

ON THE PROGENITORS OF CERTAIN PLANT ALKALOIDS AND THE MECHANISM OF THEIR FORMATION IN THE PLANT STRUCTURE¹

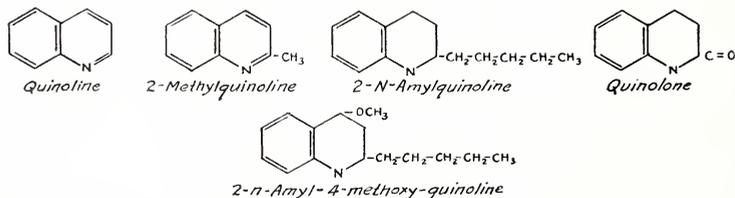
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In this paper we desire to review briefly work of certain investigators aimed at discovery of precursors of plant alkaloids, and to outline, in a preliminary way, several experiments which have been in progress in this laboratory for some time, reserving experimental details for later publication when our work is completed.

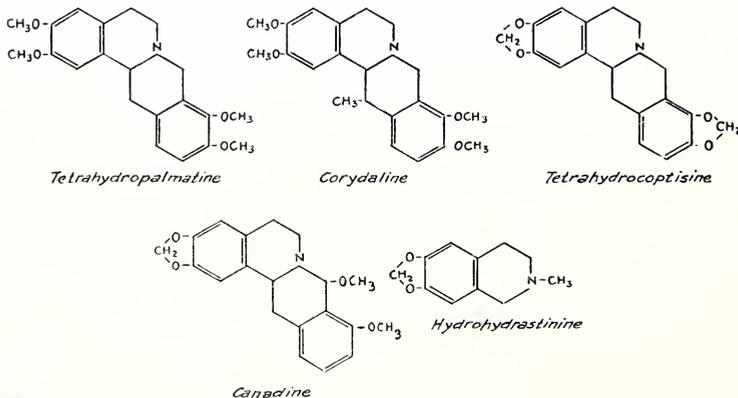
Two types of experimental work might be employed in attacking this problem. The first would comprise a careful isolation of the natural products found in any one plant to the end that substances occurring even in minute quantities might be isolated, for it is these substances which may prove to be intermediates in the synthetic processes of the plant. Such intermediates may point out the way which the plant takes in its synthesis of large molecules, and thereby throw light upon all the chemical happenings in the cell structure.

Work of this type has not often been done heretofore. In the realm of alkaloids, two plants which have been carefully investigated by Späth and his collaborators illustrate strikingly the possibilities in such work. One of these is the *Angostura*² and the other *Corydalis*.³ In the former the quinoline nucleus predominates, in the latter the isoquinoline nucleus.

Späth and Pikel, for example, have isolated from *Angostura* the following alkaloids:



From *Corydalis cava* the following alkaloids were isolated:



¹ Preliminary communication.

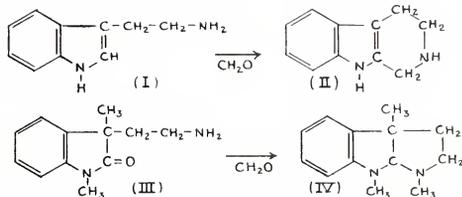
² Späth and Pikel, Ber. 62:2244 (1929); M. 55:352 (1930).

³ Späth and Tröthandl, Ber. 56:875 (1923); Späth and Julian, Ber. 64:1131 (1931).

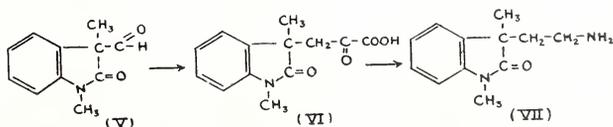
Our isolation of Hydrodrastinine seems to me of significance for several reasons: 1. Let us recall that from the Cactus plant, for example, Homoamines of the type, $RCH_2CH_2NH_2$, have been isolated. In certain plants, then, these homoamines can exist, and it has been assumed that they are produced through enzymatic action from the corresponding amino-acids, $R-CH_2-CH(NH_2)COOH$. 2. Decker long years ago⁵ showed that homoamines could be converted into N-Methyl-tetrahydroisoquinolines. Looking at the formula for Hydrodrastinine, it seems reasonable to suppose that here we have one of the first substances which the plant produces in its synthesis of the isoquinoline alkaloids. In the one direction formaldehyde is polymerized to sugars, in the other it may be converted by homopiperonylamine into hydrodrastinine.

The second type of experiment then which, in my opinion, should be more often carried out by present-day organic chemists, is an attempt to duplicate such syntheses as Decker carried out under physiological conditions. We can then be reasonably sure of our hypotheses as to the course taken by the plant. Such experiments have been carried out on Angostura alkaloids by Schöpf⁶ who made good use of the results of Späth and Piki on these compounds. Moreover, the organic chemist should seek to employ as far as is possible such methods of synthesis, even under "laboratory conditions," as the plant might take, and I wish to report in this connection in a preliminary manner certain of our experiments, in which we have attempted to do this.

In view of what has been said we may assume with a fair degree of certainty that the Homoamines and Formaldehyde are progenitors of the isoquinoline alkaloids, indeed of even the most complex ones. As further illustration let us take two classes of alkaloids, the Harmala Alkaloids (II) and those alkaloids of the Calabar Bean containing the Physotigmine Ring (IV). It is reasonable to suppose that (II) might very well be synthesized by the plant from (I) and (IV) from (III).



The first of these syntheses has been carried out in a manner similar to that which the plant would take⁷ and we wish to describe experiments which have had as their objective the obtention of the amine (III), and ultimately the compound (IV). Certain stages in our synthesis may be represented by the following formulae:

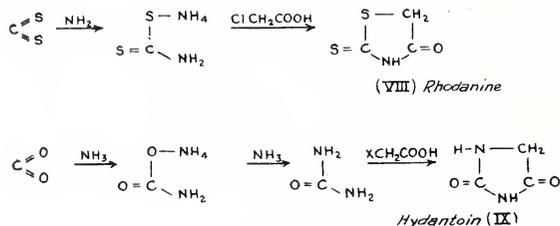


⁵ Ann. 395:345 (1913).

⁶ Ann. 497:1 (1932).

⁷ Späth and Lederer, Ber. 63:120 (1930).

In order to secure as much amine as possible from difficultly accessible aldehydes such as (V) we are compelled to work out a method which would yield homoamines in better yield than the methods hitherto employed have done. Such a method was found in Gränacher's reaction between the aldehydes and rhodanine, and we have recently reported this work⁸. At this time we wish to call attention to the biological significance of our Rhodanine condensations. The substance Rhodanine has the formula represented by (VIII) and our improved method prepares it quite readily from carbon disulphide, ammonia and chloroacetic acid.

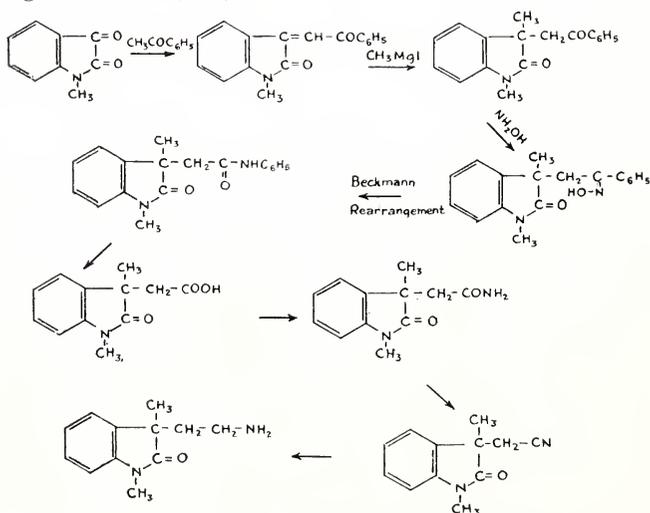


It is possible for the plant to build up products exactly similar to Rhodanine (IX) and by a method paralleling that for Rhodanine. Condensation of aldehydes with a skeleton like (IX) would exactly duplicate our condensations with Rhodanine and yield ketimino-acids of the general formula, R-CH₂-C-COOH, which Knoop and Oesterlin⁹ have assumed as



intermediates in their synthesis of amino acids.

As a means of checking the structures of our products produced by the above-mentioned synthesis, we have in progress another method for preparing the amine (VII).



⁸ Julian and Sturgis—Read at Fall Meeting of Am. Chem. Soc., Chicago, Sept. 12, 1933.

⁹ Zeit. für physiol. Chemie, 170:186 (1927).

Obviously this is an extravagant way which the plant would not take, but it involves certain types of reactions which have been studied in detail and indicates clearly the way in which such work may assist the "organic chemistry under biological conditions."

Our greatest difficulties up to the present time have been in securing in good yield certain of the basic substances in the synthesis of the amine (VII). The preparation of N-Methyl Isatin in large quantity had to be carefully worked out as the old Friedlander method does not give satisfactory results. Likewise the preparation of 1,3-Dimethyl Oxindole-3-Aldehyde (V) was secured in good yield only after numerous experiments. We have not yet been successful in obtaining smooth ring closure to (IV) but hope to report success in this direction when the complete experimental results are published. Our purpose in this review has been largely to stimulate interest in such work by reviewing briefly our own experiences and those of others.

SEPARATION OF IRON FROM INDIUM WITH CUPFERRON

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Experiments conducted some years ago upon the methods for the separation of iron from indium showed this separation to be difficult and unsatisfactory by any of the methods and they led to a new method based upon the precipitation of the iron with nitroso-B-naphtho¹. More recently the use of cupferron as a reagent for the precipitation of iron, suggested the idea that it might be substituted advantageously for the nitroso-B-naphthol. Experiments by various authors² have shown that a six per cent solution of cupferron will completely precipitate iron, copper and certain other metals in hydrochloric acid solutions while aluminum remains in solution. Indium is so closely related to aluminum in the Mendeleeff Periodic Table that a similar behavior towards cupferron was to be expected.

Preliminary experiments with the cupferron method for precipitating iron showed that an error of 0.4 to 0.8 mg. was made when using 0.07 g. Fe₂O₃ as ferric chloride, 0.7 g. cupferron and 1 to 3 cc. of hydrochloric acid, in a total volume of 40 cc. Portions of an indium chloride solution to which portions of a standard ferric chloride solution were added, were precipitated with cupferron. The precipitates were ignited and weighed as ferric oxide (Fe₂O₃). The filtrates were precipitated with ammonium hydroxide and the residues thus obtained were ignited

¹ Mathers, *This Jour.*, 30:209 (1908).

² Fresenius, *Z. anal. Chem.*, 50:35 (also a review with references). Becculi and Grassi, *Gazz. chim. ital.*, 43 I 570; through *C. A.* 7:1688.

Thornton, *Am. J. Sci.*, (4) 37:137 and 407.