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Review

Fifty years of alkaloid biosynthesis in *Phytochemistry* ☆

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ABSTRACT

An overview is presented of the studies related to the biosynthesis of alkaloids published in *Phytochemistry* in the past 50 years.

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* This manuscript dedicated to the Memory of Prof. Meinhart H. Zenk.

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1. Introduction

Since *Phytochemistry* was first published in October, 1961, it has evolved to become a flagship international journal for publications in many areas of natural product chemistry and biology, including studies on the isolation, structure elucidation, biosynthesis, and biological evaluation of numerous groups of natural products. One group which has received a great deal of coverage in the annals of *Phytochemistry* over the years is the alkaloids, in all of their structural diversity.

The first article on alkaloids was published in the first issue (Wightman et al., 1961). Subsequently, there have been several thousand articles appearing in the journal relating to various aspects of alkaloids, their origin, occurrence, chemistry, biosynthesis, ecology, and biology. For this contribution, the choice was made to consider only the aspect of alkaloid biosynthesis, and to indicate, briefly, some of the publications that appeared in *Phytochemistry* over the past 50 years. Not all of the published papers can be cited, and not all of the alkaloids studied can be discussed. This article is not intended, and could not be, a comprehensive overview of alkaloid biosynthesis in *Phytochemistry* in 50 years! Some authors have contributed ground-breaking studies to the field of alkaloid biosynthesis through the medium of *Phytochemistry*. These contributions have been an integral aspect of the growth and respect that the journal has engendered over the years. Apologies are tendered to the many authors whose studies on alkaloid biosynthesis were published in *Phytochemistry*, but whose work is not cited here. What is hoped is that a flavor of the coverage of alkaloid biosynthesis in *Phytochemistry* will evolve, and that some sense of the vast changes that have occurred in the strategies and techniques being used will be reflected. It is also hoped that there will be an appreciation of the crucial role that certain specific publications, and certain areas of alkaloid biosynthesis research which have appeared in *Phytochemistry*, have made to the field over these 50 years. The principal groups of alkaloids whose biosynthesis are described are listed, and within each section the discussion is essentially chronological. Sometimes one alkaloid serves as a representative of a group of alkaloids, or as way to introduce how the technologies that have related to alkaloid biosynthesis have changed over these past 50 years.

The first issue of *Phytochemistry* contained two publications on alkaloids (Wightman et al., 1961; Fairbairn and Suwal, 1961). Incredibly, the first dealt with the biosynthesis of tryptophan and gramine in barley, *Hordeum vulgare* L. (Poaceae), and showed that shikimic acid, anthranilic acid, indole acetic acid, and serine were precursors of tryptophan, and that tryptophan was a good precursor of gramine (1) (Wightman et al., 1961). The second paper examined the metabolism of the major alkaloids in hemlock, *Conium maculatum* L. (Apiaceae). It demonstrated the rapid changes in alkaloid levels which occurred within a 24 h period, and showed how the increased level of coniine (2) corresponded with a decline in the level of γ -coniceine (3) (Fairbairn and Suwal, 1961). Another paper on alkaloid biosynthesis also appeared in the first volume of *Phytochemistry*. This article concerned the formation of stachydrine (4), and demonstrated that ornithine was incorporated without randomization, and that proline was a direct precursor in mature plants of *Medicago sativa* L. (Fabaceae) (Essery et al., 1962).

With that meaningful start, the reports of alkaloid biosynthesis in *Phytochemistry* grew, and the journal became a popular venue for the leading researchers in the field to publish some of their most important results on the biosynthesis of alkaloids. Two names stand out for their numerous dynamic contributions to *Phytochemistry*, Professor Edward Leete and Professor Meinhart Zenk, both now deceased. The efforts of these groups, which resulted in numerous and diverse studies, revolutionized the thinking in several areas of alkaloid biosynthesis. Leete and co-workers conducted numerous decisive studies to clarify the tropane and nicotine pathways, while Zenk and co-workers carried out innovative studies at the enzyme and gene level which brought new clarity, and overturned many paradigms associated with earlier proposed biosynthetic pathways. Zenk also provided two important overviews of alkaloids and their biosynthesis. The first of these, in 1991 (Zenk, 1991), provided a perspective on the developments of the application of plant cell culture systems for secondary metabolite biosynthesis in the search for the enzymes; a particular emphasis was placed on advances in elucidating the enzymes of alkaloid biosynthesis. The second review was of the evolution and current status of the phytochemistry of nitrogenous compounds (Zenk and Juenger, 2007). Based on an overview of three types of nitrogen-containing plant products (alkaloids, cyanogenic glucosides, and nonprotein amino acids), it was concluded that the integration of the disciplines of chemistry, pharmacognosy, medicine, analytical sciences, cell biology, molecular biology, botany, and chemotaxonomy across traditional borders will lead to new achievements in phytochemistry, and presumably also in *Phytochemistry*.

1.1. Ornithine-derived alkaloids

An early stage in the formation of several simple alkaloid groups is the formation of putrescine from either ornithine or arginine, and the dimerization to spermidine, from which several derivatives are formed, including those which are acylated; among these alkaloids is lunarine (5). Zenk's group (Sagner et al., 1997) showed that lunarine (5) was formed by stereoselective phenol oxidative coupling of N_1,N_{10} -bis(*p*-coumaroyl)spermidine in the seeds of *Lunaria annua* L. (Brassicaceae). *p*-Coumaric acid was formed from *l*-phenylalanine via *trans*-cinnamic acid, and the spermidine, derived through putrescine, was preferentially synthesized from arginine. Following enzyme studies, it was suggested that a cytochrome P450 might be responsible for the phenol-oxidative coupling of N_1,N_{10} -bis(*p*-coumaroyl)spermidine to afford the hexahydrodibenzofuran ring of lunarine (5).

The first committed step in the nicotine and tropane alkaloid pathways is the formation of *N*-methylputrescine (6). Putrescine:SAM *N*-methyltransferase (PMT) catalyzes the *N*-methylation of the diamine putrescine to form *N*-methylputrescine (6). The *pmt* gene of *Nicotiana tabacum*, under the regulation of the CaMV 35S promoter, was introduced into the genome of a scopolamine-rich *Duboisia* hybrid. Although *N*-methylputrescine levels of the resulting engineered hairy roots increased (2 to 4-fold), there was no significant increase in alkaloid production (Moyano et al., 2002).

A phylogenetic tree of 27 PMT and 14 SPDS proteins (Biastoff et al., 2009) demonstrated the separation of plants in the

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