ALKALOIDS

A TREASURY OF POISONS AND MEDICINES

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by

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FOREWORD

Professor Shinji Funayama (left) and Professor Geoffrey A. Cordell at the Medicinal Plant Garden, Nihon Pharmaceutical University, Saitama, Japan (April, 2013)

Since the earliest application of plants as medicinal and stimulant agents, alkaloids have been a part of the human experience. Over the millennia, numerous plants were introduced into systems of medicine around the world, and many of these have alkaloids as their active principles. When alkaloids were first isolated as bioactive agents from medicinal plants in the early part of the 19th century, it also became clear, as their structures began to be unraveled, that they offered tremendous challenges in terms of both complete structural and stereochemical assignment, and subsequently in synthesis. Indeed, some of the legendary organic syntheses of the 20th century are of complex alkaloids. When microorganisms were investigated for their bioactive principles, more novel groups of alkaloids were disclosed. The profound challenges to unraveling the exquisite processes for the formation of their amazing structural diversity continue to this day.

Their wide spectrum of biological activities provides numerous classes of useful medicinal agents, and yet, at the same time, they provide a global paradox. In spite of many health beneficent effects, two alkaloids, cocaine and morphine (and its derivative heroin), are the focus of a counter culture of illicit use of biological powerful alkaloids, and many alkaloids, because of their profound toxicity, are to be feared. On the other hand, the xanthine alkaloids, caffeine and threobromine, are an integral aspect of providing pleasure in the daily lives of most of the world in the consumption of tea, coffee, and chocolate.

Professor Shinji Funayama joined me at the University of Illinois at Chicago as a postdoctoral fellow studying the fascinating chemistry of acridone alkaloids. He returned to Japan to become a very prominent author of

more than 11 single author books on various aspects of natural products and society. This volume was originally published in Japan in Kyoritsu-Shuppan with the title "アルカロイド–毒と薬の宝庫 (Alukaroido - Doku to Kusuri no Houko)". Following the translation, the name of the original volume has been retained, as "Alkaloids - A Treasury of Poisons and Medicines," a reflection of the paradox.

This is not a comprehensive treatise on alkaloids. It is a short volume, focused on some perspectives of the history and diverse biology of a selected group of alkaloids, with an emphasis towards their presence in the materials of Kampo medicines (Japanese Traditional Medicine) in Japan and their toxic potential. It is offered as an introduction, as a stimulant to further inquiry on these amazing natural products.

Geoffrey A. Cordell
Natural Products Inc., Evanston, IL

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Introduction

Papaver somniferum (Papaveraceae)

Before describing the various groups of alkaloids individually, the place of alkaloids among the naturally occurring organic compounds, and in society will be discussed briefly in this chapter.

An understanding of what an alkaloid is will be mentioned in the first section, and in the second section, the aspects of classifying alkaloids on the basis of their biosynthetic origin will be presented. This method will be compared with a classification based on their carbon or heterocyclic skeleton, such as indole, isoquinoline alkaloids, or a classification of the alkaloids based on a chemotaxonomic approach, such as Rutaceae and Apocynaceae alkaloids. A short history of the study of alkaloids and the crude drugs as the origin of various alkaloids, and their relevance in the history of natural products chemistry will be described. Through these discussions, it will be established that the natural products classified as alkaloids relate to our life deeply, and on an everyday basis, as medicines, as dyestuffs, as flavors, as stimulants, and as toxic substances.

It is known that alkaloids show a broad range of biological activities. Among the biologically active compounds, there are especially many alkaloids which affect the central nervous system (CNS) and the autonomic nervous system. Some of the CNS stimulants will be described in the final sixth section.

Readers of this book will discover that alkaloids are a very important group of organic compounds which show a variety of highly significant, clinically and biologically useful properties. Among these activities of alkaloids are hypotensive, cardiotonic, hormone, pheromone, growth acceleration, antimalarial, antitumor, antiparasitic, sedative, analgesic, anti-Alzheimer's, and antimicrobial activities.

There are probably over 25,000 alkaloids derived from higher plants as presented in the *Dictionary of Alkaloids*. This modest volume offers a brief

http://dx.doi.org/10.1016/B978-0-12-417302-6.00017-9

overview of the main alkaloid groups, their structures, their activities, and their basic biosynthetic pathways from a historical perspective.

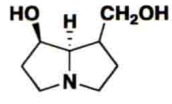
1. THE DEFINITION OF AN ALKALOID

The word "alkaloid" was proposed in 1818 by K. F.W. Meissner (1792–1853), a pharmacist in Halle, Germany. The word alkaloid was coined from the word alkali (implying basicity), from "*al qalī*" (referring to soda) in Arabic. The "-oid" suffix, meaning "like", derives from the Greek.

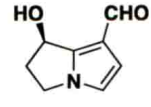
The definition of an alkaloid has changed significantly over the years, as more "alkaloids" have been structurally elucidated and the sources of alkaloids have broadened.

1. At the beginning, alkaloids were discovered only from higher plants, and those compounds showed basic properties and strong biological activities. Consequently, at that time, an alkaloid was defined as "the plant component which shows basic properties and strong biological effect." The basicity of alkaloids is derived from the presence of a nitrogen atom in the molecule in the form of an amine.

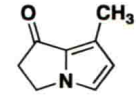
   Such a definition is no longer possible for the alkaloids. First of all, alkaloids are obtained from an extremely broad range of natural sources, not just the plant kingdom. For example, retronecine, danaidone, and hydroxydanaidal (derivatives of pyrrolizidine alkaloids) were isolated from the hair pencil of the male butterfly of the *Danaid* genus. Batrachotoxin, a poison arrow toxin component, was isolated from the skin of a frog. In addition, there are many examples of alkaloids of microbial, marine, and human origin, including a vast array of nitrogen-containing antibiotics.



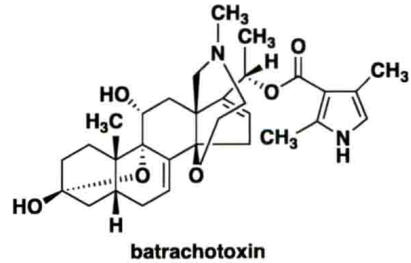
retronecine



hydroxydanaidal

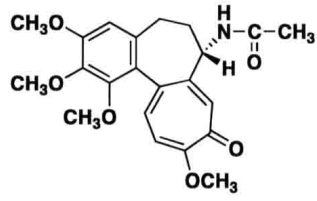


danaidone

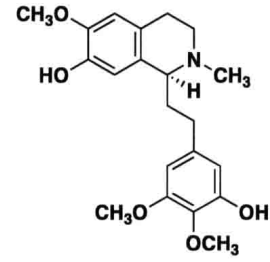


batrachotoxin

2. Alkaloids are not limited to those natural products which are basic in character. For example, colchicine isolated from *Colchicum autumnale* (Liliaceae) and used for the treatment of gout, etc. is not basic because the nitrogen atom in the molecule is present in a neutral amide group. However, the biosynthetic precursor of colchicine is autumnaline, a typical, basic phenethylisoquinoline alkaloid. Therefore any compound derived from such an intermediate should be classified as an alkaloid.

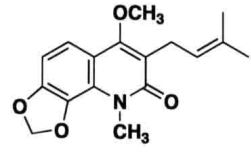


colchicine

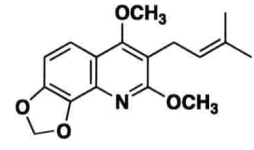


autumnaline

Another example pertains to the close structural isomers, pteleprenine and isopteleprenine, which were isolated from *Orixa japonica* (Rutaceae). In pteleprenine, the nitrogen is in the form of an amide, and therefore it lacks basicity. On the other hand, in isopteleprenine the nitrogen atom, being in a quinoline ring, is weakly basic. Given their common biosynthetic origin both compounds are classified as alkaloids.

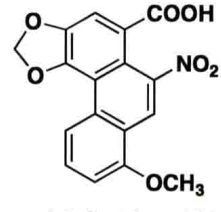


pteleprenine



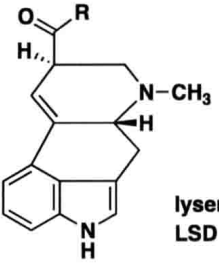
isopteleprenine

In the case of the phenanthrine derivative aristolochic acid-I, the skeleton is derived from an aporphine alkaloid precursor which has undergone oxidation, to the point where the nitrogen atom exists as a nitro group. Biosynthetically, this compound is also classed as an alkaloid.

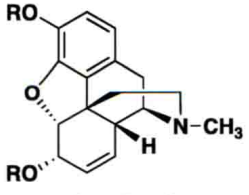


aristolochic acid-I

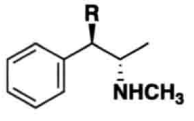
3. It is not appropriate to include the existence of biological activity in the definition for an alkaloid. Several years ago [1] it was shown that about 75% of known "alkaloids" had never been tested in a single bioassay. In addition, when an alkaloid with biological activity is isolated, compounds with a closely related chemical structure with no, or greatly diminished, biological activities will also be isolated. In such a case, all of these compounds are regarded as alkaloids, irrespective of whether they have a demonstrated biological activity.
4. Alkaloids are always compounds isolated from nature. However, there are many examples of alkaloid derivatives with a high profile which may be confused and sometimes classified as alkaloids. For example, **L**yserg **S**äure **D**iäthylamid (LSD) (LSD-25) is prepared by the amidation of lysergic acid, itself derived from the ergot alkaloids. Methamphetamine is prepared by the reduction of (−)-ephedrine, and heroin is prepared by the acetylation of morphine, and there are many derivatives of alkaloids which are pharmaceutical products. These semisynthetic compounds can be classed as alkaloid derivatives.



lysergic acid R = OH
LSD R = $N(C_2H_5)_2$



morphine R = H
heroin R = $COCH_3$

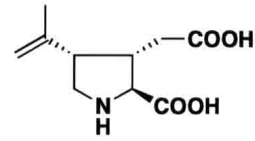


(-)-ephedrine R = OH
methamphetamine R = H

5. There are a significant number of unusual amino acids, simple peptides, pyrrole derivatives, and comparatively simple nitrogen-containing organic compounds, including purines and pyrimidines, which may be excluded from classification as alkaloids.

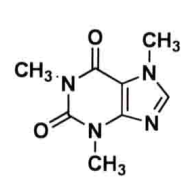
   For example, L-α-kainic acid, obtained from the red algae *Digenea simplex* (Rhodomelaceae), might not be regarded as an alkaloid. However,

this unusual amino acid is biosynthesized from L-glutamic acid and an hemiterpenoid unit, and therefore it is classified as an alkaloid rather than unusual amino acid.

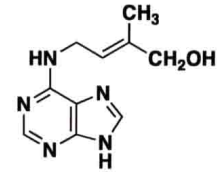


L-α-kainic acid

The pyrazolopyrimidines, such as caffeine of tea and coffee origin, are alkaloids, as is the phytohormone zeatin from maize.

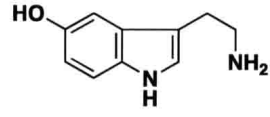


caffeine

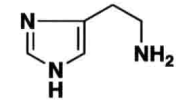


zeatin

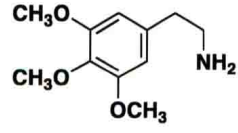
Also, comparatively simple *N*-containing compounds (amines), such as serotonin and histamine, are alkaloids, as are mescaline, isolated from the peyote cactus, *Lophophora williamsii*, and (+)-coniine obtained from *Conium maculatum*.



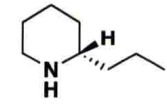
serotonin



histamine



mescaline



(+) -coniine

Based on the above discussion, the precise definition of an alkaloid is rather unclear. That is appropriate for such a broadly available, structurally diverse group of metabolites. It may be said that alkaloids are naturally occurring, nitrogen-containing compounds. The group excludes the amino acids of primary metabolism, complex peptides

and proteins constructed from those amino acids, and nucleic acids. Thus we see alkaloids, not in terms of a comprehensive definition, but rather as a way to classify a large number of natural metabolites containing nitrogen possessing great structural diversity and derived from any natural source. As has been suggested previously, with experience, "you know one when you see one" [2]. Our task then is to classify them so that the breadth and depth of their molecular frameworks can be assimilated into the larger organization of natural product structures.

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[1] G.A. Cordell, M.L. Quinn-Beattie, N.R. Farnsworth, Phytother. Res. 15 (2001) 183–205.
[2] G.A. Cordell, Introduction to Alkaloids. A Biogenetic Approach, Wiley Interscience, New York, NY, 1981. 1055 pages.

2. CLASSIFICATION OF ALKALOIDS

Several approaches to the classification of alkaloids are available, including, chemical, taxonomic, biological, and biosynthetic. At various times, each of these approaches has been used in terms of the presentation and discussion of alkaloid development. We will discuss these approaches in turn.

Alkaloids were often classified on the basis of their chemical structure. According to this system, alkaloids are organized based on a common, typically heterocyclic, nucleus, such as isoquinoline, indole, quinolone, quinazoline, pyrrolizidine, and tropane alkaloids, etc. Another method to classify the alkaloids, is to use their natural origin. So we could organize them based on a plant family, such as Amaryllidaceae, Solanaceae, and Rutaceae alkaloids, or based on a genus, such the *Catharanthus* alkaloids. Classification may use the name of a prototypical alkaloid of the group such as aconitine-type or morphine-type alkaloids. Frequently, this approach also follows a common biosynthetic or biogenetic origin.

Using this type of chemical classification is useful, and such a classification is used predominantly in this book. However, this approach also encounters some challenges. For example, autumnaline and (*S*)-reticuline are typical isoquinoline alkaloids, whereas colchicine and morphine, which