THE ALKALOIDS

Chemistry and Physiology

Edited by

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VOLUME IV

1954
ACADEMIC PRESS INC., PUBLISHERS
NEW YORK

Library of Congress Catalog Card Number: (50-5522)

Printed in the United States of America

PREFACE

The present volume contains an account of the chemistry and biosynthesis of the various classes of isoquinolines in ten separate chapters; we hope that it will serve as a textbook in this field of chemistry.

The two additional chapters on two classes of alkaloids whose structures are as yet unknown are designed to provide an up-to-date critical summary.

This completes the chemistry portion of our series, except for a chapter on miscellaneous alkaloids which will appear in Volume V along with the chapters on pharmacology.

Once more we are pleased to thank not only our fellow chemists for their generous reception of our past volumes but also our very conscientious and patient contributors. We also thank the many authors who have sent us reprints of their recent work to aid us in the compilation of a supplement.

R. H. F. M.
H. L. H.

March, 1954

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CHAPTER 25

The Biosynthesis of Isoquinolines

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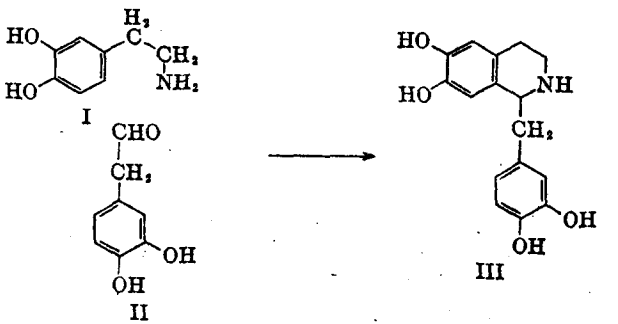
It can be said that the exact mechanism by which a plant cell elaborates an isoquinoline alkaloid is not yet known. Nevertheless the cumulative circumstantial evidence which has been amassed is so complete that a series of biosynthetic reactions can be written which leave only detail for further research. It was Pictet (1) in 1906 who first drew attention to some similarities of and possible synthetic routes to a number of alkaloids. The following four decades witnessed a gradual realization that alkaloids are derivable from the naturally occurring common precursors such as amino acids. Biological oxidations and reductions as well as carboxylations came to light particularly in studies with animals. For example it was demonstrated that phenylalanine is convertible into tyrosine (2) in the normal rat, thus lending strong support to the supposition that dioxyphenylalanine (dopa) (3, 4) is in fact derived or derivable from tyrosine and that the trihydroxy compound may also be so derived. Having available 3,4-dihydroxyphenylalanine it is only necessary to assume that the plant cell can effect the changes of decarboxylation, deamination, and oxidation to arrive at the two intermediates, 3,4-dihydroxyphenethylamine (I) and 3,4-dihydroxyphenacetaldehyde (II), necessary for the synthesis of norlaudanosine (III) (5). The combination of a β-arylethylamine and

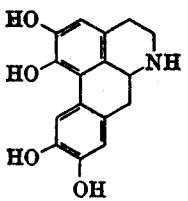


a carbonyl compound to yield isoquinolines has been the subject of a series of researches by Schöpf and by Hahn and their associates (6, 7, 8, 9). The free aldehydes as well as the corresponding pyruvic acids condense

with the amines under conditions which might prevail in the plant cell, although the participation of enzymes is not excluded (10, 11) because of the fact that practically all 1-substituted isoquinolines occur in an optically active form. Those isoquinolines in which there is no substituent in position 1 are theoretically derivable from formaldehyde as second component. It is very doubtful whether formaldehyde ever occurs in plant cells even in very low concentrations, so that some equivalent must be looked for. Supplying plants with possible labeled precursors may help in solving this problem although it should be borne in mind that the anabolic facilities of plants are very considerable. Consequently a large number of compounds which may be regarded as formaldehyde equivalents are easily suggested, the more obvious being glyoxylic acid and formic acid, the former having the merit that it is known to be widely distributed in vegetable matter and that decarboxylation may take place during or after condensation. In the following discussion the term "formaldehyde" will be understood to mean any compound which, after a series of events, will produce the same result that might be anticipated with the use of formaldehyde. The subsequent changes involving methylation of nitrogen or of oxygen, and methylenation of oxygen require only those reactions which have become so well known (12).

It is reasonable to assume that the benzylisoquinolines are the intermediates which a plant must synthesize before it can elaborate most of the other isoquinolines.

The aporphines are derivable from III by the removal of two hydrogen atoms, one from each of the benzene nuclei, and III can yield two different



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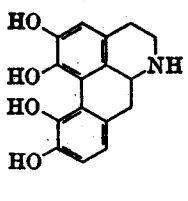
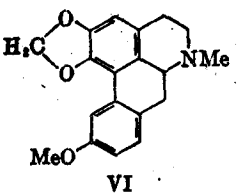


V

aporphines (IV or V) depending upon whether ring closure takes place ortho or para to a hydroxyl (13). In general a particular plant elaborates aporphines of either one or the other type, but a number are now known which elaborate representatives of both types (14, 15, 16), and it is more reasonable to assume a common precursor than to envision two separate sets of precursors. It should be noted that the final oxidative ring closure (i.e., dehydrogenation between the benzene nuclei of III) requires positions activated by an ortho or a para hydroxyl, and the natural occurrence of both laureline (VI) and pukateine (VII) (17) can best be explained by assuming



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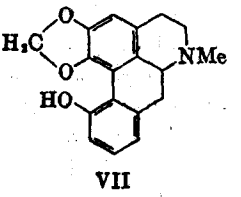

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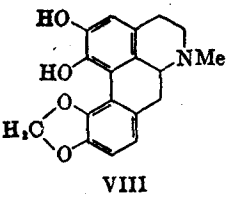
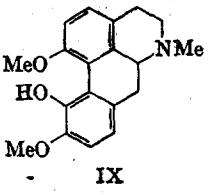


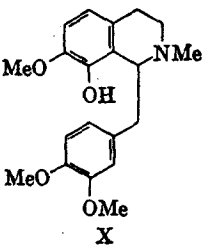
VIII



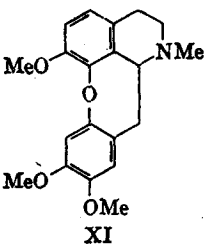
IX

the ultimate elimination of a hydroxyl from the intermediate tetrahydroxy compound formed from III. Convincing credence is lent to this view because of the copresence of laurepukine (VIII) in the same plant. It is very probable that the biosynthesis of isothebaine (IX) (18) is also via a tetrahydroxy compound because the original ring closure to a benzylisoquinoline (hetero ring formation) meta to a hydroxyl is not possible (19).

Until recently, the hetero ring closure of a benzylisoquinoline ortho to a hydroxyl was not known, but the formation of cularine (XI) from X by the removal of two hydrogens offers a satisfactory biosynthesis of this alka-

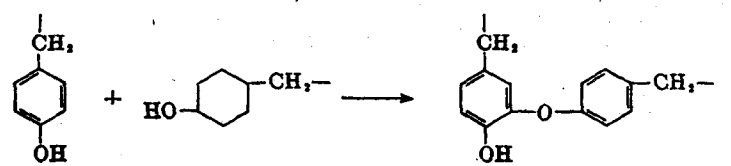


X



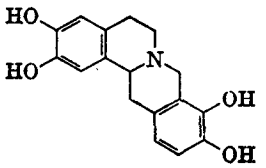
XI

loid (20). This is the first known example in which diphenyl ether formation in alkaloids has proceeded by the abstraction of a hydrogen para to a hydroxyl. In the bisbenzylisoquinolines such ether formation usually takes place ortho to a hydroxyl whether the ultimate alkaloid is of the double

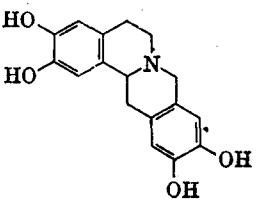


diphenyl ether type with the large rings or of the single diphenyl ether open type. The alkaloid magnolamine has recently been shown to be an example in which diphenyl ether formation is the result of the abstraction of a hydrogen para to a hydroxyl (21, 22).

The protoberberines are examples of the formation of a second isoquinoline ring by a reaction which must be strictly analogous to the first step although only "formaldehyde" is thus far known as the condensing agent. Here, however, the ring closure, with one known exception, takes place in a position ortho to the hydroxyl (III → XII). The attempted condensation

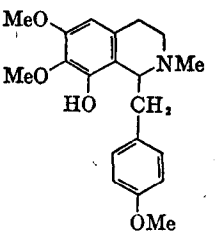


XII



XIII

in vitro always yields the isomer XIII when the hydroxyls are methylated, and the recent observation that coreximine (16, 23) has the oxygens in the positions shown in XIII lends strong support to the supposition that the benzylisoquinolines are also the precursors here. A still more convincing observation is the isolation of corpaverine (XIV) from a plant which elaborates protoberberines almost exclusively (24). It is quite evident that this



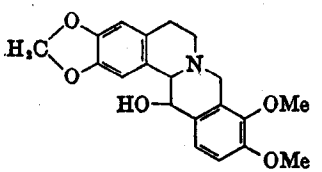
XIV

alkaloid survives as the ultimate product because there is no activating hydroxy ortho or para to the position at which condensation could take place (benzyl nucleus).

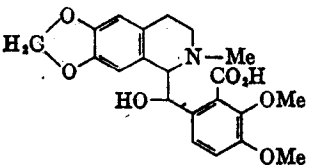
The presence of a methyl group in position 13 (the position of the hydroxyl in XV) in the protoberberines and in the protopine bases is readily explicable. It may be assumed that the aldehyde II on condensation with "formaldehye" can give rise either to a hydroxymethyl derivative or to a methylene compound, which upon hydrogenolysis or reduction, respectively,

ould generate the *C*-methyl drivative of II and consequently the methyl group would ultimately appear at position 13. There is the closest possible analogy for the above-mentioned hydroxymethyl derivative in the well-known tropic acid, $C_6H_5 \cdot CH(CH_2OH)COOH$.

The protoberberines, however, are not in themselves necessarily end products in all plants. They are very susceptible to oxidation, and the two most likely points of attack are those which would give rise to XV and XVI. The former (XV) is ophiocarpine, an alkaloid accompanying other protoberberines (25) as well as phthalideisoquinolines, and the further oxidation of a methylene to a carboxyl and *N*-methylation complete the syn-

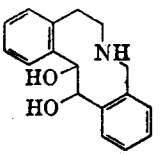


XV

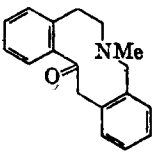


XVI.

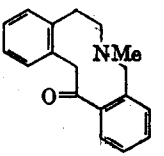
thesis of these lactonic alkaloids. However, the 1-position of the isoquinoline is also vulnerable to chemical attack, and if XV is hydrated in the appropriate manner the product may be XVII, which on *N*-methylation



XVII



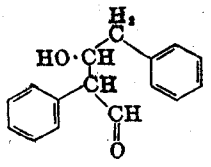
XVIII



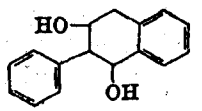
XIX

and loss of water can give rise to either XVIII or XIX, that is, either the protopine type or the cryptocavine type. It is, of course, possible to arrive at XVIII by oxidation at only one carbon followed by *N*-methylation, and such a mechanism would account for the genesis of the protopine group but another kind of mechanism would be required for XIX. It is simpler to assume that XVII is the intermediate for both forms.

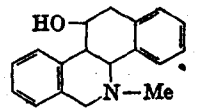
The chelidonine group of alkaloids cannot conveniently be looked upon as derived from benzylisoquinolines. In view, however, of the copresence of chelidonine with those already mentioned, it is to be expected that the ultimate precursors are the same. It can be assumed that the dihydroxyphenylalanine is converted to a substituted phenylacetaldehyde, and two molecules of this can give rise to the aldol XX, which could conceivably ring-close to XXI, in strict analogy with the mechanism which must be involved in the well-known formation of β-phenylnaphthalene from phenyl-



XX



XXI



XXII

acetaldehyde. Replacement of the thus formed hydroxyl by amino or methylamino followed by ring closure with "formaldehyde" is sufficient to form the nucleus (XXII) of chelidonine and related alkaloids. Turner and Woodward (26) have suggested a biosynthetic route to the benzophenanthridenes from the berberines, but the position of the secondary hydroxyl would not by this mechanism be unambiguously fixed.

In conclusion it is admitted that the biosynthetic route of no alkaloid is known with certainty. The main routes are nevertheless known with a reasonable degree of assurance, and it is confidently expected that much of the detail will be revealed when the tools of labeled carbon and nitrogen compounds are brought to bear on the problem.

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CHAPTER 26

Simple Isoquinoline Alkaloids

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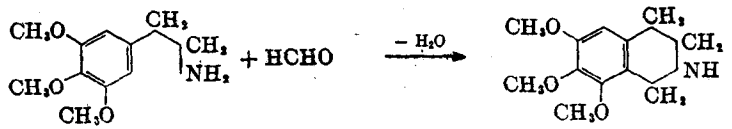
I. Introduction

The large group of alkaloids of the isoquinoline type ranges in complexity from the simple isoquinolines, more exactly defined as simple tetrahydroisoquinolines, with only one aromatic nucleus, to the complicated structures of the bisbenzylisoquinolines.

According to suggestions first made by Pictet and Spengler (1) and later by Späth (2), the substituted β-phenethylamines may be considered as the precursors of the simple isoquinolines. For example, mescaline and formal-

dehyde would yield anhalinine:



The simultaneous occurrence of substituted phenethylamines and isoquinoline derivatives in the same species (*Anhalonium lewinii* Hennings) and the facility with which similar ring closures are performed *in vitro*, under conditions which can be considered as being comparable to physiological ones, make the above hypothesis seem reasonable.

Comparatively few simple isoquinoline alkaloids have been found to occur naturally. Until now such compounds have been encountered in three or four species of the Cactaceae, in a Chenopodiaceae [*Salsola arbuscula* Pall. (*S. richteri* Karel)], in three species belonging to the family of the Fumariaceae [*Corydalis pallida* (Thunb.) Pers., *C. aurea* Willd., *C. tuberosa* DC.] and in one Papaveraceae (*Papaver somniferum* L.). While no doubt exists as to the native occurrence of the anhalonium and salsola isoquinolines, hydrohydrastinine and hydrocotarnine may have been artifacts from the benzylisoquinoline alkaloids of *Corydalis tuberosa* and *Papaver somniferum*.

II. The Anhalonium Alkaloids

In chemical literature *Anhalonium lewinii*, *A. williamsii* Lem. and *A. jourdanianum* Lewin are mentioned as different species. However, botanists definitely recognize only one species (*Anhalonium williamsii* Britton and Rose; *Lophophora williamsii* (Lemaire) Coulter). It would be worth while to investigate, using fresh and well-identified material, whether only pellotine is present in *A. williamsii*, as stated by Heffter. Such findings may give support to a revision of the taxonomy of these cacti.

These small cacti grow from central Mexico to southern Texas and are the material of an illicit commerce, carried out by some Indian tribes. The globular plants are sliced into three or four sections and then dried in the sun; these dried pieces are the "mescal buttons" of the trade. The plant is also known as pellote, peyote, and peyotl; it is called challote in Starr County, Texas. Interest in the cactus alkaloids arose when the remarkable use by the Indian tribes and the strange pharmacological properties of this little cactus became known. (See Mescaline, Vol. III, pp. 331–334, and Cactus Alkaloids, Vol. IV, chap. 27).

Eleven bases have been isolated from *Anhalonium lewinii*; three phenethylamines: mescaline, *N*-methylmescaline, and *N*-acetylmescaline (see *β*-Phenethylamines Vol. III, chap. 22); and eight simple isoquinolines: anhalamine, anhalidine, anhalinine, anhalonidine, pellotine, *O*-methyl-*d*-

anhalonidine, anhalonine, and lophophorine. An extensive study on various varieties of pellote and their alkaloidal contents was published by Beccari (3).

The clarification of the structure and the syntheses of all of the *Anhalonium* alkaloids must be credited to Späth and his coworkers. The accomplishment is all the more remarkable since Späth had to contend with a scarcity of material; several fundamental structures were determined on very small samples, left over from Heffter's and Heyl's experiments.

III. Extraction and Separation of the Anhalonium Alkaloids

Extraction of the drug and isolation of the alkaloids from *A. lewinii* have been described by Heffter (4), Kauder (5), Tomaso (6), and Späth and Becke (7), as well as by Steiner-Bernier (8).

The total alkaloidal content and the relative amount of the individual alkaloids varies widely; Heffter's figures (%) are: mescaline 6.3; anhalonidine 5.3; anhalonine 3.0; lophophorine 0.5; anhalamine 0.1. Späth's yields, working with old material, are much lower. The other bases occur in very small quantities: anhalamine 0.1 %; anhalinine 0.01 %; anhalidine 0.001 %.

In Heffter's opinion (9), *A. lewinii* does not contain pellotine, the main alkaloid of *A. williamsii*. Kauder found pellotine in the "mescal buttons," but Heffter attributes this to contamination by *A. williamsii*. This opinion is shared by Lewin (10). Morphologically, these species are difficult to separate. Späth and Becke's extraction and isolation process is as follows:

The drug is extracted with cold alcohol, and water is added to the sirup obtained by evaporating the extract *in vacuo*. The insoluble residue is treated with dilute hydrochloric acid. The solutions are united and filtered, and the filtrate is made alkaline with strong potassium hydroxide and extracted with ether. At this point the ether solution (*a*) contains the non-phenolic bases, while the aqueous solution (*b*) contains the phenolic alkaloids.

(*a*) After evaporation of the solvent, the free bases are distilled *in vacuo* and the mescaline recovered as its crystalline sulfate. The regenerated bases from the mother liquor are redistilled *in vacuo* and treated with dilute hydrochloric acid when anhalonine hydrochloride crystallizes. The filtrate, after concentration, yields anhalinine hydrochloride. By a complicated treatment of the mother liquors, a further quantity of mescaline and a little lophophorine can be obtained.

(*b*) The solution is acidified with hydrochloric acid, made alkaline again with excess potassium carbonate, and extracted exhaustively with ether. The residue from the extract is dissolved in dilute hydrochloric acid and anhalamine hydrochloride recovered. From the mother liquors anhalonidine hydrochloride is obtained by concentrating and adding alcohol. Pellotine may be recovered as picrate from the filtrate.