ALKALOIDS: CHEMICAL AND BIOLOGICAL PERSPECTIVES

Volume Three

Edited by

S. WILLIAM PELLETIER

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Preface

Volume 3 of *Alkaloids: Chemical and Biological Perspectives* presents timely reviews of seven important alkaloid topics.

Chapter 1 reviews both the chemistry and pharmacology of the pyridine and piperidine alkaloids, compounds that are widespread in nature. To our knowledge this chapter is the first that treats both the chemistry and the pharmacology of major representatives of these two classes of alkaloids.

Chapter 2 treats the indolosesquiterpene alkaloids, a class of compounds that may formally be divided into indole and sesquiterpene subunits.

The cyclopeptide alkaloids, reviewed in Chapter 3, are a rapidly growing group of closely related polyamide bases of plant origin. Alkaloids of the class are sometimes called "ansapeptides" and "phencyclopeptines," the latter term representing the fundamental para-bridged 14-membered ring nucleus common in most of these macrocyclic alkaloids.

Cannabis sativa L., the plant from which marijuana, hashish, and hash oil are obtained, has been known in medicine for thousands of years. It has been recommended for treatment of rheumatism, beriberi, neuralgia, asthma, malaria, hysteria, insomnia, tetanus, epilepsy, and constipation, though in 1942 *Cannabis* was denied admission into the U.S. Pharmacopeia because of lack of acceptable medical use in the United States. Though over 400 chemical compounds are known to exist in *Cannabis,* only a few alkaloids have been isolated and characterized. Chapter 4 reviews the alkaloids, amino acids, amino sugars, proteins, and enzymes that occur in *Cannabis,* and summarizes the biological properties of the alkaloids.

Since the synthesis of alkaloids has become increasingly important during the past 20 years, we have included three chapters on alkaloid synthesis in this volume. Chapter 5 presents an excellent review of the biosynthesis and total synthesis of the *Lycopodium* (club moss) alkaloids. Chapter 6 reviews syntheses directed toward indolizidine and quinolizidine alkaloids found in *Tylophora, Cryptocarya, Ipomoea, Elaeocarpus,* and related species. A final chapter surveys recent work on the total synthesis of the important pentacyclic *Aspidosperma* alkaloids.

Each chapter in this volume has been reviewed by an authority in the field. Indexes for both subjects and organisms are provided.

The editor invites prospective contributors to write him about topics suitable for review in future volumes of this series.

S. WILLIAM PELLETIER

Athens, Georgia
October 1984

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Chapter One

The Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology

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1. INTRODUCTION

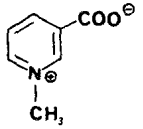
The pyridine alkaloids and the hydrogenated species are widespread in nature. Among others, the first alkaloid to be synthesized was a piperidine, coniine. The chemistry of the unsaturated aromatic and the saturated group has usually been reviewed together. Starting in 1950 the Manske Alkaloids series gave three reviews, two by Leo Marion in 1950 and 1960 [1, 2], and one in 1969 by W. Ayer [3]. The latest review was written by D. Gross in 1970 in Fortschritte [4]. Since then there has been no extensive treatise of the chemistry of the piperidine alkaloids, except for some subgroups; several representatives of the class have been recognized and the biosynthesis of many compounds has been established. The stereochemistry including absolute configuration of many alkaloids is known. Nevertheless there is no review that treats both the chemistry and pharmacology of the major representatives of these two classes. Therefore it is of interest to update our picture of these important areas.

There are a few limitations. Because an excellent review has appeared recently in the present series on the biosynthesis of tobacco alkaloids [5] that treats a substantial number of the pyridines, like nicotine itself, and the piperidines such as anabasine, we have a priori excluded details of the biosynthesis of the tobacco alkaloids from this review. We have not followed the biogenetic pattern as it has been presented on other alkaloids in two recent monographs [6], [7], nor have we followed the plant source as a chief indicator for the sequence in which the individual alkaloids were treated. We feel that the pyridine alkaloids should be treated separately from the piperidine alkaloids. There is no close biochemical connection between the two groups except for some tetrahydropyridines that are derived in nature by the reduction of a pyridine ring, for example, anatabine. Therefore, we wish to present, in Table 1, the pyridine alkaloids and, in Table 2, the piperidines that we shall discuss. We are aware of the fact that every system is arbitrary. Starting with *N*-methylnicotinic acid betaine, it is easy to recognize that most of the pyridine alkaloids that we are dealing with are derived from nicotinic acid in one way or another. The family of nicotine alkaloids shall be presented in chemical sequence. Our major point of view is chemistry which is immediately followed, at the end of the description of the individual representative, by pharmacology. Concerning structure determination, we shall put emphasis on recently discovered alkaloids and on modern chemical and spectral methods. Syntheses will be reported, but only one in most cases. Preference will be given to the most recent method that, in addition to supporting a structure, may eventually lead to practical application.

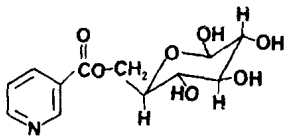
2. PYRIDINE ALKALOIDS (TABLE 1)

We are proceeding from simple derivatives like the betaine of *N*-methylnicotinic acid to an ester with glucose, to arecoline, then to a nicotinonitrile that has been oxygenated to ricinine, to gentianine that is reminescent of the nicotinic acid

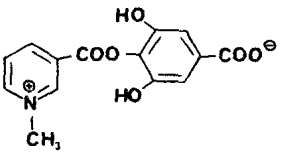
Table 1. Pyridine Alkaloids



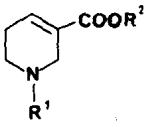
1 TRIGONELLINE



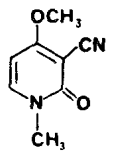
2a BUCHANANINE



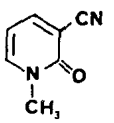
2b PRECATORINE



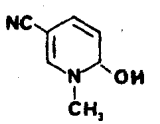
	R^1	R^2	
3a	H	H	GUVACINE
b	H	CH_3	GUVACOLINE
c	CH_3	H	ARECAIDINE
d	CH_3	CH_3	ARECOLINE



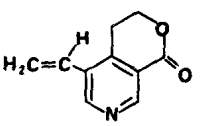
4 RICININE



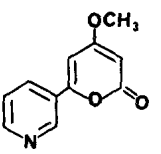
5 RICINIDINE



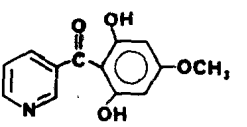
6 NUDIFLORINE



7 GENTIANINE*

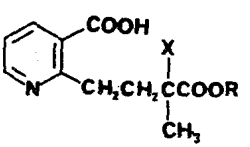


8 ANIBINE

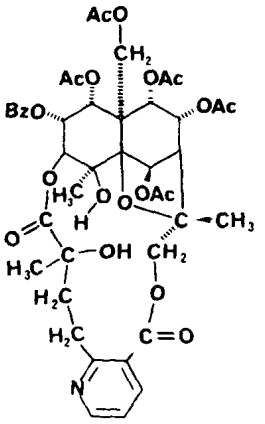


9 DUCKEIN

* = non-natural product

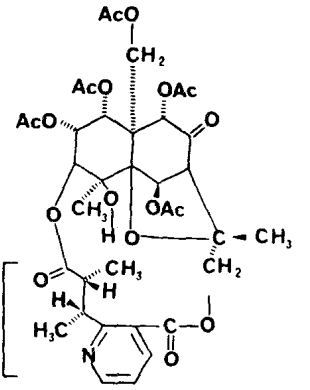


	X	
10a	H	WILFORIC ACID
b	OH	WILFORDIC ACID

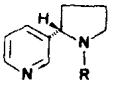


11 WILFORDINE

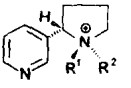
EVONINIC ACID



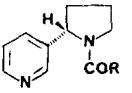
12 EVONINE



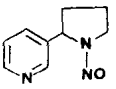
	R	
13	CH_3	S(-) NICOTINE
16	H	S(-) NORNICOTINE



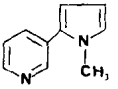
	NICOTINE N-OXIDES	
	R^1	R^2
14	CH_3	O
15	O	CH_3



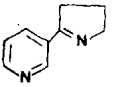
	R	NORNICOTINES
17	H	N-FORMYL
18	CH_3	N-ACETYL
19	$n\text{-}C_5H_{11}$	N-HEXANOYL
20	$n\text{-}C_7H_{15}$	N-OCTANOYL



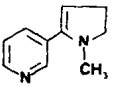
21 N-NITROSO NORNICOTINE



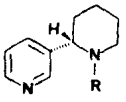
22 NICOTYRINE



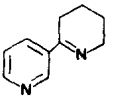
23 MYOSMINE



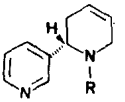
24 N-METHYL-MYOSMINE



	R	
25	H	S(-)ANABASINE
26	CH_3	N-METHYL ANABASINE

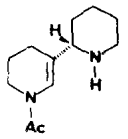


27 ANABASEINE

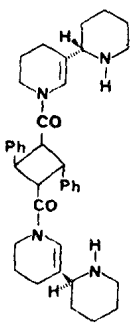


	R	
28	H	ANATABINE
29	CH_3	N-METHYL ANATABINE

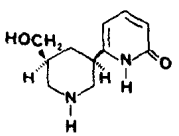
Table 1. (*Continued*)



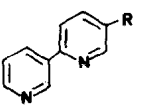
30 CH_3CO AMMODENDRINE
31 trans, cinnamyl ORENSINE ≡ (·) ADENOCARPINE
32 *cis*-cinnamyl *ISOORENSINE*



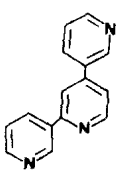
33 SANTIAGUINE



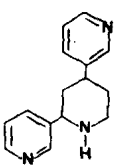
34 KURARAMINE



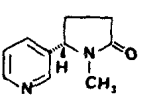
R
35 H 2,3′-DIPYRIDYL
36 CH_3 5-METHYL-2,3′-DIPYRIDYL



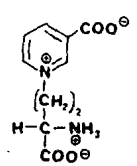
37 NICOTELLINE



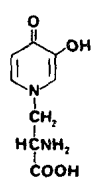
38 ANATALLINE



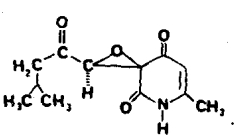
39 COTININE



40 NICOTIANINE

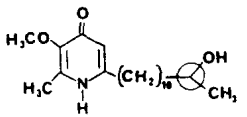


41 MIMOSINE and LEUCAENINE

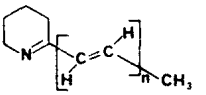


42 FLAVIPUCINE

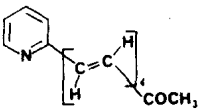
Table 1. *(Continued)*



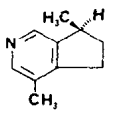
43 S(-) MELOCHININE



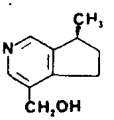
44 n=3 NIGRIFACTIN
45 n=2 ALKALOID of STREPTOMYCES NA-337



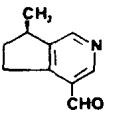
46 NAVENONE A



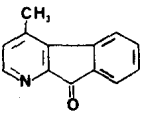
47 S(-) ACTINIDINE



48 S(-)TECOSTIDINE



49 R(-)BOSCHNIAKINE



50 ONYCHINE

skeleton, to the tobacco alkaloids, and finally to pyridines, dihydropyridines, and pyridines, some of which are structurally unrelated to nicotinic acid.

2.1. Trigonelline

2.1.1. Chemistry. Trigonelline **(1)** was discovered in the seeds of *Trigonella foenum,* but it is also present in the seeds of *Pisum sativum* and *Cannabis sativa* and in coffee, soybeans, and potatoes. It gives methylamine upon heating with barium hydroxide, and based on its elemental analysis, ($C_7H_7NO_2$), it was assumed to be the methyl betaine of nicotinic acid. This was indeed proven by comparison with authentic *N*-methylnicotinic acid that was obtained by quaternization of nicotinic acid with methyl iodide followed by neutralization [8].

2.1.2. Pharmacology. Although trigonelline is formed in the liver in both dogs and man after oral administration of nicotinic acid (niacin), trigonelline is not the major metabolite of this essential vitamin. The principal metabolic pathway of moderate doses of nicotinic acid as well as of nicotinamide, the chemical form of nicotinic acid after its incorporation into adenine nucleotides, involves the formation of *N*-methyl nicotinamide. This major metabolite, in turn, can undergo further degradation, with the formation of several pyridones. After administration of extremely high doses of nicotinic acid, little metabolism occurs, and the majority of the administered vitamin is excreted in the urine unchanged [9].

Nicotinic acid is widely recognized mainly as an essential dietary constituent.

A lack of nicotinic acid in the diet leads to the disease entity known as pellagra in man and to an equivalent condition termed black tongue in dogs. To perform its function as a vitamin, nicotinic acid is first converted in the body to both nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These two compounds then serve as coenzymes for a number of enzymes that catalyze oxidation–reduction reactions essential for tissue respiration.

Nicotinic acid itself produces several important attendant pharmacological effects not seen after administration of nicotinamide. This vitamin rapidly reduces plasma levels of cholesterol and triglycerides by several diverse mechanisms [10]. Nicotinic acid also produces vasodilation. The blush areas are much more affected than the extremities, however, and neither skin nor muscle blood flow is consistently increased [11]. Nicotinic acid is used therapeutically for both hypolipidemic effect and, without basis, as a vasodilator. Its therapeutic use as prophylaxis and treatment of pellagra is, fortunately, rarely necessary in the United States today. It has been claimed that high doses of nicotinic acid possess therapeutic value in the treatment of schizophrenia. The assumption underlying the presumed effectiveness of this vitamin is that, by providing excess methyl acceptors, a postulated abnormal transmethylation of catecholamines is inhibited [12]. The actual usefulness of nicotinic acid after a host of clinical trials in schizophrenic patients, however, remains controversial.

Unlike nicotinic acid or nicotinamide, neither *N*-methyl nicotinamide nor trigonelline reverses the condition of black tongue in dogs. Because *Trigonella* seeds ("chilbe") have long been included in the diet of diabetic Yemenites in Israel in accordance with regional medical folklore, trigonelline was examined for, and reported to possess, hypoglycemic activity [13]. In subsequent studies trigonelline was found to exert some degree of an effect in both laboratory animals and diabetic patients [14]. In rabbits this alkaloid counteracted the hyperglycemic effect of cortisone when administered concomitantly with the latter steroid or 2 h earlier, but not when given 2 h after cortisone administration. After administration of trigonelline to diabetic patients, however, a transient hypoglycemic effect occurred in only 50% of the subjects. In a more comprehensive study several alkaloids of *Trigonella* seeds, as well as nicotinamide, were examined for hypoglycemic activity in both alloxan-diabetic and nondiabetic rats [15]. In this species trigonelline produced only a mild and transient hypoglycemia in the diabetic animals, while both nicotinic acid and nicotinamide exerted a profound effect of much longer duration in the same experimental group. Of these three compounds, only nicotinic acid exerted an effect in normal rats. On the basis of these results, the mild hypoglycemic activity of trigonelline was ascribed to its slowing down of the metabolism of nicotinic acid.

It is noteworthy that the acute toxicity of both trigonelline and nicotinic acid in the rat is quite low. The total minimal daily dietary requirement of nicotinic acid in man is in the range of 10–20 mg. In contrast, the lethal dose of either trigonelline or nicotinic acid in 50% of the rodents tested amounted to quantities ranging from 5 to 9 g/kg of body weight [15].

2.2. Buchananine

Buchananine **(2)** from *Cryptolepis buchanani* gave upon hydrolysis glucose and nicotinic acid. Since it consumed two molecules of periodic acid, the primary hydroxyl was involved in the esterification with nicotinic acid [16]. It has been synthesized [17] from nicotinoyl chloride and 1,2-isopropylidene glucofuranose, followed by acetal cleavage. There is nothing known about its biological or pharmacological activity. Precatorine **(2b)** from *Abrus precatorius* is 4-*N*-methyl nicotinoyl gallic acid betaine [18].

2.3. Chemistry of the Areca nut alkaloids

Guvacine **(3a)**, guvacoline **(3b)**, arecaidine **(3c)**, and arecoline **(3d)** are the major alkaloids of *Areca catechu* nut. Arecaidine is the free carboxylic acid *N*-methyl-1,2,5,6-tetrahydronicotinic acid **(3c)** and arecoline is its methyl ester **(3d)** while guvacine and guvacoline are their *N*-nor derivatives. The structures of **3c** and **3d** are based on an unambiguous total synthesis [19] from 3-methyliminodipropionaldehyde-tetraethylacetal that upon reaction with hydrochloric acid gave 1-methyl-Δ^3-tetrahydropyridine-3-aldehyde. The latter by oxidation was converted into the free carboxylic acid that proved identical with arecaidine. Action of methyl iodide on guvacine gave arecaidine methyl betaine, which proved the constitution of guvacine as **3a** [20].

2.4. Pharmacology of the Areca Nut Alkaloids: Arecoline, Arecaidine, Guvacine

Of the alkaloids occurring within the *Areca* nut, arecoline has by far received the most attention with regard to pharmacological properties. Arecoline is one of three major natural alkaloids known to possess cholinomimetic activity. While the other two alkaloids, that is, muscarine and pilocarpine, act predominantly at muscarinic receptor sites, arecoline acts at nicotinic receptor sites as well.

The muscarinic actions of arecoline encompass a variety of organ systems. Prominent effects are exerted on the cardiovascular system. Low doses produce vasodilation within the major vascular beds and thus a fall in both systolic and diastolic blood pressure. Pressor–receptor mechanisms cause reflex activation of sympathetic activity, with resultant tachycardia. At higher doses arecoline also exerts a direct depressant effect on the heart, and both blood pressure and heart rate fall.

Arecoline exerts stimulatory effects on the gastrointestinal tract, with an increase in both resting tone and force of contractions of the smooth muscle lining the tract. Bronchial smooth muscle is also stimulated; the resultant bronchoconstriction may precipitate asthmatic attacks. Arecoline similarly

stimulates the salivary, lacrimal, and sweat glands. Diaphoresis is marked because the direct effect on the sweat gland is enhanced by cutaneous vasodilation.

Other prominent peripheral muscarinic actions of arecoline include pupillary constriction, urinary bladder contraction, and decreased bladder capacity. Centrally, arecoline induces a characteristic cortical EEG arousal response that is also muscarinic in nature, as the response is blocked by atropine.

The nicotinic effects of arecoline are seen after the administration of large doses. Nicotinic receptor stimulation results in the release of catecholamines from both postganglionic sympathetic nerve fibers and the adrenal medulla; the net effect is an increase in sympathetic activity. An additional nicotinic action consists of skeletal muscle stimulation.

Structure-activity relationships for the production of muscarinic effects by both naturally occurring and synthetic arecaidine derivatives have been examined [21, 22]. Arecoline (i.e., arecaidine methyl ester) is a tertiary amine that is active in the protonated form. The activity of the carboxylic acid, arecaidine, is markedly reduced. Tertiary esters with a side chain longer than an ethyl group likewise show considerably less activity. Quaternization considerably decreases the intrinsic activity of arecaidine methyl ester and confers antagonistic activity to the remaining esters. Hydrogenation of the double bond in the ring, as in the case of arecolidine, markedly lowers both affinity and intrinsic activity.

Although both arecaidine and guvacine possess only weak cholinomimetic properties, these two alkaloids are potent inhibitors of the uptake of gamma amino butyric acid (GABA) into brain slices *in vitro* [23]. After electrophoretic administration both amino acids also enhanced the inhibitory actions of GABA on the firing of spinal neurons [24]. In the latter study the uptake of GABA by cerebellar slices was likewise inhibited by arecaidine, as expected, and the effect of GABA on the firing of cerebellar Purkinje cells was correspondingly enhanced by electrophoretically administered arecaidine. After intravenous administration, however, arecaidine had no effect on synaptic inhibitions presumably mediated by GABA. On the basis of these results, it was concluded that the reduction of GABA inactivation by arecaidine and guvacine resulting from GABA uptake inhibition does not likely play a major role in the mediation of the behavioral effects of the *Areca* nut.

In spite of the large differences in the pharmacological profiles of arecaidine and arecoline, some of the behavioral effects exerted by these two alkaloids are quite similar. Both compounds decrease spontaneous motor activity and food intake in rodents [25, 26], and both are effective in reversing chlorpromazine sedation [25, 27]. The effects of these alkaloids on barbiturate sleeping time, however, were quite divergent, with arecoline shortening the duration [27] and arecaidine prolonging it [25].

Focus on the behavioral effects of the *Areca* nut alkaloids arose from the time-honored consumption of a masticatory mixture containing *Areca* nut by Oriental natives for its euphoric effects. The masticatory mixture, dubbed *betel*

quid, consists of the leaves of *Piper betle* (a climbing species of pepper), *Areca* nut, catechu, and lime; some users also add tobacco. This mixture is commonly known as *paan* in India.

The physiological effects resulting from the chewing of betel quid are primarily referable to the prominent cholinomimetic activity of the major *Areca* nut alkaloid, arecoline. The neuropharmacological mechanisms involved in the production of the psychic changes, by contrast, remain obscure. Although arecaidine probably contributes to this effect because it is formed from arecoline after the chewing of betel, the inhibition of GABA uptake produced by arecaidine is thought not to be involved [24].

A relationship between betel quid chewing and oral cancer has been suggested since the early 1960s [28, 29]. Cellular changes such as leukoplakia have subsequently been produced by a number of investigators after application of betel quid to the buccal mucosa of a variety of species [30]. Tobacco did not have to be present in the betel mixture in order for carcinogenic properties to appear [31]. The *Areca* nut alkaloid arecoline was later shown to induce *in vitro* neoplastic transformation [32], and potentiation of its genotoxicity by other constituents of betel quid has recently been reported [33].

Although the major *Areca* nut alkaloids are quite valuable as pharmacological tools, current clinical use of any of these compounds is restricted to veterinary medicine, where arecoline is employed as an anthelmintic. The *Areca* nut itself, however, still retains an important position in the Indian way of life [30]. In addition to its use for chewing purposes, it still plays an important role in many of the religious ceremonies of India. The medicinal properties of the *Areca* nut, which have been extolled in older Indian literature for treatment of conditions ranging from bad breath to urinary tract disorders, are still utilized in several remote parts of the country.

2.5. Ricinine

2.5.1. Chemistry. Ricinine (4) has been known for over 100 years. It was extracted from the *Ricinus communis* plant, which contains 1.1%. The structure elucidation was done by conventional methods, such as distillation with zinc dust [1]. Coloration with ferric chloride was significant indicating an α-pyridone structure. Among several total syntheses of ricinine, the simplest is the condensation of two molecules of cyanoacetyl chloride to give 6-chloro-*O,N*-bisnorricinine. This upon methylation on *N*(1) and *O*(4) followed by reductive dechlorination with zinc and acid gave rise to ricinine [34, 35]. This synthesis proves its structure and it is certainly the simplest way to get to the molecule. There is no need for the preparation of ricinine by synthetic methods, however, because the *Ricinus* extract gives an abundant amount of the natural product.

The biosynthesis of ricinine is a fascinating subject. The methyl group originates from methionine [36], but the total pyridine skeleton arises from quinolinic acid, that is, pyridine-2,3-dicarboxylic acid, via the nicotinic acid mononucleotide (Scheme 1). The oxidation pathway is not perfectly elucidated;