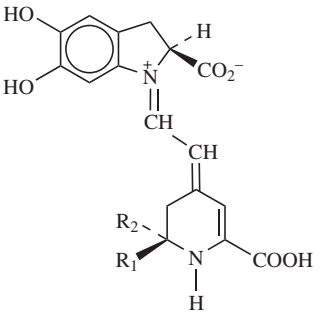


(**95**)

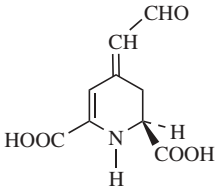


(**96**)

The structures of the brightly colored (red-violet and yellow) alkaloids found in the order *Centrospermae* (cacti, red beet, etc) remained unknown until the 1960s. In part this was doubtlessly due to the fact that these pigments, called betacyanins or betaxanthins, are relatively unstable and they are water soluble zwitterions. Invariably, in these plants they are found as acetals or ketals of sugars and one of two aglycone fragments called betanidine (**97**, $R_1 = H$, $R_2 = COOH$) and isobetanidine (**97**, $R_2 = H$, $R_1 = COOH$). Furthermore, it would appear that all betacyanins or betaxanthins may simply be imine derivatives (with the appropriate amino acid) of betalamic acid (**98**).

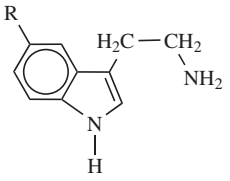


(**97**)

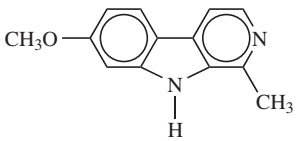


(**98**)

5.5. Tryptophan-Derived Alkaloids. The last decade has seen dramatic progress in genetic engineering and related work on many of these materials. There are a few simple indole derivatives that are arguably derived, or have actually been shown to be derived, from tryptophan (**27**) (31,33–36,48,52,73,74). Serotonin (5-hydroxytryptamine [50-67-9], (**99**), R = OH) was first isolated (75) as a vasoconstrictor substance from beef serum and shown to be derived from tryptophan (27). It has also been isolated from bananas and the stinging nettle but its genesis in plants has not yet been established. *N*,*N*-Dimethylserotonin [487-93-4] (bufotenine, **19**) has been found in such widely diverse sources as the shrub *Piptadenia peregrina*, the seeds of which are said to be the source of a ceremonial narcotic snuff; the parotid gland of the toad (*Bufo vulgaris* Laur.); certain fungi (eg, *Amantia mappa* Batsch.); and human urine. The only slightly more complicated base harmine (100) is found widely distributed in the *Leguminoseae* and *Rubiaceae*, extracts of which were at one time used therapeutically against tremors in Parkinson's disease. The seeds of the African rue, *Peganum harmala* L., which are rich in harmine and related alkaloids, have also been used as a tapeworm remedy. Harmine has been shown to be derived from tryptamine (99, R = H) by ^{14}C- and ^{15}N-labeling experiments (76).



(**99**)

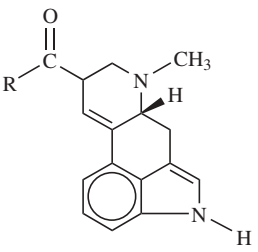


(**100**)

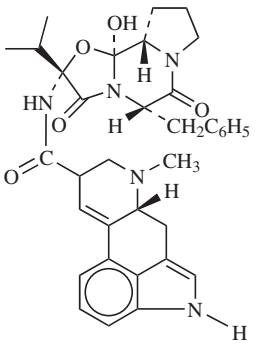
The C_6 building block, mevalonic acid (**31**), has been shown again and again to lose CO_2 and then serve as the progenitor of C_5, C_{10}, C_{15}, C_{20}, and C_{30} systems via the isomeric pair 3,3-dimethylallyl pyrophosphate (**33**)-isopentenyl pyrophosphate (**32**). This explains the genesis of a variety of bases containing the pattern defined by the five-carbon branched chain common to them and to the derivatives of mevalonic acid (**31**). Included among these are that small group of alkaloids that correspond to a joining of a tryptophan (**27**) and a C_5 unit to produce bases such as the potent uterine stimulant agroclavine (**18**) and its relatives, among which are the peptide amides of lysergic acid (**101**, R = OH).

The pistil of rye and certain other grasses may be infected by the parasitic fungus *Claviceps purpurea* (Fries). Unless the infected grain is sieved, the fungus passes into the flour, and bread made from such contaminated flour apparently retains activity from some of the alkaloids elaborated by and present in the fungus. Thus ingestion of the contaminated flour results in the disease called ergotism (St. Anthony's Fire). Convulsive ergotism causes violent muscle spasms that bend the sufferer into otherwise unattainable positions and frequently leaves physical and mental scars; outbreaks of the disease have been recorded into the twentieth century (22). Agroclavine (**18**) and derivatives of lysergic acid (**101**, R = OH) are considered responsible. Nonetheless, extracts of *C. purpurea* have long been used medicinally since they effect smooth muscle contraction and, even today, compounds related to lysergic acid and agroclavine are used for the same purpose. In the early 1940s, it was discovered that the diethylamide of lysergic acid [**101**, $R = N(CH_2CH_3)_2$] (LSD-25, as the tartrate salt) could be absorbed through the skin with resulting inebriation. In a bold experiment, it was then demonstrated that oral ingestion resulted in symptoms characteristic of schizophrenia which, although temporary, were quite dramatic (77).

There are currently two medicinally valuable alkaloids of commercial import obtained from ergot. Commercial production involves generation parasitically on rye in the field or production in culture because a commercially useful synthesis is unavailable. The common technique today (78) is to grow the fungus in submerged culture. *Claviceps paspali* (Stevens and Hall) is said to be more productive than *C. purpurea* (Fries). In this way, ergotamine (**102**) and ergonovine [**101**, $R = NHCH(CH_3)CH_2OH$] are produced. Ergotamine (**102**) is obtained from crude extract by formation of an aluminum complex.



(**101**)

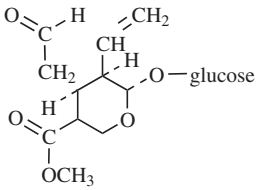


(**102**)

Destruction of the aluminum complex with ammonia then permits hydrocarbon extraction of the alkaloid. The alkaloid is subsequently both isolated and used as its tartrate salt. This nonnarcotic drug, for which tolerance may develop, is frequently used orally with caffeine (**16**) for treatment of migraine; it acts to constrict cerebral blood vessels, thus reducing blood flow to the brain.

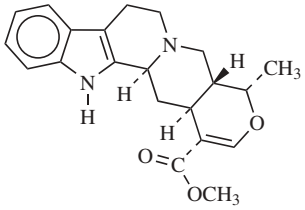
Ergonovine [**101**, R = $NHCH(CH_3)CH_2OH$] was found to yield lysergic acid (**101**, R = OH) and (+)-2-aminopropanol on alkaline hydrolysis during the early analysis of its structure (79) and these two components can be recombined to regenerate the alkaloid. Salts of ergonovine with, eg, malic acid are apparently the drugs of choice in the control and treatment of postpartum hemorrhage.

Loganin (35), the iridoid derived from the dimer (**34**) of the isomeric pair of C_5 isoprenoid units, isopentenyl pyrophosphate (**32**) and 3,3-dimethylallyl pyrophosphate (**33**), has been recognized for some years (80) as the C_9–C_{10} unit which, along with tryptophan (**27**), makes up the huge group of bases, nearly 1000 well-characterized compounds, found in the *Corynanthe-Strychnos*, *Cinchona*, *Iboga*, *Aspidosperma*, and *Eburna*. Loganin is known to undergo oxidative cleavage to secologanin [19351-63-4] (**103**), and this fragment, combined with what appears to be tryptamine [61-54-1] (**99**, R = H), $C_{10}H_{12}N_2$, or its biological equivalent, leads to compounds whose permuted structures are often novel and quite complicated. Numerous single examples of rearranged, oxidized, and convoluted structures abound, but the subdivision into the families given below is convenient for description of the majority of structural types of bases (81).

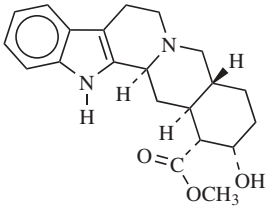


(**103**)

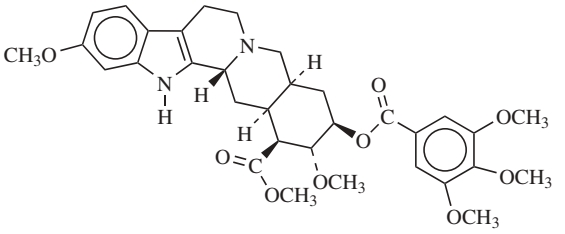
Thus in the *Corynanthe-Strychnos* are found bases such as ajmalicine (**104**), yohimbine (**105**), reserpine (**106**), ajmaline (**107**), and strychnine (**13**); in the Cinchona, quinine (17, R = OCH_3) and cinchonidine (**17**, R = H); in the *Iboga*, catharanthine (**108**); in the *Aspidosperma*, tabersonine (**109**); and in the *Eburna*, vincamine (**110**).



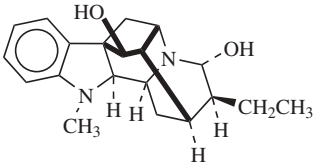
(**104**)



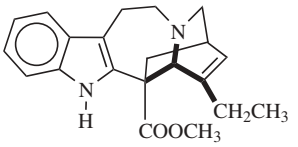
(**105**)



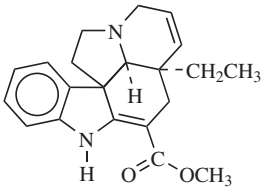
(**106**)



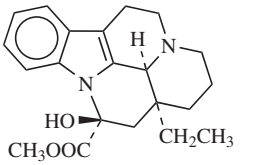
(**107**)



(**108**)



(**109**)



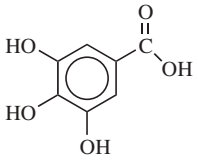
(**110**)

Ajmalicine (**104**) has been isolated (frequently as the weakest base present) numerous times from a variety of sources, eg, from the bark of *Corynanthe yohimbe* K. Schum. (*Rubiaceae*), from the roots of *Rauwolfia serpentina* (L.) Benth. (*Apocynaceae*), and from many other species of the genus *Rauwolfia*, and it is also found in plants of the genus *Catharanthus* (*Apocynaceae*). It is included here to demonstrate the pattern in secologanin (**103**)–tryptamine (**99**, R = H) coupling, the subsequent elaboration of which will give rise to the other bases to be considered. Thus ajmalicine (**104**) can be visualized, as is actually the case (**52**), as arising from the formation of an imine between the exposed aldehyde in the secologanin (**103**) and the basic nitrogen of tryptamine (**99**, R = H). This is followed by cyclization to the 2-position of the indole nucleus to form the C ring, opening of the glucose-masked acetal, and carbon–carbon bond rotation changing the cis ring junction stereochemistry found in secologanin to the trans stereochemistry of the D/E ring juncture in ajmalicine. The process continues with a second cyclization. That is the freshly exposed aldehyde resulting from opening of the acetal, the latter having swung around so that it is close to the secondary amine of the newly created C ring closes and this is followed by a reduction of the imine so created and a final cyclization of the liberated enol onto the alkene. In short, all 10 carbon atoms of secologanin and the entire tryptamine skeleton, as well as the geometry of the product, have been accounted for. This pathway, broadly painted above, is supported in detail by numerous labeling experiments with isotopes of carbon, hydrogen, and nitrogen, as well as the actual isolation of some of the intermediates described and enzymes involved in their production. All of the work has been summarized (34,48). Ajmalicine (**104**) increases cerebral blood flow and commercial mixtures of ajmalicine with one or more ergot alkaloids have been used in treating vascular disorders and hypertension.

Yohimbine (**105**), also from the bark of *C. yohimbe* K. Schum. and from the roots of *R. serpentina* (L.) Benth., has a folk history (unsubstantiated) of use as

an aphrodisiac. Its use has been confirmed experimentally as a local anesthetic, with occasional employment for relief in angina pectoris and arteriosclerosis, but is frequently contraindicated by its undesired renal effects. Yohimbine and some of its derivatives have been reported as hallucinogenic (82). In addition, its pattern of pharmacological activities in a variety of animal models is so broad that its general use is avoided. All 10 carbon atoms of secologanin (**103**) as well as the entire skeleton of tryptamine (**99**, R = H) are clearly seen as intact portions of this alkaloid.

Reserpine (**106**), also from the roots of *R. serpentina* (L.) Benth. and other *Rauwolfia* spp., is currently used as a hypotensive. There are reports in the older popular literature showing its use for a wide variety of ailments in the tropics and subtropics where the plants grow. Apparently, it was originally used to treat both high blood pressure and insanity. The former use has been replaced by substances of greater value. Even its use as a tranquilizer and sedative, which has shown some apparent successes with neuroses, at lower doses (0.05–1.5 mg/day), is no longer in vogue for treatment of psychoses (at 0.5–5.0 mg/day); better materials have been found. Nonetheless, although no analgesic effect has been noted, reserpine does act as a sedative that reduces aggressiveness. At higher doses, reserpine has been reported to cause depression as well as peptic ulceration. There is some evidence that chronic administration in women results in an increased incidence of breast cancer (83). In other experimental systems it has shown antitumor activity (84). Its interesting structure contains, as expected, a tryptamine (**99**, R = H) unit (this time substituted with a 6-methoxy group), a secologanin (**103**) C_{10} fragment, and a trimethoxybenzoic acid unit. This is presumably derived by methylation of gallic acid [149-91-7] (**111**), typically derived oxidatively from shikimic acid (**58**) and normally associated with tannins in nutgalls, from which it is obtained by hydrolysis. It is not known for *Rauwolfia spp.* if methylation of the gallic acid to produce the trimethoxybenzoic acid unit found in reserpine (**106**) occurs before the acid is esterified with the remainder of the system or if methylation occurs later. Indeed, the involvement of gallic acid (**111**), $C_7H_6O_5$, itself is, as noted above, presumptive. The total synthesis of resperpine was a landmark synthesis (85).



(**111**)

In ajmaline (**107**), also obtained from the roots of *R. serpentina* (L.) Benth., a more deeply rearranged secologanin (**103**) fragment is embedded in the molecular framework and there has been a decarboxylation from the masked β-keto carboxylic acid to generate a C_9 unit. Interestingly, the C_9 unit found in ajmaline actually began (34,48,52) as the same C_{10} unit already seen in ajmalicine (**104**), yohimbine (**105**), and reserpine (**106**), but the additional cyclization to the C ring and subsequent bonding to the 3-position on the indole nucleus creating a sixth

ring is accompanied by decarboxylation. Ajmaline has aroused some interest because it appears to possess antiarrhythmic activity (**86**), but care is required for this use when there is liver disease.

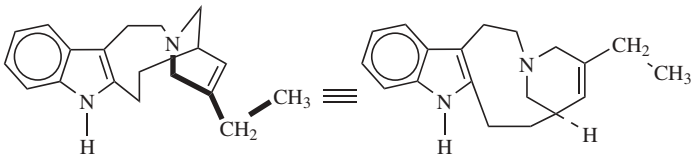
The synthesis of strychnine was a truly monumental undertaking (21). Strychnine (**13**, R = H), although only moderately toxic when compared to other poisons, both naturally occurring and produced synthetically, probably owes its reputation to its literary use. Obtained from the seeds and leaves of *Strychnos nux vomica* L. and other *Strychnos* spp., it has some history of use as a rodenticide. Poisoning is manifested by convulsions, and death apparently results from asphyxia. As little as 30–60 mg has been reported as fatal to humans, although at lower dosage it has received some medical use as an antidote for poisoning by central nervous system depressants, as a circulatory stimulant, and in treatment of delirium tremens. The useful medicinal dosage is normally <4 mg. As was the case for ajmaline (**107**), also derived from tryptamine (**99**, R = H) and secologanin (**103**), the pattern for the formation of strychnine (**13**) has been extended to even more deep seated rearrangement as well as the loss of one carbon atom, the same carboxylate as was lost in ajmaline (**107**). In addition, an acetate (C_2) unit has been added (to the indole nitrogen) and another ring created. Novel synthetic techniques continue to be applied to members of this family of alkaloids (87).

Quinine (**17**, R = OCH_3) and cinchonidine (**17**, R = H), which occur together along with other bases, eg, materials epimeric at the one-carbon bridge joining the aromatic nucleus with the 1-azabicyclo[2.2.2]heptane system, are constituents of the root, bark, and dried stems of various *Cinchona* species, but the main source remains *Cinchona officinalis* L. A crude preparation from this source was introduced into use as a palliative for malaria in the seventeenth century but several hundred years then elapsed before the first mixture of crystalline bases was obtained. Until the second World War quinine (**17**, R = OCH_3) and crude *Cinchona* preparations were the only antimalarials available. As supplies became unobtainable, synthetic materials capable of replacing quinine were developed. Recently, however, quinine has again become the treatment of choice for malaria as *Plasmodium falciparum* resistant to other drugs developed. Apparently, resistance to quinine is more difficult for the rapidly changing parasite population to acquire. Nonetheless, because quinine is not a prophylactic drug but rather a material which suppresses the overt manifestations of malaria, work continues on better treatment. The isolation of quinine from *Cinchona* bark generally involves conversion of the salts of the basic alkaloids to the free bases with, eg, calcium hydroxide (88), and extraction of the alkaloids into benzene or toluene.

Examination of the structures of the alkaloids (**17**) obtained from *Cinchona* suggests that they probably have a different pattern of formation than those already discussed. However, the differences are more formal than profound. Thus the 1-azabicyclic system is formed from one of the aldehyde equivalent carbons of a secologanin (**103**) bound fragment with the terminal nitrogen of tryptamine (**99**, R = H). Cleavage of that nitrogen away from the indole leaves behind the carbon to which it was bound, formally, at the oxidation level of an aldehyde. Then, oxidative opening of the five-membered ring between the indole nitrogen and the adjacent carbon is followed by recyclization from the aryl amine

so liberated to the aldehyde function set free in the previous step. Thus the nine expected carbons, one of the original carbons in the C_{10} fragment having been lost by decarboxylation, remain.

An understanding of the chemistry and structure of catharanthine (**108**), an otherwise minor alkaloid found in *Vinca rosea* Linn. or *Catharanthus roseus* G. Don. which is a potent diuretic in rats, was critical in unraveling the structure of two of the alkaloids cooccurring in *Vinca* which had been shown to be active against leukemia, first in mice and later in humans, ie, leurocristine (vincristine [57-22-7], **23**, R = CHO) and vincaleukoblastine (vinblastine [865-21-4], **23**, $R = CH_3$). Interestingly, the genera *Vinca* and *Catharanthus* (*Apocynaceae*) appear to be used interchangeably, ie, *Vinca rosea* Linn. is frequently called *Catharanthus roseus* G. Don. by some but not by others and vice versa (89) although the latter is now generally preferred (see below). Both catharanthine (108) and vincaleukoblastine in concentrated hydrochloric acid, when treated with stannous chloride yielded, among other fragments, the (+)-cleavamine [1674-01-7] (**112**), so called because it is a "broken" or "cleaved" amine.



(**112**)

After the structure and absolute stereochemistry of cleavamine (**112**), $C_{19}H_{24}N_2$, was established, its synthesis was completed and impetus to unravel the structure of the dimeric bases (**23**) was bolstered (90). Again, the C_9 fragment, now only slightly modified from that originally present in secologanin (**103**), is readily seen in catharanthine (**108**).

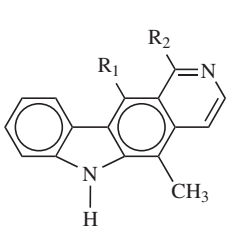
Tabersonine (**109**), clearly a reduced and simplified version of the "second-half" of the alkaloids **23**, was originally isolated from *Amsonia tabernaemontane* L. and is considered to be a simplified parent of a rather more elaborate subgroup of indole alkaloids.

Among the examples of monoindole bases being discussed, vincamine (**110**) is the principal alkaloid of *Vinca minor* L. and has received some notoriety because it apparently causes some improvement in the abilities of sufferers of cerebral arteriosclerosis (91). It is believed that this is the result of increasing cerebral blood flow with the accompanying increase in oxygenation of tissue as a result of its action as a vasodilator.

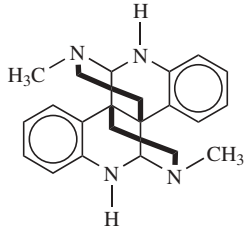
Finally, for this group of tryptophan (**27**)-derived bases there are those in which a tryptamine (**99**, R = H) residue is not obvious. Nonetheless, the pyridocarbazole bases originally isolated from *Ochrosia elliptica* Labill. (*Apocynaceae*) and subsequently from the genus *Aspidosperma*, among others, which include ellipticine (**113**, $R_1 = CH_3$, $R_2 = H$) and olivacine (**113**, $R_1 = H$, $R_2 = CH_3$), are derived from tryptophan and the normal C_9–C_{10} fragment expected. These alkaloids are known to inhibit proliferation of cells and continue to be of interest in

chemotherapeutic treatments. They appear to inhibit nucleic acid synthesis irreversibly by interacting strongly with DNA.

Bisindole Alkaloids from Tryptophan. There are two widely different types of alkaloids derived from two tryptophan (**27**) units. The first is a rather small group of compounds based simply on the dimers of tryptophan that includes compounds such as calycanthine (**114**). isolated from the seeds of the flowering aromatic shrubs Carolina Allspice (*Calycanthus floridus*) and Japanese Allspice (*Chimonanthus fragans*). The second type is that group in which the two halves arise in two distinct ways (92). Both halves may be composed of identical fragments, as in C-toxiferine (**10**), the arrow poison packed in gourds and derived from, eg, *Strychnos froesii* Ducke and *Strychnos toxifera*. The more common and very numerous (nearly 1000 compounds) family is characterized by two halves derived from different fragments, eg, leurocristine (vicristine (**23**), R = CHO) and vincaleukoblastine (vinblastine (**23**), $R = CH_3$), along with nearly 100 other compounds, from *Catharanthus roseus* (L.) G. Don, occasionally referred to in the earlier literature (see above) as *Vinca rosea* L. (93). This second group has in common the genesis of each half from tryptophan (**27**) and at least one fragment derived from mevalonic acid (**31**) itself (ie, a C_5 fragment) or derived from a monoterpene such as geraniol (**34**), −OH in place of −OPP), ie, loganin (**35**) or secologanin (**103**), a C_{10} fragment.



(**113**)



(**114**)

The search for the bisindole derivatives (**23**) was originally (94) initiated on the basis of folklore. A brew made from Jamaican periwinkle had established itself in local medicine as a treatment for diabetes and it was this material that was investigated and found to contain the cytotoxic compounds (**23**), among others. No materials useful in the treatment of diabetes have been reported from this source.

Although the compounds were isolated in quantities of only a few milligrams per kilogram of crude plant leaves, extensive work on a variety of animal tumor systems led to eventual clinical use of these bases, first alone and later in conjunction with other materials, in the treatment of Hodgkin's disease and acute lymphoblastic leukemia. Their main effect appears to be binding tightly to tubulin, the basic component of microtubules found in eukaryotic cells, thus interfering with its polymerization and hence the formation of microtubules required for tumor proliferation (95).

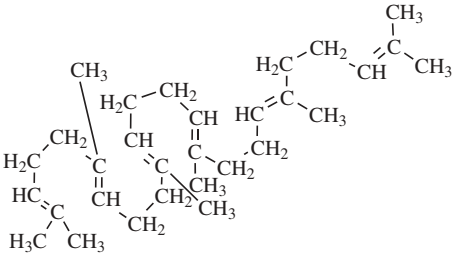
Initial attempts to synthesize the compounds (**23**) were hampered by the failure to obtain the correct stereochemical configuration about the vindoline–catharanthine linkage, a most difficult problem eventually solved by insight and hard work (96).

5.6. Introduction of Nitrogen into a Terpenoid Skeleton. The acetate-derived fragments (43) mevalonic acid (**31**), which yields isopentenyl pyrophosphate (**32**) and its isomer, 3,3-dimethylallyl pyrophosphate (**33**); a dimeric C_5 fragment, geranyl pyrophosphate (**34**), which gives rise to the iridoid loganin (**35**); and the trimer farnesyl pyrophosphate (**36**), which is also considered the precursor to C_{30} steroids, have already been mentioned. Three of the fragments [(**31**), the pair (**32**–**33**), and (**35**)] have been invoked as descriptive progenitors of alkaloids such as emetine (**67**), lysergic acid (**101**, R = OH), and many other bases already discussed and broadly categorized as monoterpenoid indole alkaloids, eg, ajmalicine (**104**). The path that links (**31**) to (**36**) and hence to the steroids is clear (97) and the details of the relationships with some of the subfragments on that path and the alkaloids resembling them and included here is well defined in some cases (34,49,52) where enzymatic pathways have been detailed. The relatively incomplete examination of alkaloidal material seems to arise only because the techniques are new and the investigators few. Historically, simpler labeling experiments led to less well defined results and were fraught with difficulty. The techniques for feeding suitably labeled precursors such as ^{13}C- and/or ^{14}C-labeled and ^{2}H- and/or ^{3}H-labeled acetate or even larger fragments (those further along on the metabolic pathway to alkaloidal product) such as mevalonic acid (**31**) and loganin (**35**) to many actively growing plants have been worked out. This is shown by the incorporation of the labeled material into alkaloids. However, it needs to be appreciated that lack of incorporation does not rule out utilization by the plant of the material fed to it. This is because there is no guarantee that the fed material reached the site of alkaloid synthesis. Thus, a negative result may simply mean that the particular feeding technique, stage of plant growth, feeding cycle, photocycle or some other variable was inappropriate for the specific material fed, rather than implying that the material is not capable of incorporation. In this vein, it is generally true that the larger fragments are more difficult to incorporate. Even though they may enter the plant when they might be actively metabolized, the particular form in which they arrive at the cell wall may be wrong for transport across the wall. Smaller fragments are less likely to have transport problems. Thus mevalonic acid (**31**) generated endogenously from exogenous labeled acetate is frequently more easily traced than suitably labeled exogenous mevalonic acid itself. However, the value is correspondingly diminished because everything may be thought of as derived from acetate and whatever the precursor, the label will have been incorporated. Thus a balance must be struck between what can be fed as labeled material and what will be incorporated into the plant. Frequently, the largest useful fragment that can be incorporated is mevalonic acid (or its corresponding lactone).

A second experimental problem is that incorporation of a material such as loganin (35), or even an amino acid that seems clearly to be a precursor by some biogenetic hypothesis, does not necessarily prove it is a precursor. The material fed may so completely swamp the normal pathways in the plant that the utilization of what was fed generates an aberrant path that nonetheless produces the same product.

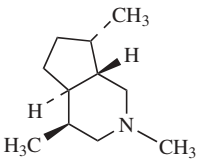
These considerations are particularly important when the description of the alkaloids is based on a presumed biosynthesis from terpene fragments because the experimental work linking the smaller pieces with the larger has yet to

succeed. That is, the well worked out paths from acetate, through (**31**) to the steroids, via geranyl pyrophosphate (**34**), farnesyl pyrophosphate (**36**), and the universal steroid precursor squalene [111-02-4] (**115**), $C_{30}H_{50}$, (97) have not been clearly demonstrated to apply in the higher, alkaloid producing, plants. Furthermore, in almost all of the alkaloids whose presumed biosynthesis derives from an insertion of nitrogen into the mevalonic acid-derived fragment, it is not quite clear at what stage the nitrogen insertion occurs. Introduction of the nitrogen at a very late stage might be an artifact of isolation because basification with ammonia of the acidic extract initially employed to isolate the basic materials is common and reaction of water soluble materials with ammonia, followed by cyclizations, etc, might occur.

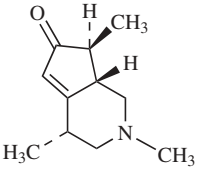


(**115**)

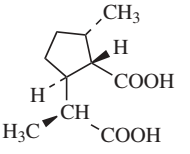
When racemic mevalonic acid as the corresponding lactone and labeled at C-2 with ^{14}C is fed to the Chilean shrub *Skytanthus acutus* Meyen., labeled β-skytanthine [24282-31-3] (**116**) is obtained. Skytanthus alkaloids are reputed to be tremorgenic (98).



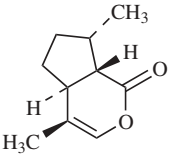
(**116**)



(**117**)



(**118**)

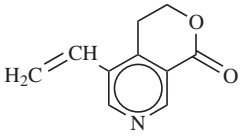


(**119**)

Tecomanine [6878-83-7] (**117**), $C_{11}H_{17}NO$, said to be a potent feline attractant (99) and material clearly related to β-skythathine (**116**), $C_{11}H_{21}N$, as well as to nepetalinic acid [485-06-3] (**118**), $C_{10}H_{16}O_4$, a degradation product of nepetalactone [490-10-8] (**119**), $C_{10}H_{14}O_2$, which is a major constituent of volatile oil of catnip (*Nepeta cataria* L.), is obtained from *Tecoma stans* Juss. Extracts of the latter (100) have some history demonstrating antidiabetic properties. Both of these bases (**115** and **116**) are derived from geranyl pyrophosphate (**34**) or loganin (**35**) or suitable similar precursor(s) before cleavage of the precursor to secologanin (**103**) or its equivalent.

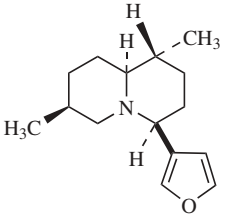
Alternatively, there are those alkaloids, such as gentianine [439-89-4] (120), $C_{10}H_9NO_2$, isolated from *Gentiana tibetica* King, among others, which are presumably derived from secologanin (**103**) and exhibit antiinflammatory action

along with being muscle relaxants.

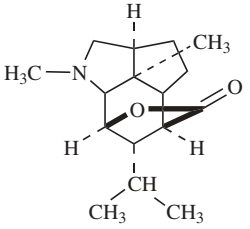


(**120**)

The C_5 trimer farnesyl pyrophosphate (**36**), in addition to serving as a progenitor of steroids via squalene (**115**), is also the progenitor of the C_{15} compounds known as sesquiterpenes. It has been suggested (101) that farnesyl pyrophosphate (**36**) similarly serves as the carbon backbone of alkaloids such as deoxynupharidine (**121**) from *Nuphar japonicum* (*Nymphaceae*) (water lilies) and dendrobine (**122**) from *Dendrobium nobile* Lindl. (*Orchidaceae*). The latter is the source of the Chinese drug Chin-Shih-Hu. Compared to the other families of bases discussed earlier, the numbers of alkaloids supposedly derived from farnesyl pyrophosphate or a close relative is small. However, given the wide variety of plant families containing sesquiterpenes, it is most likely that the numbers of compounds to be found will dramatically increase.

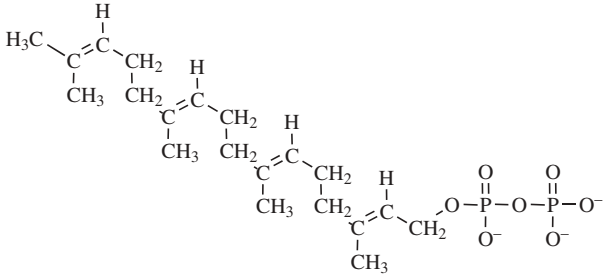


(**121**)



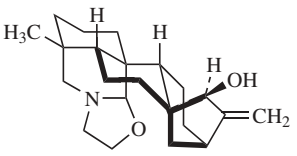
(**122**)

Whereas dimerization of two farnesyl pyrophosphates (**36**) generates squalene (**115**) on the path to steroids (102), the addition of one more C_5 unit, as isopentenyl pyrophosphate (**32**) or its isomer, 3,3-dimethylallyl pyrophosphate (**33**), to the C_{15} compound farnesyl pyrophosphate produces the C_{20} diterpene precursor geranylgeranyl pyrophosphate [6699-20-3] (**123**).

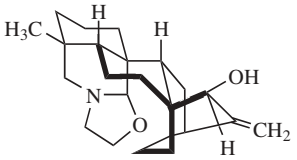


(**123**)

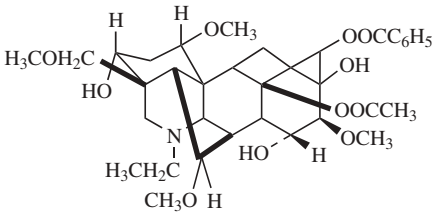
This C_{20} pyrophosphate (**123**), $C_{20}H_{36}O_7P_2$, is thought to provide the carbon framework of the diterpene alkaloids such as veatchine (**124**), atisine (**125**), and aconitine **126**). It is not known at what stage the nitrogen is incorporated into the framework established by the skeleton. The potential for terpene rearrangements and the observation that the alkaloids are frequently found esterified, often by acetic or benzoic acid, as well as free, has led to permutations and combinations producing over 100 such compounds.



(**124**)



(**125**)

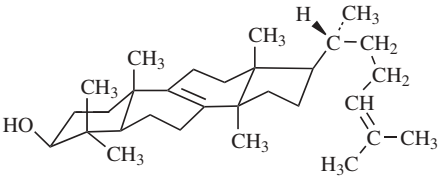


(**126**)

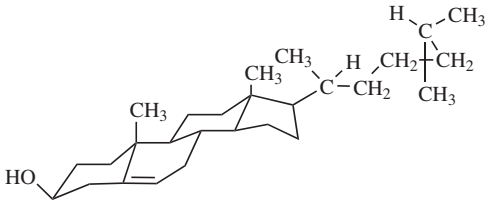
The diterpene alkaloids elaborated by most species of *Aconitum* and *Delphinium* (family *Ranunculaceae*) are apparently not found in other genera (*Ranunculus, Trollius, Anemone*, etc.) in the same family. Similar bases are, however, found in *Garrya* (eg, *Garrya veatchii* Kellog., family *Cornaceae*). Monkshood (occasionally wolf's bane, friar's cowl, or mouse bane) is obtained from the dried tuberous root of *Aconitum napellus* L. agg., and the plant is said to occur wild (103) in England and Wales as well as in the Swiss and Italian Alps. It is considered among the most dangerous of plants, all parts of it being poisonous, although the bases appear to be most concentrated in the roots. As has usually been the case, this alkaloid-bearing plant, along with the others containing diterpene alkaloids, was initially examined based on folklore and in the hope of finding medicinally valuable palliatives. Crude plant material has long been used internally as a febrifuge to lower fever and externally for neuralgia.

The base veatchine (**124**) and related materials are found in the bark of, eg, *G. veatchii* Kellog., and structural elucidation of this complicated and reactive material required massive efforts (104). Its relationship to atisine (**125**) from the roots of the atis plant, *Aconitum heterophyllum* Wall., is clearly seen as that of the well known terpene rearrangement of an *exo*-methylene octa[3.2.1]bicyclic system to that of its [2.2.2] isomer, the remainder of the molecule remaining unchanged. More deep seated rearrangements in the same part of the molecule (ie, a 6-6-5 set of rings with an *exo*-methylene group yielding a 7-5-6 set now incorporating the methylene) generates aconitine (**126**).

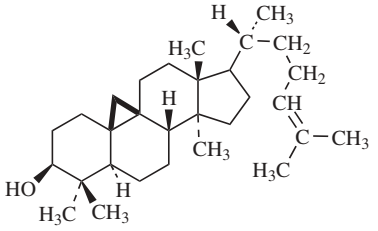
The path from squalene (**115**) to the corresponding oxide and thence to lanosterol [79-63-0] (**127**), $C_{30}H_{50}O$, cholesterol [57-88-5] (**128**), and cycloartenol [469-38-5] (**129**) has been demonstrated in nonphotosynthetic organisms. It has not yet been demonstrated that there is an obligatory path paralleling the one known for generation of plant sterols despite the obvious structural relationships of, eg, cycloartenol (**129**), $C_{30}H_{50}O$, to cyclobuxine-D (**130**), $C_{25}H_{42}N_2O$. The latter, obtained from the leaves of *Buxus sempervirens* L., has apparently found use medicinally for many disorders, from skin and venereal diseases to treatment of malaria and tuberculosis. In addition to cyclobuxine-D [2241-90-9] (**130**) from the *Buxaceae*, steroidal alkaloids are also found in the *Solanaceae, Apocynaceae*, and *Liliaceae*.



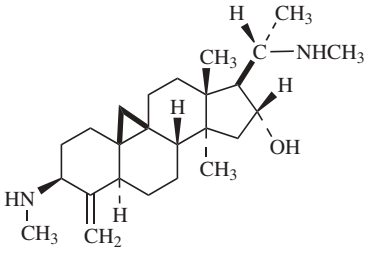
(**127**)



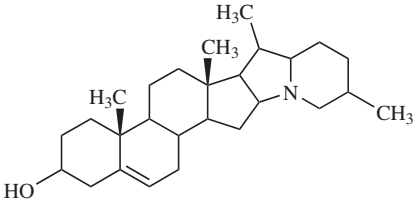
(**128**)



(**129**)



(**130**)



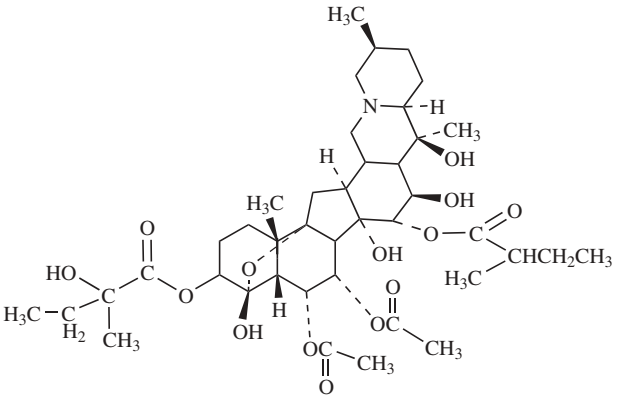
(**131**)

The plants of *Solanum* include, among others, the potato (*Solanum tuberosum* L.) and the tomato (*Solanum lycoperisicum* L.). Frequently, the plant bases occur as the aglycone portion of a glycoalkaloid bonded to one or more six-carbon sugars. Hydrolysis of the sugar portion and, somewhere along the degradative pathway, excision of the nitrogen (usually via a Hoffmann-type elimination) results in a steroid-like fragment, the analysis of which falls back on the large

body of accumulated information about steroids and their degradation products. Solanidine [80-78-4] (**131**) is typical of the kind of bases present and has been isolated from a number of Solanum.

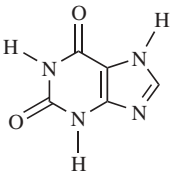
Interestingly, feeding experiments in *Solanum chacoense* L. (105) demonstrate that cholesterol (**128**), $C_{27}H_{46}O$, can be incorporated into solanidine (**131**), $C_{27}H_{43}NO$, but the amount of steroid incorporated is very low and there has been more than one suggestion (106) that the route involves initial degradation of the fed cholesterol to acetate, followed by recreation of the entire skeleton.

In addition to the alkaloids such as cyclobuxine-D (**130**) and solanidine (**131**) where the structural similarities to steroids are clear (although it must be remembered that detailed evidence actually linking the compounds is lacking) there are the less obvious (but nonetheless also clearly related) *Veratrum* alkaloids. These compounds, of which protoveratrine A [143-57-7] (**132**), $C_{41}H_{63}NO_{14}$, obtained from the rhizome of *Veratrum album* L. (*Liliaceae*), is a typical example, produce dramatic declines in blood pressure on administration and have been received by the medical community as good antihypertensive agents. Generally, however, the dosage must be individualized (slowly) from ~2 mg in 200 mL of saline upward. Because the therapeutically valuable dosage is similar to the toxic dose, and even nonlethal large doses may cause cardiac arrhythmias and peripheral vascular collapse, use of these compounds has frequently been limited to extreme cases where close attention can be accorded the patient.

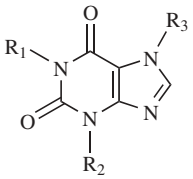


(**132**)

5.7. Purine Alkaloids. The purine skeleton is not derived from histidine (**30**), as might be imagined, nor is it derived from any obvious amino acid progenitor. As has been detailed elsewhere (41,43), the nucleus common to xanthine [69-89-6] (**133**), $C_5H_9N_4O_2$, and found in the bases of caffeine (**16**), theophylline [58-55-9] (**134**, $R_1 = R_2 = CH_3$; $R_3 = H$), and theobromine [83-67-0] (**134**, $R_1 = H$; $R_2 = R_3 = CH_3$), $C_7H_8N_4O_2$, is created from small fragments that are attached to a ribosyl unit during synthesis and can presumably be utilized in a nucleic acid backbone subsequently. All three alkaloids, caffeine, theophylline, and theobromine, occur widely in beverages commonly used worldwide.



(**133**)



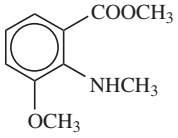
(**134**)

The leaf and leaf buds of *Cammelia sinensis* (L.) O Kuntze and other related plants and most teas contain, depending on climate, specific variety, time of harvest, etc., somewhat < 5% caffeine (**16**) and smaller amounts of theophylline (**134**, $R_1 = R_2 = CH_3$; $R_3 = H$) and theobromine (**134**, $R_1 = H$; $R_2 = R_3 = CH_3$). Coffee consists of various members of the genus *Coffea*, although the seeds of *Coffea arabica* L., believed to be indigenous to East Africa, are thought to have been the modern progenitor of the varieties of coffees currently available and generally cultivated in Indonesia and South America. The seeds contain less than ~3% caffeine which, bound to other agents, is set free during the roasting process. The caffeine may be sublimed from the roast or extracted with a variety of agents, such as methylene chloride, ethyl acetate, or dilute acid (eg, an aqueous solution of carbon dioxide) to generate decaffinated material (107). Supercritical extraction with carbon dioxide has also found to be useful.

Two other commonly found sources of caffeine (**16**) are kola (Cola) from the seeds of, eg, *Cola nitida* (Vent.) Schott and Engl., which contains 1–4% of the alkaloid, but little theophylline or theobromine, and cocoa (from the seeds of *Theobroma cacao* L.), which generally contains ~3% theobromine and significantly less caffeine.

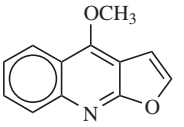
All three of these materials are apparently central nervous system (CNS) stimulants. It is believed that for most individuals caffeine causes greater stimulation than does theophylline. Theobromine apparently causes the least stimulation. There is some evidence that caffeine acts on the cortex and reduces drowsiness and fatigue, although habituation can reduce these effects.

5.8. Miscellaneous Alkaloids. Shikimic acid (**58**) is a precursor of anthranilic acid (**29**) and, in yeasts and *Escherichia coli* (a bacterium), anthranilic acid (*o*-aminobenzoic acid) is known to serve as a precursor of tryptophan (**27**). A similar but yet unknown path is presumed to operate in higher plants. Nonetheless, anthranilic acid itself is recognized as a precursor to a number of alkaloids. Thus damascenine [483-64-7] (**135**), $C_{10}H_{13}NO_3$, from the seed coats of *Nigella damascena* has been shown (108) to incorporate labeled anthranilic acid when unripe seeds of the plant are incubated with labeled precursor.

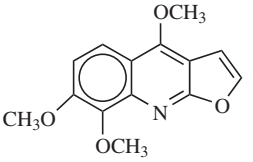


(**135**)

Similarly, anthranilic acid (**29**) has been suggested as a reasonable precursor and some early labeling studies have been carried out showing that dictamnine [484-29-7] (**136**), $C_{12}H_9NO_2$, from *Dictamnus albus* and skimmininanine [83-95-4] (**137**), $C_{14}H_{13}NO_4$, from *Skimmia japonica* incorporate anthranilic acid in a nonrandom fashion (109).

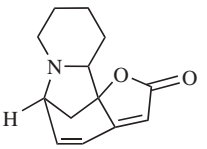


(**136**)



(**137**)

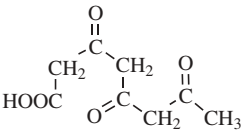
Securinine [3610-40-2] (**138**), $C_{13}H_{15}NO_2$, is the major alkaloid of *Securinega surroticosa* Rehd. and has been shown to arise from two amino acid fragments, lysine (**25**) and tyrosine (**26** R = H) (110).



(**138**)

Reactions at the aromatic nucleus that are quite different from the usual mild condensations and rearrangements that apparently generate the typical alkaloids already discussed must be involved. Securinine (**138**) is reported to stimulate respiration and increase cardiac output, as do many other alkaloids, but it also appears generally to be less toxic (111).

Coniine (**12**), implicated by Plato in the death of Socrates, is the major toxic constituent of *Conium maculatum* L. (poison hemlock) and, as pointed out earlier, was apparently the first alkaloid to be synthesized. For years it was thought that coniine was derived from lysine (**25**), as were many of its obvious relatives containing reduced piperidine nuclei and a side chain, eg, pelletierine (**47**). However, it is now known (112) that coniine is derived from a polyketooctanoic acid [7028-40-2] (**139**), $C_8H_{10}O_5$, or some other similar straight-chain analogue.



(**139**)

6. Economic Aspects

As the twenty-first century dawns, many alkaloids, such as atropine (**42**) and reserpine (**106**), that have served humanity since early history are being

replaced by synthetic materials. Others, such as the *Vinca* bases, eg, vincristine (leurocristine, **23**, R = CHO) remain as powerful medical tools. Replacement of naturally occurring alkaloids is desireable in order to maintain and augment favorable properties while eliminating undesireable properties and effects. Through strides in biochemical research, especially structure–reactivity studies, design of model compounds, combinatorial synthesis, and genomic modification synthetic and semisynthetic materials are under development or have been developed. These new materials, while occasionally related to alkaloids, either because they are derived from alkaloids or alkaloid precursors, or because their structures are similar, are not naturally occurring (unless coming from modified genomic material) and thus are not "alkaloids". However, they are generally much more specific in their action and since they are protected by patents, much more expensive.

There are four broad classes of alkaloids whose general economic aspects are important: (*1*) the opiates such as morphine and codeine (**2**, R = H and R = CH_3, respectively); (*2*) cocaine (**11**) (both licit and illicit); (*3*) caffeine (**16**) and related bases in coffee and tea, and (*4*) the tobacco alkaloids such as nicotine (**22**).

6.1. The Opiates. The International Narcotics Control Board (INCB), Vienna, tracks the licit production of narcotic drugs and annually estimates world requirements for the United Nations.

Their most recent publication (113) contains the estimate for 2001 that the primary sources of opiates are 568,539 kg of poppy straw concentrate and 1,663,576 kg of opium. The 2000 numbers were 603,899 kg and 2,154,304 kg, respectively It is estimated that worldwide opiate requirements for 2001 are ~277,713 kg of morphine (2, R = H), 384,539 kg of codeine (2, R = CH_3) and 68,952 kg of thebaine (**85**), with lesser amounts of related materials used for medicinal purposes being generated from these.

6.2. Cocaine. Production of cocaine [50-36-2] (**11**) for licit purposes (113) takes place in Bolivia and Peru. In 1988 the former exported 204 t and the latter 47 t of coca (not cocoa) leaves into the United States. The average total licit production of cocaine as a by-product in the extraction of flavoring agents from coca leaves was reported (112) to be only 425 kg in the United States in 1988. INCB estimates that 503 kg of cocaine will be used for licit purposes in 2002. The 2000 use was 923 kg (112) This must be weighed against the estimates by the U.S. Drug Enforcement Administration that the value of illegal annual exports of coca from Bolivia (1987) is $2 billion (114). It has been suggested (114) that this dollar sum is three times as much as the earnings from legal exports of tin, coffee, etc, and that it is a significant support to the Bolivian economy.

6.3. Caffeine. About 3% by weight of the roasted coffee bean is caffeine (**16**). The United Nations (UN) Food and Agriculturial Organization (FAO) reports the 1999 world production of coffee beans as 6,831,537 Mt (115). World coffee consumption is predicted to rise in the foreseeable future at the rate of 1–2% per year and thus the total amount of caffeine and related alkaloids ingested from this source can also be expected to increase. Caffeine and related bases (eg, theophylline) are also found in various teas as well as in cocoa. Again, the UNFAO reports that 3.744,714 Mt of tea and 2,943,169 Mt of cocoa beans were produced in 1999 (115).

6.4. Tobacco. Tobacco is the principal source of the alkaloid nicotine (**22**), which, it is claimed, is at least partially responsible for the addicting properties of tobacco. The FAO data currently available (115) show that over the last decade tobacco production worldwide has remained nearly constant with 7,064,272 Mt produced in 1989 and 6,971,648 Mt in 1999. It is apparently understood that tobacco is an economically valuable crop, the use of which is deleterious to the health of the users and it may be that a steady state has been reached. Its production is advocated on the one hand as it generates revenue for growers, governments, and others, but discouraged on the other hand as health problems for its users commonly result.

BIBLIOGRAPHY

"Alkaloids, Manufacture" in *ECT* 1st ed., Vol. 1, pp. 507–516, by N. Applezweig, Hygrade Laboratories, Inc.; "Alkaloids, History, Preparation, and Use" in *ECT* 2nd ed., Vol. 1, pp. 778–809, by G. H. Svoboda, Eli Lily and Co.; "Alkaloids, Survey" in *ECT* 2nd ed., Vol. 1, pp. 758–778, by W. I. Taylor, Ciba Pharmaceutical Co.; "Alkaloids" in *ECT* 3rd ed., Vol. 1, pp. 883–943, by Geoffrey A. Cordell, College of Pharmacy, University of Illinois."Alkaloids," in *ECT* 4th ed., Vol. 1, pp. 1039–1087, by David R. Dalton, Temple University; "Alkaloids" in *ECT* (online), posting date: December 4, 2000, by David R. Dalton, Temple University.

CITED PUBLICATIONS

1. T. I. Williams, *Drugs from Plants*, Sigma, London, 1947, p. 87; L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology*, 3rd ed., Macmillan, New York, 1965, pp. 247–266.
2. C. Derosne, *Ann. Chim. (Paris)* **45**, 257 (1803).
3. F. W. Serturner, *Ann. Chim. Phys.* **(2)5**, 21 (1817).
4. H.-G. Boit, *Ergebnisse der Alkaloid-Chemie Bis 1960*, Akademie-Verlag, Berlin, 1961.
5. J. S. Glasby, *Encyclopedia of the Alkaloids*, Vols. 1–4, Plenum Press, New York, 1975.
6. S. W. Pelletier, *Alkaloids. Chemical and Biological Perspectives*, Vol. 1, John Wiley & Sons, Inc., New York, 1983, pp. 25–27.
7. I. W. Southon and J. Buckingham, eds., *Dictionary of Alkaloids*, Chapman and Hall, New York, 1989.
8. R. H. F. Manske and H. L. Holmes, eds., *The Alkaloids: Chemistry and Physiology*, Vol. 1, Academic Press, Inc., New York, 1950. This series gives a detailed exposition of the chemistry and pharmacology of the alkaloids, by structural class. Vol. 57, G. A. Cordell, ed. was published in 2001.
9. T. M. Kutchan, in G. A. Cordell, ed., *The Alkaloids, Chemistry and Biology*, Vol. 50, Academic Press, New York, 1998, pp. 257–316; D. A. Rathbone, D. L. Lister, and N. C. Bruce in G. A. Cordell, ed., *The Alkaloids, Chemistry and Biology*, Vol. 57, Academic Press, New York, 2001, pp. 1–74.
10. E. Hasse, *Biblotheca Zoologica* **8**, 1 (1892).
11. J. V. Euw, T. Reichstein, and M. Rothschild, *Israel J. Chem.* **6**, 659 (1968).
12. J. A. Edgar, P. A. Cockrum, and J. L. Frahn, *Experientia* **32**, 1535 (1976).

13. J. Meinwald, *Ann. N. Y. Acad. Sci.* **471**, 197 (1986).
14. T. Eisner, M. Goetz, D. Aneshansley, G. Ferstandig-Arnold, and J. Meinwald, *Experientia* **42**, 204 (1986).
15. J. Smolanoff, A. F. Kluge, J. Meinwald, A. McPhail, R. W. Miller, Karen Hicks and T. Eisner, *Science* **188**, 734 (1975).
16. J. J. Tufariello, H. Meckler, and K. P. A. Senaratne, *J. Am. Chem. Soc.* **106**, 7979 (1984).
17. P. J. Pelleiter and J. B. Caventou, *Ann. Chim. Phys.* **8**, 323 (1818); **10**, 142 (1819).
18. J. Geiger, *Berzelius'* Jahresber. **12**, 220 (1870).
19. A. Ladenburg, *Berzelius* **19**, 439 (1886).
20. A. F. Peerdeman, *Acta Crystallogr.* **9**, 824 (1956).
21. R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *Tetrahedron* **19**, 247 (1963).
22. L. R. Caporael, *Science* **192**, 21 (1976).
23. H. Weiland, F. Konz, and K. Mittasch, *Ann.* **513**, 1 (1934).
24. G. J. Cardinale and co-workers, *Life Sci.* **40**, 301 (1987).
25. O. Dragendorff, *Z. Anal. Chem.* **137** (1866); *The Merck Index*, 5th ed., Merck & Co., Rahway, N. J., 1940, p. 687.
26. H. Mayer, *Am. J. Pharm.* **35**, 20 (1863); *The Merck Index*, 5th ed., Merck & Co., Rahway, N.J., 1940, p. 883.
27. N. R. Farnsworth, *J. Pharm. Sci.* **55**, 225 (1966).
28. R. W. Kondrat, R. G. Cooks, and J. L. McLaughlin, *Science* **199**, 978 (1978).
29. G. Zweig and J. Sherma, eds., *CRC Handbook of Chromatography*, CRC Press, Cleveland, Ohio, 1972.
30. E. Stahl, Dunnschicht-Chromatographie, Springer, Berlin, 1969.
31. V. de Luca in P. M. Dey and J. B. Harborne, eds. *Methods in Plant Biochemistry*, Vol 9, P. J. Lea, ed, *Enzymes of Secondary Metabolism*, Academic Press, New York, 1993, pp. 345–368.
32. T. Hashimoto and Y. Yamada, in P. M. Dey and J. B. Harborne, eds. *Methods in Plant Biochemistry*, Vol 9, P. J. Lea, ed, *Enzymes of Secondary Metabolism*, Academic Press, New York, 1993, pp. 369–379.
33. T. M. Kutchan, in B. E. Ellis, and co-workers, eds., *Genetic Engineering of Plant Secondary Metabolism*, Plenum Press, New York, 1994, pp. 35–59.
34. M. F. Roberts, in M. F. Roberts and M. Wink, eds., *Alkaloids, Biochemistry, Ecology and Medicinal Applications*, Plenum Press, New York, 1998, pp. 109–146.
35. K. Saito and I. Marakoshi, in M. F. Roberts and M. Wink, eds., *Alkaloids, Biochemistry, Ecology and Medicinal Applications*, Plenum Press, New York, 1998, pp. 147–157.
36. J. Berlin and L. F. Fecker, in R. Verpoorte and A. W. Alfermann, eds., *Metabolic Engineering of Plant Secondary Metabolism*, Kluwer Academic, Boston, 2000, pp. 195–216.
37. R. Bentley and I. M. Campbell, in M. Florkin and E. H. Stotz, eds., *Comprehensive Biochemistry*, Vol. 20, Elsevier, New York, 1968, pp. 415ff.
38. E. Winterstein and G. Trier, *Die Alkaloide*, Berntrager, Berlin, 1910.
39. Sir Robert Robinson, *The Structural Relations of Natural Products*, Oxford University Press, Oxford, 1955.
40. A recent redefinition of "secondary metabolism" has been set forth. See, R. Verpoorte, in R. Verpoorte and A. W. Alfermann, eds., *Metabolic Engineering of Plant Secondary Metabolism*, Kluwer Academic, Boston, 2000, p1 ff.
41. I. D. Spenser, in M. Florkin and E. H. Stotz, eds., *Comprehensive Biochemistry*, Vol. 20, Elsevier, New York, 1968, pp. 231ff.
42. G. A. Cordell, *Introduction to Alkaloids: A Biogenetic Approach*, Wiley-Interscience, New York, 1981.

43. D. R. Dalton, *The Alkaloids—A Biogenetic Approach*, Marcel Dekker, New York, 1979.
44. R. W. Herbert, in S. W. Pelletier, ed., *Alkaloids, Chemical and Physiological Perspectives*, Vol. 3, Wiley-Interscience, New York, 1985.
45. E. Leete and S. H. Kim, *J. Am. Chem. Soc.* **110**, 2976 (1988).
46. G. Grue-Sorensen and I. D. Spenser, *J. Am. Chem. Soc.* **105**, 7401 (1983).
47. H. D. Boswell, B. Drager, R. McLauchla, A. Portsteffen, D. J. Robins, R. J. Robins, and N. J. Walton, *Phytochemistry* **52**, 871 (1999).
48. P. J. Facchini, *Ann. Rev. Plant Physiol. Plant Molec. Biol.* **52**, 29. (2001)
49. E. Leistner and I. D. Spenser, *J. Am. Chem. Soc.* **95**, 4715 (1973); T. Hemscheidt and I. D. Spenser, *J. Am. Chem. Soc.* **112**, 6360 (1990).
50. D. G. O'Donovan, D. J. Long, E. Forde, and P. Geary, *J. Chem. Soc. Perkin Trans.* **1**, 415 (1975).
51. W. M. Golebiewski and I. D. Spenser, *J. Am. Chem. Soc.* **106**, 7925 (1984).
52. T. M. Kutchan, *The Plant Cell*, **7**, 1059 (1995).
53. T. Robinson, *Phytochem.*, **4**, 67 (1965).
54. E. Leete and Y.-Y. Liu, *Phytochemistry* **12**, 593 (1973).
55. S. D. Copley and J. R. Knowles, *J. Am. Chem. Soc.* **109**, 5008 (1987); W. J. Guilford, S. D. Copley, and J. R. Knowles, *J. Am. Chem. Soc.* **109**, 5013 (1987).
56. R. E. Schultes and A. Hofmann, *Plants of the Gods*, McGraw-Hill Book Co., Inc., New York, 1979.
57. W. La Barre, D. P. McAllister, J. S. Slotkin, O. C. Stewart, and S. Tax, *Science* **114**, 582 (1952).
58. W. I. Taylor and A. R. Battersby, eds., *Oxidative Coupling of Phenols*, Marcel Dekker, New York, 1967.
59. Ref. 43, pp. 197ff.
60. A. W. Gerrard, *Pharm. J.* **8**, 214 (1877).
61. O. Moller, E. M. Steinberg, and K. Torssell, *Acta Chem. Scand.* **B32**, 98 (1978).
62. J. Bolssier, G. Combes, and J. Pagny, *Ann. Pharm. Fr.* **18**, 888 (1960).
63. T. Kametani and co-workers, *J. Chem. Soc. C*, 1043 (1971).
64. H. M. Fales, J. Mann, and S. H. Mudd, *J. Am. Chem. Soc.* **85**, 2025 (1963).
65. W. C. Wildman and D. T. Bailey, *J. Am. Chem. Soc.* **91**, 150 (1969).
66. W. C. Wildman, in R. H. F. Manske, eds., *The Alkaloids*, Vol. 11, Academic Press, New York, 1968, pp. 308ff.
67. E. H. Herman and D. P. Chadwick, *Pharmacology* **12**, 97 (1974); E. J. Gralla, G. L. Coleman, and A. M. Jonas, *Cancer Chemother. Rep. Part 3* **5**, 79 (1974).
68. D. H. R. Barton and T. Cohen, *Festschrift A. Stoll*, Birkhauser Verlag, Basel, 1957, p. 117.
69. M. A. Barbier, *Ann. Pharm.* **5**, 121 (1947).
70. M. Gates and G. Tschudi, *J. Am. Chem. Soc.* **78**, 1380 (1956).
71. H. I. Parker, G. Blaschke, and H. Rapoport, *J. Am. Chem. Soc.* **94**, 1276 (1972).
72. D. H. R. Barton, C. J. Potter, and D. A. Widdowson, *J. Chem. Soc. Perkin Trans.* **1**, 346 (1974); D. H. R. Barton, R. D. Bracho, C. J. Potter, and D. A. Widdowson, *J. Chem. Soc. Perkin Trans. 1* 2278 (1974).
73. M. H. Zenk, *Special Publication of the Royal Society Chemistry*, 1995, Vol. 148, *Organic Reactivity: Physical and Biological Aspects*, pp. 89–109.
74. J. E. Saxton, ed., *Indoles, Part Four, The Monoterpenoid Indole Alkaloids*, Wiley-Interscience, New York, 1983.
75. M. M. Rapport, A. A. Green, and I. H. Page, *J. Biol. Chem.* **176**, 1243 (1948).
76. K. Stolle and D. Groger, *Arch. Pharm. (Weinheim)* **301**, 561 (1968).
77. A. Hofmann, *Botanical Museum Leaflets*, Vol. 20, Harvard University, Cambridge, Mass., 1963, p. 194.

78. Fr. Add. 91,948 (Aug. 30, 1968), J. Rutschmann and H. Kobel (Sandoz Ltd.).
79. W. A. Jacobs and L. C. Craig, *Science* **82**, 16 (1935).
80. A. R. Battersby, A. R. Burnett, and P. G. Parsons, *Chem. Commun.*, 1280 (1968).
81. I. Kompis, M. Hesse, and H. Schmid *Lloydia* **34**, 269 (1971) (gives a much more elaborate classification scheme).
82. G. Holmberg and S. Gershon, *Psychopharmacologia* **2**, 93 (1961); M. L. Brown, S. Gershon, W. J. Lang, and B. Korol, *Arch. Intern. Pharmacodyn.* **160**, 407 (1966).
83. B. Armstrong, N. Stevens, and R. Doll, *Lancet* **2**, 672 (1974).
84. J. L. Hartwell, *Cancer Treatment Rep.* **60**, 1031 (1976).
85. R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).
86. M. L. Chatterjee and M. S. De, *Bull. Calcutta School Trop. Med.* **5**, 173 (1957); *Chem. Abstr.* **52**, 8356a (1958).
87. S. A. Kozmin, T. Iwama, Y. Huang and V. H. Rawal, *J. Am. Chem. Soc.* **124**, 4628 (2002).
88. J. Schwyzer, *Die Fabrikation Pharmazeutischer and Chemisch, Technischer Produkte*, Springer-Verlag, Berlin, 1931.
89. W. I. Taylor and N. R. Farnsworth, eds., *The Catharanthus Alkaloids, Botany, Chemistry, Pharmacology and Clinical Uses*, Marcel Dekker, New York, 1973; W. I. Taylor and N. R. Farnsworth, eds., *The Vinca Alkaloids, Botany, Chemistry and Pharmacology*, Marcel Dekker, New York, 1973.
90. G. Buchi, P. Kulsa, K. Ogasawara, and R. L. Rosati, *J. Am. Chem. Soc.* **92**, 999 (1970) and references therein.
91. A. Ravina, *Presse Med.* **74**, 525 (1978).
92. G. A. Cordell in Ref. 74, pp. 539ff.
93. W. T. Stearn, *Lloydia* **29**, 196 (1966).
94. W. A. Creasey, in F. Hahn, ed., *Antibiotics*, Vol. 5, Springer-Verlag, Berlin, 1979, p. 414.
95. E. K. Rowinsky, L. A. Cazenave, and R. C. Donehower, *J. Natl. Cancer Inst.* **82**, 1247 (1990) (deals with antimicrotubule agents, albeit with a nonalkaloidal agent).
96. J. P. Kutney and co-workers, *J. Am. Chem. Soc.* **97**, 5013 (1975); M. E. Kuehne and T. C. Zebovitz, *J. Org. Chem.* **52**, 4331 (1987); M. E. Kuehne, T. C. Zebovitz, W. G. Bornmann, and I. Marko, *J. Org. Chem.* **52**, 4340 (1987).
97. G. Popjak and J. W. Cornforth, *Biochem. J.* **101**, 553 (1966); J. W. Cornforth, R. H. Cornforth, A. Pelter, M. G. Horning, and G. Popjak, *Tetrahedron* **5**, 311 (1959); R. B. Clayton in T. W. Goodwing, ed., *Aspects of Terpenoid Chemistry and Biochemistry*, Academic Press, New York, 1971, pp. 1ff.
98. T. Sakan, *Tampakushitsu Kakusan Koso* **12**, 2 (1967); *Chem. Abstr.* **73**, 42351c (1970).
99. G. L. Gatti and M. Marotta, *Ann. Ist. Super. Sanita* **2**, 29 (1966); *Chem. Abstr.* **65**, 14293e (1966).
100. W. C. Wildman, J. LeMen, and K. Wiesner, in W. I. Taylor and A. R. Battersby, eds., *Cyclopentanoid Terpene Derivatives*, Marcel Dekker, New York, 1969, pp. 239ff.
101. O. E. Edwards, in W. I. Taylor and A. R. Battersby, eds., *Cyclopentanoid Terpene Derivatives*, Marcel Dekker, New York, 1969, pp. 357ff.
102. T. T. Tchen and K. Block, *J. Am. Chem. Soc.* **77**, 6085 (1955); R. B. Clayton and K. Block, *J. Biol. Chem.* **218**, 319 (1956); L. J. Goad, *Symp. Biochem. Soc.* **29**, 45 (1970).
103. G. A. Swan, *An Introduction to the Alkaloids*, John Wiley & Sons, Inc., New York, 1967, p. 274.
104. S. W. Pelletier, N. V. Mody, and H. K. Desai, *J. Org. Chem.* **46**, 1840 (1981).
105. H. Ripperger, W. Mortiz, and K. Schreiber, *Phytochemistry* **10**, 2699 (1971).
106. S. J. Jadav, D. K. Salunkhe, R. E. Wyse, and R. R. Dalvi, *J. Food Sci.* **38**, 453 (1973).

107. U. S. Pat. 3,108,876 (Oct. 29, 1963), H. H. Turken and T. P. Daley (to Duncan Coffee Co.); U. S. Pat. 3,361,571 (Jan. 2, 1968), L. Nutting and G. S. Chong (to Hills Bros. Coffee, Inc.).
108. E. J. Miller, S. R. Pinnell, G. R. Martin, and E. Schiffman, *Biochem. Biophys. Res. Commun.* **26**, 132 (1967).
109. E. Monkovic, I. D. Spenser, and A. O. Plunkett, *Can. J. Chem.* **45**, 1935 (1967).
110. M. Matsuo and Y. Kasida, *Chem. Pharm. Bull. (Tokyo)* **14**, 1108 (1966).
111. V. A. Snieckus, *Alkaloids (N.Y.)* **14**, 425 (1973).
112. E. Leete, *Acc. Chem. Res.* **4**, 100 (1971).
113. International Narcotics Control Board—;Vienna, (www.incb.org) *Narcotic Drugs, Estimated World Requirements for 1990, Statistics for 1988*, United Nations Publ. E/F/S.89.XI.3, New York, 1989, pp. 33ff. Current statistics are from (http://www.incb.org/e/index.htm?) Statistics for 2000–2002.
114. L. Mahnke, *Aach. Geog. Arbeit.* **19**, 137 (1987).
115. http://apps. fao. org/page/form?collection=CBD. CropsAndProducts& Domain=CBD &servlet=1&language=EN&hostmane=apps.fao.org&version=default.

DAVID R. DALTON
Temple University
LINDA M. MASCAVAGE
Arcadia University
MICHAEL WILSON
Wilson Technologies, Ltd.