THE ALKALOIDS

Chemistry and Physiology

Edited by

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VOLUME VI

SUPPLEMENT TO VOLUMES I AND II

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PREFACE

Since the publication of Volumes I through V of "The Alkaloids" remarkable advances have been made in all areas of research on alkaloid chemistry. The two volumes numbered as VI and VII have been organized on the same plan as the first five volumes and are designed to bring the chemistry of the alkaloids up to date by linking these new developments to the content of the earlier volumes.

In preparing all of these volumes the aim has been to bring together the important knowledge of the chemistry and pharmacology of the alkaloids. Since the appearance of Volume V many syntheses, bordering on the spectacular, have been achieved; new and hitherto unsuspected structures have been revealed; a surprisingly large number of new alkaloids have been discovered; many structural problems have been solved; and biogenetic pathways have been formulated, explored, and proved.

In reviewing these advances the authors have keyed this new knowledge to the related material in the earlier volumes. Thus the reader will find in Volumes VI and VII notations of the numbers of the chapters in earlier volumes which the chapters in these volumes supplement. In most cases the numbering of structural formulas is continuous with the sequence in the corresponding chapter in the original volume; in a few cases the numbering of such formulas starts with unity.

The scheme followed for numbering references to the literature is not strictly uniform in all chapters. In most cases the numbers are continuous with those cited in the related chapter of the earlier volume, but in some chapters the reference list in the supplementary material forms a new sequence.

In order to confine the subject index to a manageable length the entries have been limited to only the most important ones for each substance or group of substances. This means that the substance may not be named in the index if its mention is only incidental to the topic under discussion.

The Editor once more is most grateful to the many authors who have contributed so conscientiously and to the chemists throughout the world who have so generously received the previous volumes.

June, 1959 R. H. F. MANSKE

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CHAPTER 1

Alkaloids in the Plant

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I. Introduction*

This chapter is a supplement to the one by W. O. James in Volume I of this series. The author has endeavored to take into consideration the most significant but by no means the whole of the literature published since 1948. There has been intense activity in this field within the last 20 years, and if important investigations have been overlooked this is in part due to the inaccessibility of the publications, often in languages not easily read. Whatever the cause of the omissions, the writer begs for indulgence. References to literature prior to 1948 are included only where it was felt necessary to supplement the earlier chapter. Some references have been omitted intentionally either because they did not seem germane to the limited scope of this chapter or because they seemed to be of minor significance only.

The subjects specially emphasized are the biosynthesis, ontogeny, and inheritance of the plant alkaloids. Speculation is held to a minimum, and few of the theories of biosynthesis are mentioned because much work is in progress and it is confidently expected that the near future will witness important advances in this field.

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* This material is supplementary to Volume I, page 16.

II. Taxonomic Position of the Alkaloids in Plants*

It may be suggested that phylogenetical evolution not only involved morphological differentiation but that chemical differentiation is parallel to it and even forms its basis. It remains unproved that the evolution of higher plants requires the formation of more complex substances. The higher animal organism undoubtedly does require complex compounds that function in the hormonal system, but such compounds are often found in lower organisms where they seem to be of minor or of no obvious significance.

The view that Gymnospermae, Pteridophytae, Fungi, etc., are not able to elaborate alkaloids because of their early phylogenetic age and their primitive status, has been shown to be erroneous by recent investigations. *Equisetum* and *Lycopodium* do in fact elaborate them. The Fungi, the chemistry of which has been extensively explored in the study of the so-called antibiotics, have been found to produce the most elementary protoalkaloids as well as a variety of extremely complicated substances. The following examples will illustrate these points: bufotenine, the specific poison from toads, has been isolated from *Amanita* species (Basidiomycetes) (176); aspergillic acid (I) from *Aspergillus flavus*, and picroroccelline (II) from *Roccella fuciformis* (Lichenes) are pyrazine derivatives which may be looked upon as derivatives of isoleucine and phenylalanine, respectively. The red pigment, pulcherrimine of *Candida pulcherrima*, is believed to be a polymeric iron complex of a dibutyldiketo-piperazine (177). The alkaloids of ergot represent a group of lysergic acid derivatives confined apparently to the genus *Claviceps*. Iodinine is a phenacine derivative from *Chromobacterium iodinum*. Cultures of *Aspergillus glaucus* have yielded echinuline (III); fusaric acid (IV) is elaborated by *Fusarium heterosporum*, a fungus which causes wilt in tomato seedlings; and viridicatine (V) is produced by *Penicillium viridicatum* (178).

Since the greater majority of plants still remain to be examined, the taxonomic distribution of alkaloids cannot be fixed with any certainty, and their total number and occurrence can only be guessed. About one thousand are now known, the structures of many of them being still undetermined (179). The chemistry of the flora of only a few regions of the world has been intensively studied (Australia: Webb (180); Siberia: Sokolov (181)). It is estimated that 10% to 20% of all plants contain alkaloids, but such estimates are uncertain to the extent that our analytical methods often fail to detect traces. Improved methods have led to the finding of nicotine in tomatoes (182) and of alkaloids in

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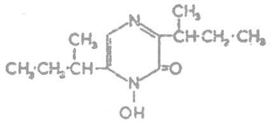
* This material is supplementary to Volume I, pages 1–14.

garden peas (*Pisum sativum* L.) in an amount of about 2% of those found in "sweet" lupines (183).

The existence of larger quantities of alkaloids in plants depends not only upon the plant's capacity to synthesize them but also upon its capacity to tolerate them. The widespread occurrence of nicotine has often been noted, but it frequently is present only in traces (*Lycopersicon, Atropa, Lycopodium, Equisetum, Asclepias*). When tomato or belladonna is grafted upon *Nicotiana* stock considerable quantities of nicotine migrate into the scion, and characteristic chlorosis and necrotic browning arise there undoubtedly as a result of the presence of nicotine (184). Hence tomato and belladonna do not differ from *Nicotiana* by their inability to produce nicotine but by their inability to tolerate it. Similarly, mutants of *Nicotiana rustica* L. and of *Datura* specially rich in nicotine were stunted (185).



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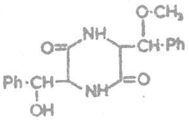

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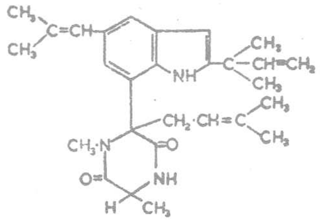

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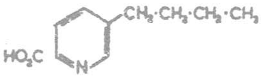

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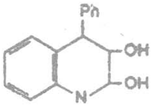


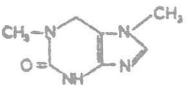
V

A remarkable example of tolerance to a considerable accumulation of nicotine is that of *Zinnia elegans* Jacq. (Compositae), which surprisingly grows well when grafted upon a tobacco root. Strangely enough, it also contains nicotine when grown on its own roots (186).

Hegnauer (187) has discussed the resistance factor to alkaloids in plants. He notes the widespread occurrence of nicotine and regards it and anabasine, sedamine, cuscohygrine, hyoscyamine, the *Lobelia* and *Punica* alkaloids, and the pyrrolizidines and quinolizidines, as biochemically related and based upon similar syntheses. The widespread occurrence of nicotine (182, 188, 189) should be a warning to apply chemical structure cautiously to taxonomic problems. Sokolov (190) has sounded this warning, but he recognizes that with increasing morphological-anatomic advance the complexity of the alkaloids is increased. However, in narrow taxonomic groups alkaloids are significant and characteristic features (191, 192).

In the Amaryllidaceae the alkaloids seem to be confined to the subfamily Amaryllidoidae. Though the structural types are not uniform they seem to be confined to these monocotyledons with one remarkable exception, namely, the phenolic cocculine present in the Caucasian variety of *Cocculus laurifolius* DC. (Menispermaceae). This base, which appears to be absent from the East Asiatic varieties of the same species, apparently has the same ring skeleton as has lycorine, which is remotely related to the isoquinolines so common in the Dicotyledonae (193).

Our knowledge of alkaloids in animals is scant. The so-called protoalkaloids (biogenic amines and their derivatives) are widespread in lower animals (194, 195), and the parallelism between plant and animal metabolism is extensive. Betaines, methylated purines (e.g., paraxanthine (VI)), derivatives of histidine (spinacine (VII) of the shark), and kynurenic acid (VIII) are not rare in animals. The animal alkaloids, with the exception of samandarine (Vol. V, p. 321), are characterized as weak bases; this is perhaps of importance for their excretion.



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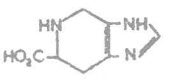

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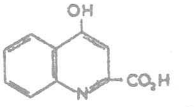

VIII

Brief mention may be made of the phenoxazones, which in the form of the xanthommatins (196) are important pigments in the eyes of insects and as actinomycetins occur in some Actinomycetae (197).

III. Genetics

In general, plants that do elaborate alkaloids elaborate more than one. Only a few investigations with adequate plant material have been made to determine the limits of the alkaloid spectrum in hereditarily uniform material under a varied environment.

Ergot, the sclerotium of the fungus *Claviceps purpurea*, which grows on grasses and especially on rye, contains not only a number of amines derived from the amino acids but alkaloids which are derivatives of lysergic acid. Because of its probable haploid nature and its capacity for vegetative reproduction it is possible to study the constituents of homozygous populations occurring in a number of geographical regions (198). The ergotoxine alkaloids predominate in the ergots of southwestern Europe, whereas those of the ergotamine type predominate in the middle and southeastern European ergots. In East Asia and in Africa ergot races are found which elaborate simple lysergic acid derivatives, whereas ergots from northern regions often yield few or no alkaloids.

Pure strains of *C. purpurea* have been selected from single-spore saprophytic cultures, and some of them yield only a single alkaloid aside from some water-soluble bases (199–203). Table 1 gives a résumé of the alkaloid content of a number of strains studied by Gröger (200, 201).

Extensive investigations have shown that the nature of the alkaloids is influenced slightly or not at all by such variables as climate, the host plant, or the stage of development of the sclerotium (204, 205). During the prolonged cultivations of a single strain aberrant types occasionally appear. In most cases these variants may not be mutants but vegetative segregations of sclerotia formed from mycelia of different strains. Such mixed sclerotia may be formed experimentally (206, 207).

TABLE 1

ALKALOID CONTENT OF THE ERGOT STRAINS SELECTED AT GATERSLEBEN

Strain Gatersleben No.	Per cent total alkaloids (as ergotamine) (1956)	Qualitative composition of the alkaloid mixture					
		Ergonovine	Ergotamine	Ergosine	Ergocristine	Ergocornine	Ergokryptine
III	0.290	tr	***	–	–	–	–
IV	0.320	*	tr	tr	***	–	–
V	0.390	*	*	tr	–	*	*
VI	0.400	tr	*	*	*	–	–
VII	0.640	*	*	*	**	–	–
VIII	0.300	*	tr	–	***	–	–
X	0.400	*	*	–	**	–	–
XII	0.340	*	*	*	–	**	*
XX	0.470	tr	***	–	–	–	–
XXI	0.540	tr	***	–	–	–	–
XXII	0.720	tr	***	–	–	–	–
XXIV	0.560	tr	***	–	–	–	–
XXV	0.440	tr	***	–	–	–	–
XXVI	0.380	tr	–	tr	–	–	***
XXVII	0.440	tr	tr	tr	*	–	**
XXVIII	0.440	tr	tr	–	–	**	**
XXIX	0.580	tr	***	–	tr	–	–
XXX	0.320	tr	–	tr	–	**	**
XXXI	0.430	tr	–	–	–	**	**
XXXII	0.510	tr	–	***	–	tr	tr

Key to the signs used:
– = not detectable.
tr = only traces.
* = existent.
** = more than 50% of total alkaloid.
*** = more than 90% of total alkaloid.

Plant races which have limited geographical distribution and which are distinguished by their alkaloid content have been reported by a number of investigators. Some examples follow: Sokolov (190) described chemically distinguishable races of *Salsola richteri* Karel; Poethke (208) and Tomko (209) of *Veratrum album* L.; Annett (210), Basilewskaja (211), and Heeger and Poethke (212) of *Papaver somniferum* L.; Hills and Rodwell (213), Barnard (214), and Hills *et al.* (188) of *Duboisia myoporoides* R. Br., in which the total of 3% of alkaloids is either largely hyoscine or hyoscyamine; Marion *et al.* (215) found sedamine and nicotine in *Sedum acre* L. of Canadian origin, whereas material from Amsterdam and from Darmstadt examined by Beyerman and Muller (216) and by Schöpf and Unger (217), respectively, yielded only sedridine. Different strains of barley show chemical differences in which hordenine may be replaced by *N*-methyltyramine (218). Exhaustive genetic analyses correlating alkaloid inheritance have been carried out only with *Lupinus*, the "sweet" variants of which have become economically important because of their selection and breeding by v. Sengbusch. According to him a number of genes control the alkaloid content (219–222).

Less is known of the alkaloid heredity in tobacco, although the great variability in kind and amount has often been noted (223–225). In spite of some efforts to do so the problem of the inheritance-dominance of nicotine and of anabasine has not been solved (226), partly because earlier analyses did not differentiate between anabasine and nornicotine. According to Valleau (227) and Griffith *et al.* (228) the demethylation of nicotine to nornicotine is controlled by one gene. In examining the dominance relations of nicotine and nornicotine inadequate attention has hitherto been paid to the stage of development of the plant (229), since there is no "nornicotine" tobacco. The nornicotine in tobacco is produced in the leaves from nicotine often not before the aging of the leaf.

The inheritance of alkaloids in *Cinchona* species has been the subject of an extensive program (230). If two *Solanum* species containing demissine and solanine, respectively, are hybridized a plant results which elaborates both alkaloids (231).

Artificially induced mutations have not yet yielded alkaloid-free plants. Ergots exposed to X-rays and ultraviolet radiation yielded some types which lacked pigment. Such leucosclerotia in general contained less alkaloid than the original forms (201, 232–235). Evans and Menéndez (236) obtained *Datura tatula* L. (*D. stramonium* L.) mutants in which the ratio of hyoscine to hyoscyamine was altered. Similar results have been reported by Mothes and associates (185) in which mutants of *Datura* and of *Nicotiana* containing more nicotine than their respective parents were obtained.

Attempts to increase the alkaloid content by inducing polyploidy were not invariably successful (237, 238). Tetraploid *Datura stramonium* L. was richer in alkaloids than the diploid strain (239). The alkaloid content of the grafts in reciprocals of 4*n* and 2*n* plants was that of the stock. The grafting of 2*n* tomatoes on 4*n* *Datura* inhibits alkaloid synthesis, as does the grafting of 4*n* tomatoes on the same stock but to a lesser degree. Of special interest are the grafts of 2*n* and 4*n* *Datura* on the same 4*n*-*Datura* stock, the latter having the greater alkaloid concentration (240). Other authors are in substantial agreement with these results (238, 241, 242).

Though it can be easily shown that the alkaloid-containing character of a genotypically alkaloid-free graft upon an alkaloid-containing stock is not inheritable, statements to the contrary have appeared frequently (243).

IV. The Site of Formation*

It is now generally recognized that the most intensively studied alkaloids (nicotine in tobacco; hyoscyamine in *Datura*, *Atropa*, and *Hyoscyamus*) are produced in quantity in the roots of intact plants, though other sites of formation are not entirely excluded. A fully developed tobacco leaf does not elaborate nicotine, but it has not yet been proved that this almost cosmopolitan alkaloid is produced only in the roots in all other plants.

The differentiation of the metabolism in the different organs is a problem of the physiological development of that organ. A tobacco leaf resembles a defect-mutant as far as its ability to synthesize nicotine is concerned but since it can generate roots the capacity to synthesize nicotine is still there though latent.

A variety of methods have played important roles in determining the site of formation of alkaloids, and all are subject to serious experimental and interpretational errors. The culture of isolated organs can lead to erroneous interpretations and the analysis of sap currents (xylem and phloem) is fraught with obvious inherent difficulties. In grafts the shoot often forms adventitious roots which may not be visible when they grow into the stock. Such a graft is not only under the influence of the stock root but under its own, and very short roots can show very great alkaloid synthesis activity (244, 245).

It is not yet certain whether a shoot behaves differently on its own

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* This material is supplementary to Volume I, page 50.