

CORDELL

INTRODUCTION  
TO ALKALOIDS:

A Biogenetic Approach

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Interscience

# INTRODUCTION TO ALKALOIDS

*A Biogenetic Approach*

GEOFFREY A. CORDELL

*University of Illinois*

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# INTRODUCTION TO ALKALOIDS



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*“It must not be assumed that atoms of every sort can be linked in every variety of combination”*

TITUS LUCRETIVS CARUS (100-55 B.C.)  
*On the Nature of the Universe*

*“What is now proved was once only imagined”*

WILLIAM BLAKE  
*The Marriage of Heaven and Hell*

# PREFACE

*"Though this be madness yet there is method in't."*

W. SHAKESPEARE

*Hamlet, II, ii.*

This monograph arose at the suggestion of the publisher after I had submitted a chapter on alkaloids for the Kirk-Othmer *Encyclopedia of Chemical Technology*. It was realized that there was no current book developing the history, chemistry, biosynthesis, and utility of this group of important compounds for the advanced graduate student or chemist unfamiliar with the area.

The critical series discussing the chemistry of alkaloids is that edited by the late R. H. F. Manske and simply called *The Alkaloids, Chemistry and Physiology*. At the time of writing, this series is at Volume 17. Two drawbacks of this series are that much of the history of alkaloids was presented in the early volumes and that for the beginning reader the coverage is very detailed.

A second series, entitled *The Alkaloids*, published by The Chemical Society of London as part of the Specialist Periodical Reports Series, covers most groups of alkaloids on a yearly basis. Again, however, the reader is generally assumed to have an exceptional background knowledge of alkaloids in order to understand the new developments.

I felt that a book was needed from which a person could become aware of the alkaloids as a group without needing to delve into the more sophisticated reviews, monographs, and series. This book then is primarily intended for the advanced graduate chemistry, biochemistry, or pharmacy student. Chemists unfamiliar with alkaloids may also find it useful, and alkaloid chemists should find the book interesting for the diverse alkaloid groups discussed.

No attempt has been made to cite *all* the references pertaining to a given group of compounds; rather key references are given at the end of each

chapter or major section to important research papers, reviews, book chapters, and monographs.

My intent has been to cover the alkaloids from a number of perspectives, including their taxonomic distribution, structure elucidation, chemistry, synthesis, biosynthesis, and pharmacology. In a book of this size however numerous compromises were necessary, and clearly some of my peers will be upset that their favorite group of compounds may have been treated with undue brevity. For this I apologize.

The title of the book also merits some explanation. When I was an undergraduate student at the University of Manchester I was privileged to receive my first lectures on natural products from the then Professor of Organic Chemistry, Arthur J. Birch. These lectures were my first exposure to biosynthesis and biogenesis. Subsequently when I was a graduate student at Manchester, I heard a lecture by Birch on the brevianamides, a particularly interesting group of indole alkaloids. One phrase used by Birch in the lecture has stuck in my mind; paraphrased, it is: "At this time, *biogenetic reasoning* suggested the structure X, which was established by. . . ." It took some years for the significance of this concept to percolate. When contemplated carefully it is essentially that nature will not produce what it cannot produce. Since it is apparent that the molecules of key biosynthetic importance are well known, any proposal for a new structure should be biosynthetically reasonable.

This is not to say that structures are not deduced which defy initial biogenetic reasoning (e.g. securinine, Chapter 8). Nor does it rule out the possibility that initial biogenetic ideas may not be correct (e.g. monoterpenoid indole alkaloids); surprises continue at an alarming rate. Rather, it is to say that nature has few fundamental precursors; be aware of the structural limitations of these, and structure elucidation will be greatly simplified.

This book has its foundations in these ideas: namely that the hundreds of diverse alkaloid skeleta can be drawn together not on the basis of their structural similarity but rather on the basis of their biogenesis or biosynthesis. Such an approach has not been attempted previously.

There is one additional concept which may be gleaned from the comment of Birch: Can the reaction in a biosynthetic pathway be mimicked or preferably duplicated in the laboratory? For years the concept of synthesis for a complex natural produce centered on the skillful, often exquisitely delicate, manipulation of polyfunctionalized intermediates. In the past 10 years a revolution in synthesis has occurred, the concept of biomimetic synthesis. This is the elaboration of a supposed or proven biosynthetic intermediate to a final natural product, preferably under mild conditions. A classic area of these two approaches is in the morphinandienone series. Consider for example the early Gates synthesis of morphine and the biogenetically modeled synthesis of morphine developed more recently (Chapter 8).

In this monograph emphasis is placed on the biogenetically modeled

synthesis of alkaloids, although the important nonbiogenetic approaches are also described.

In the period of publishing this book, three exceptional alkaloid chemists have died; R. B. Woodward, R. H. F. Manske, and H. Schmid. This book is dedicated to their scientific endeavors.

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Chicago, Illinois  
May 1981*



# CONTENTS

<b>1</b>	<b>INTRODUCTION</b>	<b>1</b>
1.1	History, 1	
1.2	Occurrence, 2	
1.3	Classification, 5	
1.4	Nomenclature, 7	
1.5	Physical and Chemical Properties, 7	
1.6	Detection, Isolation, Purification, and Structure Elucidation, 9	
1.7	Pharmacology—The Basic Concepts, 21	
<b>2</b>	<b>BIOSYNTHESIS AND BIOGENESIS</b>	<b>26</b>
2.1	Introduction, 26	
2.2	Enzymes of Alkaloid Formation, 28	
2.3	Techniques of Biosynthesis, 35	
2.4	Biosynthesis of Alkaloid Precursors, 49	
<b>3</b>	<b>ALKALOIDS DERIVED FROM ORNITHINE</b>	<b>80</b>
3.1	Simple Pyrrolidine Alkaloids, 80	
3.2	Nicotine, 84	
3.3	Tropane Alkaloids, 94	
3.4	Pyrrolizidine Alkaloids, 118	

<b>4</b>	<b>ALKALOIDS DERIVED FROM LYSINE</b>	<b>138</b>
4.1	Pelletierine and Related Alkaloids, 138	
4.2	Anabasine and Related Alkaloids, 143	
4.3	The <i>Sedum</i> Alkaloids, 145	
4.4	The Alkaloids of <i>Lobelia inflata</i> , 146	
4.5	Miscellaneous Simple Piperidine Alkaloids, 146	
4.6	Lythraceae Alkaloids, 150	
4.7	Quinolizidine Alkaloids, 153	
4.8	<i>Lycopodium</i> Alkaloids, 170	
4.9	Biosynthesis, 178	
<b>5</b>	<b>ALKALOIDS DERIVED FROM NICOTINIC ACID</b>	<b>196</b>
5.1	Arecoline, 197	
5.2	Ricinine, 197	
5.3	Anatabine, 199	
5.4	Dioscorine, 200	
<b>6</b>	<b>ALKALOIDS DERIVED FROM A POLYACETATE PRECURSOR</b>	<b>204</b>
6.1	Shihunine, 204	
6.2	Piperidine Alkaloids with Short Aliphatic Side Chains, 206	
6.3	Piperidine Alkaloids with Long Aliphatic Side Chains, 211	
6.4	9b-Azaphenylene Alkaloids, 216	
6.5	Naphthalene-Isoquinoline Alkaloids, 219	
6.6	<i>Elaeocarpus</i> Alkaloids, 222	
6.7	<i>Galbulimima</i> Alkaloids, 224	
6.8	Cytochalasans, 228	

<b>7</b>	<b>ALKALOIDS DERIVED FROM ANTHRANILIC ACID</b>	<b>236</b>
7.1	Simple Derivatives, 236	
7.2	Simple Quinoline Derivatives, 237	
7.3	Furoquinoline Alkaloids, 240	
7.4	Quinazoline Alkaloids, 253	
7.5	Acridine Alkaloids, 264	
7.6	1,4-Benzoxazin-3-one Alkaloids, 269	
7.7	Benzodiazepine Alkaloids, 270	
7.8	Cryptolepine, 273	
<b>8</b>	<b>ALKALOIDS DERIVED FROM PHENYLALANINE AND TYROSINE</b>	<b>275</b>
8.1	Simple Tyramine Derivatives, 275	
8.2	Peyote and Mescaline, 278	
8.3	Ephedrine, 284	
8.4	Khat, 287	
8.5	Cinnamic Acid Amide Derivatives, 287	
8.6	Diketopiperazines Derived from Phenylalanine, 292	
8.7	Securinine and Related Compounds, 304	
8.8	Melanin, 311	
8.9	Betalains, 311	
8.10	Tetrahydroisoquinoline Alkaloids, 317	
8.11	1-Phenyltetrahydroisoquinoline Alkaloids, 328	
8.12	Benzylisoquinoline Alkaloids, 330	
8.13	Bisbenzylisoquinoline Alkaloids, 349	
8.14	Cularine and Related Alkaloids, 367	
8.15	Dibenzopyrrocoline Alkaloids, 370	
8.16	Pavine and Isopavine Alkaloids, 372	
8.17	Proaporphine Alkaloids, 379	

- 8.18 Aporphine Alkaloids, 388
- 8.19 Aporphine Dimers, 410
- 8.20 Oxoaporphine Alkaloids, 416
- 8.21 Dioxoaporphine Alkaloids, Aristolactams, and Aristolochic Acids, 419
- 8.22 Azafluoranthene Alkaloids, 421
- 8.23 Taspine, 422
- 8.24 Morphinandienone Alkaloids, 422
- 8.25 *Erythrina* Alkaloids, 450
- 8.26 Protostephanine and Erybidine, 462
- 8.27 Hasubanan Alkaloids, 466
- 8.28 Protoberberine Alkaloids, 472
- 8.29 Protopine Alkaloids, 485
- 8.30 Rhoeadine Alkaloids, 490
- 8.31 Phthalideisoquinoline Alkaloids, 496
- 8.32 Ochotensane Alkaloids, 502
- 8.33 Benzo[c]phenanthridine Alkaloids, 509
- 8.34 Phenethylisoquinoline Alkaloids, 517
- 8.35 Colchicine, 522
- 8.36 *Cephalotaxus* and *Homoerythrina* Alkaloids, 528
- 8.37 Amaryllydaceae Alkaloids, 533
- 8.38 Mesembrine and Related Alkaloids, 554
- 8.39 Ipecac Alkaloids, 560
- 8.40 Phenanthroindolizidine Alkaloids, 567
- 8.41 Phenanthroquinolizidine Alkaloids, 572

## 9 ALKALOIDS DERIVED FROM TRYPTOPHAN

574

- 9.1 The Simple Bases, 574
- 9.2 Simple Tryptamine Derivatives, 577
- 9.3 Pyrrolnitrin, 581

- 9.4 Physostigmine and Related Compounds, 584
- 9.5 The Oligomers of Tryptamine, 590
- 9.6 Diketopiperazines Derived from Tryptophan, 594
- 9.7 Harmala Alkaloids, 610
- 9.8 Carbazole Alkaloids, 614
- 9.9 Canthin-6-ones, 619
- 9.10 Ergot Alkaloids, 622
- 9.11 Monoterpenoid-Derived Indole Alkaloids, 655
- 9.12 Nitrogenous Glycosides and Related Compounds, 658
- 9.13 Camptothecine, 665
- 9.14 Corynanthe Alkaloids, 673
- 9.15 Ajmalicine and Related Compounds, 678
- 9.16 Oxindole Alkaloids, 681
- 9.17 Yohimbine and Related Alkaloids, 684
- 9.18 *Rauvolfia* Alkaloids, 691
- 9.19 Ajmaline–Sarpagine Alkaloids, 697
- 9.20 *Cinchona* Alkaloids, 707
- 9.21 *Strychnos* Alkaloids, 721
- 9.22 Secodine Alkaloids, 736
- 9.23 *Aspidosperma* Alkaloids, 742
- 9.24 *Melodinus* Alkaloids, 758
- 9.25 Iboga Alkaloids, 761
- 9.26 Biogenetic Interconversion of Monoterpenoid Indole Alkaloids, 771
- 9.27 Pandoline and Related Compounds, 776
- 9.28 Bisindole Alkaloids, 777
- 9.29 *Catharanthus* Alkaloids, 784
- 9.30 *Vinca* Alkaloids, 790
- 9.31 Monoterpenoid Indole Alkaloids Lacking the Tryptamine Bridge, 797
- 9.32 The Biosynthesis of Indole Alkaloids, 810

<b>10</b>	<b>ALKALOIDS DERIVED FROM HISTIDINE</b>	<b>833</b>
10.1	Casimiroedine, 834	
10.2	Pilocarpine, 835	
10.3	Alkaloids Related to Pilocarpine, 837	
10.4	Miscellaneous Alkaloids, 840	
<b>11</b>	<b>ALKALOIDS DERIVED BY THE ISOPRENOID PATHWAY</b>	<b>846</b>
11.1	Hemiterpenoid Alkaloids, 846	
11.2	Monoterpenoid Alkaloids, 847	
11.3	Sesquiterpene Alkaloids, 856	
11.4	Diterpene Alkaloids, 868	
11.5	<i>Daphniphyllum</i> Alkaloids, 886	
11.6	Steroidal Alkaloids, 890	
<b>12</b>	<b>MISCELLANEOUS ALKALOIDS</b>	<b>925</b>
12.1	Toxins of the Frogs of the Dendrobatidae, 925	
12.2	Saxitoxin, 927	
12.3	Spermidine and Related Alkaloids, 930	
12.4	Macrocyclic Peptide Alkaloids, 937	
12.5	Mushroom Toxins Other Than Peptide Alkaloids, 944	
12.6	Maytansinoids, 948	
12.7	Purine Alkaloids, 952	
	<b>APPENDIX</b>	<b>961</b>
	<b>SUBJECT INDEX</b>	<b>963</b>
	<b>ORGANISM INDEX</b>	<b>1049</b>

# INTRODUCTION

The alkaloids comprise an array of structure types, biosynthetic pathways, and pharmacologic activities unmatched by any other group of natural products. How did this group of compounds reach such prominence, and why are they of such continuing interest? One aim of this book is to answer these questions by example.

This introductory chapter describes some important aspects of the history of alkaloids, an approach to their classification, some information concerning the occurrence of alkaloids, and examples of the techniques used to isolate, purify, and characterize alkaloids.

## 1.1 HISTORY

The history of alkaloids is almost as old as civilization. Humankind has used drugs containing alkaloids in potions, medicines, teas, poultices, and poisons for 4000 years. Yet no attempts were made to isolate any of the therapeutically active ingredients from the crude drugs until the early nineteenth century.

The Austrian apothecary Storck is generally attributed with the reintroduction of many plant drugs into medical practice. Because of their potent yet variable toxicities, drugs had fared poorly at a time when life and the sustenance of it was being carefully scrutinized. Some of the drugs reintroduced at this time are of classical importance and include aconite, colchicum, stramonium, henbane, and belladonna.

The first crude drug to be investigated chemically was opium, the dried latex of the poppy *Papaver somniferum*. Opium had been used for centuries in popular medicine, and both its analgesic and narcotic properties were well known. In 1803, Derosne isolated a semipure alkaloid from opium and named it narcotine. Further examination of opium by Serturner in 1805 led to the isolation of morphine, and it was Serturner who first discovered the basic character of morphine.

Twelve years passed before the lead of Serturner was pursued. What followed, in the years 1817–1820 in the laboratory of Pelletier and Caventou



at the Faculty of Pharmacy in Paris, continues to amaze alkaloid chemists. Not since that time has one laboratory isolated so many active principles of pharmaceutical importance. Among the alkaloids obtained in this brief period were strychnine, emetine, brucine, piperine, caffeine, quinine, cinchonine, and colchicine. These alkaloids are the cornerstones of all that has transpired in alkaloid chemistry in the past 160 years.

In 1826, Pelletier and Caventou also obtained coniine, an alkaloid of considerable historical significance. Not only is it the alkaloid responsible for the death of Socrates from a draught of poison hemlock, but because of its simple molecular structure, it was the first alkaloid to be characterized (1870) and the first to be synthesized (1886). This is not to imply that investigators had forgotten alkaloids in the intervening years—far from it, for by 1884 at least 25 alkaloids had been obtained from *Cinchona* bark alone.

The molecular complexity of the majority of these alkaloids precluded their structure elucidation during the nineteenth century or even the early twentieth century. The case of strychnine is a good example. First obtained in 1819 by Pelletier and Caventou, it took nearly 140 years of extremely arduous, very frustrating chemical investigation before the structure was finally determined in 1946 by Robinson and co-workers.

It should be noted that while organic chemistry grew immensely in stature during this period, to become the sophisticated science that it is today, efforts in natural products chemistry were growing at a similar pace. Indeed many reactions that are now classics in organic chemistry were first discovered from the careful study of natural product degradations.

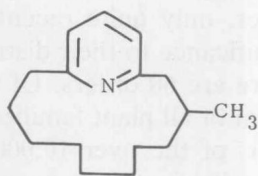
But let us look at the pace of alkaloid research in the past years. By 1939 nearly 300 alkaloids had been isolated and about 200 of these had at least reasonably well defined structures. In the first edition of Mankse's *Alkaloids* series, published beginning in 1950, more than 1000 alkaloids are noted.

With the introduction of preparative chromatographic techniques and sophisticated spectroscopic instrumentation, the number of known alkaloids has risen dramatically. A review to the middle of 1973 counted 4959 alkaloids, of which 3293 had known structures. By late 1978, the number stood at nearly 4000, structurally defined alkaloids.

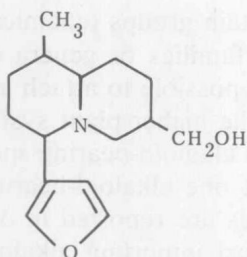
## 1.2 OCCURRENCE

The major source of alkaloids in the past has been the flowering plants, the angiosperms. In recent years however there have been increasingly numerous examples of the occurrence of alkaloids in animals, insects, marine organisms, microorganisms, and the lower plants. Some examples of this very diverse occurrence of alkaloids are the isolation of muscopyridine (1) from the musk deer; castoramine (2) from the Canadian beaver; the pyrrole derivative (3), a sex pheromone of several insects; saxitoxin (4), the neurotoxic constituent of the red tide *Gonyaulax catenella*; pyocyanine (5) from the

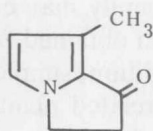




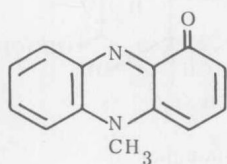
1 muscopyridine



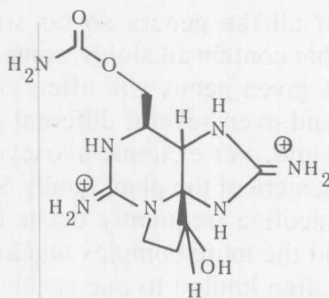
2 castoramine



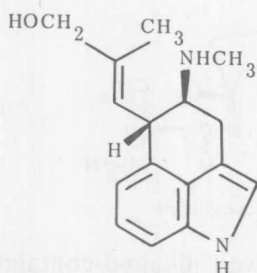
3



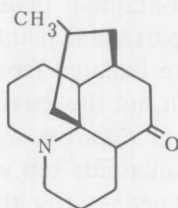
5 pyocyanine



4 saxitoxin



6 chanoclavine-I



7 lycopodine

bacterium *Pseudomonas aeruginosa*; chanoclavine-I (6) from the ergot fungus, *Claviceps purpurea*; and lycopodine (7) from the genus of club mosses, *Lycopodium*.

Because the alkaloids as a class of compounds have been found predominantly in the flowering plants, scientists interested in the systematic organization of plants have long been interested in the alkaloids.