Modern Alkaloids

Structure, Isolation, Synthesis and Biology

Edited by
Ernesto Fattorusso and Orazio Taglialatela-Scafati
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Orazio Taglialetela-Scafati
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Preface

Alkaloids constitute one of the widest classes of natural products, being synthesized practically by all phyla of both marine and terrestrial organisms, at any evolutionary level. The extraordinary variety (and often complexity) of alkaloid structures and biological properties have long intrigued natural product chemists (for structure determination and biosynthetic studies), analytical chemists, and synthetic organic chemists. Toxicologists, pharmacologists and pharmaceutical companies have used and will certainly continue to use alkaloids as biological tools and/or as lead compounds for development of new drugs.

When we started our project of a handbook on alkaloid science, we were faced with an impressive number of papers describing the structures and activities of alkaloids, and also with an intense review activity, published in excellent book series or in single books covering specific classes of alkaloids. Consequently, we decided to organize our handbook to present the different aspects of alkaloid science (e.g. the structure and pharmacology of bioactive alkaloids; recent advances in isolation, synthesis, and biosynthesis) in a single volume, aiming to provide representative examples of more recent and promising results as well as of future prospects in alkaloid science. Obviously, the present handbook cannot be regarded as a comprehensive presentation of alkaloid research, but we feel that the diversity of topics treated, ranging from bitterness to the anticancer activity of alkaloids, can provide a good idea of the variety of active research in this field.

In particular, Section I describes the structures and biological activities of selected classes of alkaloids. Almost half of the chapters focus their attention on terrestrial alkaloids (Chapters 1–5). The other half (Chapters 7–11) describe recent results in the field of marine alkaloids, while Chapter 6 is focused on neurotoxic alkaloids produced by cyanobacteria, microorganisms living in both marine and terrestrial environments. The particular emphasis on marine alkaloids undoubtedly reflects our long-standing research activity on marine metabolites, but it is also a result of the impressive amount of work carried out in the last few decades on marine natural product chemistry. Section II (Chapters 12–15) gives an account of modern techniques used for the detection and structural elucidation of alkaloids, while Section III is divided into two parts: different methodologies for the synthesis of alkaloids and accounts of modern biosynthetic studies.
Finally, we should point out that even today the term alkaloid is ambiguous (a discussion on the definition of alkaloid is presented in Chapter 4). The initial definition of Winterstein and Trier (1910) ("nitrogen-containing basic compounds of plant or animal origin") has obviously been superseded. The most recent definition of alkaloid can be attributed to S. W. Pelletier (1984): "compound containing nitrogen at a negative oxidation level characterized by a limited distribution in Nature". In the preparation of this handbook we have decided to follow this last definition and, thus, to include "borderline" compounds such as capsaicins and non-ribosomal polypeptides.

We cannot conclude without thanking all the authors who have made their expert contributions to the realization of this volume, which we hope will stimulate further interest in one of the most fascinating branches of natural product chemistry.

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Bioactive Alkaloids: Structure and Biology
1

Ecological Roles of Alkaloids

Michael Wink

1.1
Introduction: Defense Strategies in Plants

Plants are autotrophic organisms and serve as both a major and the ultimate source of food for animals and microorganisms. Plants cannot run away or fight back when attacked by a herbivore, nor do they have an immune system to protect them against pathogenic bacteria, fungi, viruses, or parasites. Plants struggle for life, as do other organisms, and have evolved several strategies against herbivorous animals, parasites, microorganisms, and viruses. Plants also compete with neighboring plants for space, light, water, and nutrients [1–8].

Apparently plants have evolved both physical and chemical defense measures, similar to the situation of sessile or slow moving animals. Among physical defense strategies we find [8]

- formation of indigestible cell walls containing cellulose, lignin, or callose;
- presence of a hydrophobic cuticle as a penetration barrier for microbes and against desiccation;
- formation of a thick bark in roots and stems against water loss, microbes, and herbivores;
- development of spines, thorns, hooks, trichomes, and glandular and stinging hairs (often filled with noxious chemicals) against herbivores;
- formation of laticifers and resin ducts (filled with gluey and noxious fluids);
- a high capacity for regeneration so that parts that have been browsed or damaged by infection can be readily replaced (so-called open growth).

Secondly, plants are masters of chemical defense, with a fascinating ability to produce a high diversity of chemical defense compounds, also known as secondary metabolites or allelochemicals [1–17]. Chemical defense involves macromolecular compounds, such as diverse defense proteins (including chitinase [against fungal cell
walls], β-1,3-glucanases [against bacteria], peroxidase, and phenolase, lectins, protease inhibitors, toxaalbumins, and other animal-toxic peptides), polysaccharides, and poly-
terpenes. More diverse and more prominent are low molecular weight secondary metabolites, of which more than 100 000 have been identified in plants (Figure 1.1).

Among the secondary metabolites that are produced by plants, alkaloids figure as a very prominent class of defense compounds. Over 21 000 alkaloids have been identified, which thus constitute the largest group among the nitrogen-containing secondary metabolites (besides 700 nonprotein amino acids, 100 amines, 60 cyanogenic glycosides, 100 glucosinolates, and 150 alkylamides) [2,3,18,19]. However, the class of secondary metabolites without nitrogen is even larger, with more than 25 000 terpenoids, 7000 phenolics and polyphenols, 1500 polyacetylenes, fatty acids, waxes, and 200 carbohydrates.

1.2 Ecological Roles of Alkaloids

Alkaloids are widely distributed in the plant kingdom, especially among angiosperms (more than 20 % of all species produce alkaloids). Alkaloids are less common but present in gymnosperms, club mosses (Lycopodium), horsetails (Equisetum), mosses, and algae [1–5,17]. Alkaloids also occur in bacteria (often termed antibiotics), fungi, many marine animals (sponges, slugs, worms, bryozoa), arthropods, amphibians (toads, frogs, salamanders), and also in a few birds, and mammals [1–5,13,17,20].

Alkaloids are apparently important for the well-being of the organism that produces them (Figures 1.1–1.3). One of the main functions is that of chemical defense against herbivores or predators [2,3,8,18]. Some alkaloids are antibacterial, antifungal, and antiviral; and these properties may extend to toxicity towards animals. Alkaloids can also be used by plants as herbicides against competing plants [1,3,8,18]. The importance of alkaloids can be demonstrated in lupins which – as wild plants – produce quinolizidine alkaloids (“bitter lupins”), that are strong neurotoxins (Table 1.1) [21,22]. Since lupin seeds are rich in protein, farmers were interested in using the seeds for animal nutrition. This was only possible after the alkaloids (seed content 2–6 %) had been eliminated. Plant breeders created so-called sweet lupins with alkaloid levels below 0.02 %. If bitter and sweet lupins are grown together in the field it is possible to study the importance of alkaloids for defense. For example, Figure 1.3 shows that rabbits strongly discriminate between sweet and bitter lupins and prefer the former. This is also true for insects, as aphids and mining flies always favor sweet lupins. In the wild, sweet lupins would not survive because of the lack of an appropriate chemical defense [8,21].

Secondary metabolites are not only mono- but usually multifunctional. In many cases, even a single alkaloid can exhibit more than one biological function. During evolution, the constitution of alkaloids (that are costly to produce) has been modulated so that they usually contain more than one active functional group, allowing them to interact with several molecular targets and usually more than one group of enemies [3,18,19,21–24]. Many plants employ secondary metabolites (rarely alka-