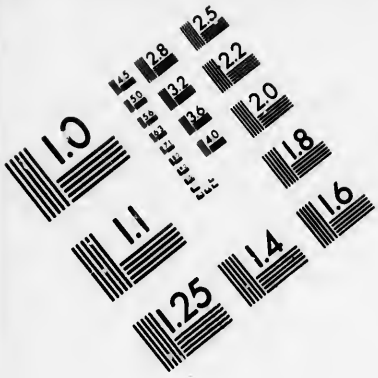

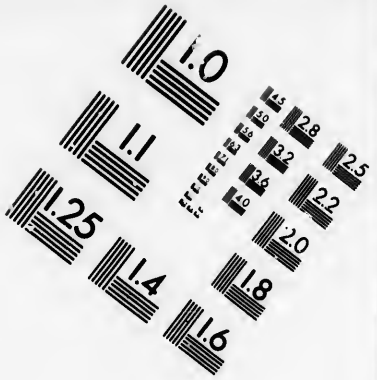

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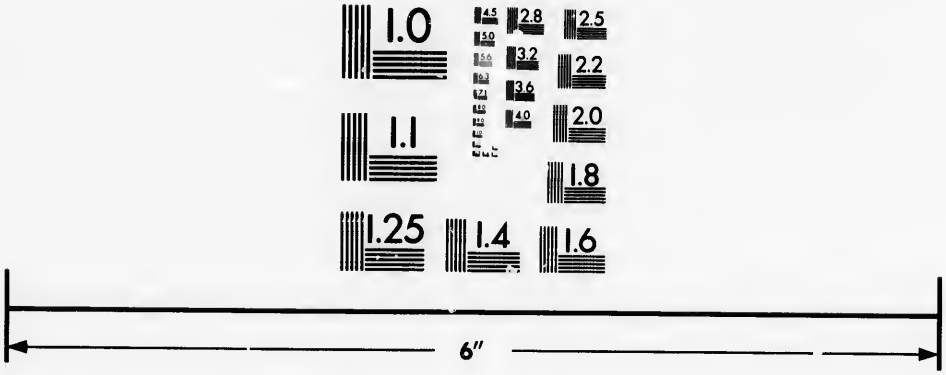

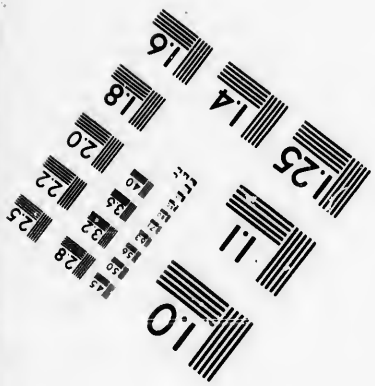

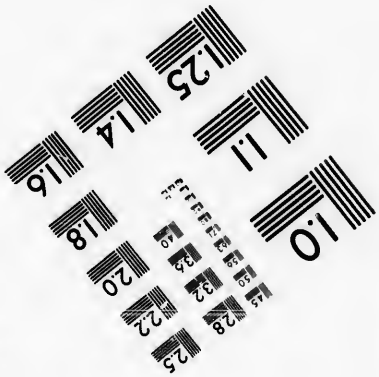

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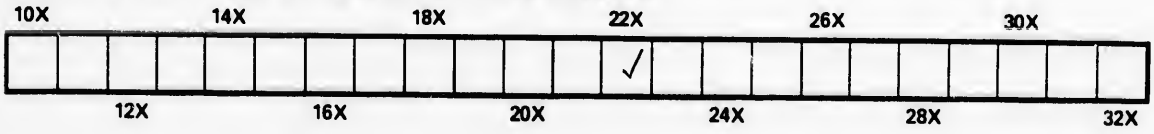

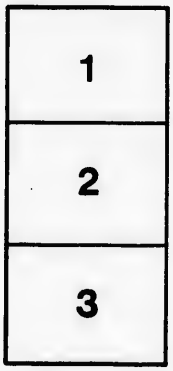

THE SYNTHESIS OF ALKALOIDS.

BY

C. G. L. WOLF, B.A., M.D.,
Demonstrator of Practical Chemistry, McGill University.

(*Reprinted from the Montreal Medical Journal, February*, 1898.)

THE SYNTHESIS OF ALKALOIDS.

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The synthetical production of alkaloids has been a task which numberless chemists have set themselves to perform since the discovery of morphine, ninety years ago, and although in the matter of actual success in comparison with the amount of work that has been done, not much has been accomplished, yet the progress which has been made in the last two decades has been so great, that it is by no means without the range of probability that in the next ten years, many of those alkaloids which are to-day only to be obtained from plants will be the products of the laboratory.

Problems, such as these, which are of almost insurmountable complexity have not only the purely scientific aspect to induce work upon them, but also the enormous commercial importance which is attached to them, and one has only to remember the indigo synthesis of A. v. Baeyer from a nitro cinnamic acid to understand how a research undertaken to solve a question of constitution will revolutionize an industry which has, for centuries almost, been the exclusive producer of a necessary domestic compound.

In the first part of this century large numbers of plants were investigated and as a result a more than an equivalent number of alkaloids was found. It was only when the observers came to investigate the constitution, that they realised the enormous difficulties with which they had to contend.

The first step which threw some light on the subject was their behaviour on distillation; many gave pyridin or a compound allied to it, and it was hence believed that they were basic bodies which

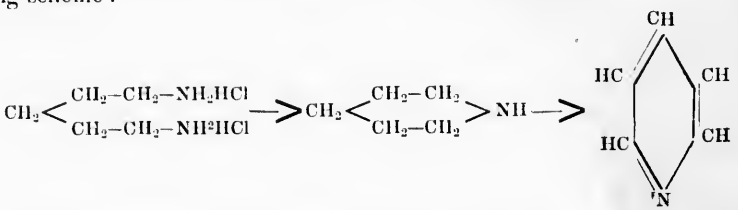
contained a pyridin nucleus. Such a definition would shut out such very important compounds as caffein and theobromin, and it is perhaps best, simply to view them as plant derivatives containing nitrogen, in which the nitrogen is contained in a cyclic atom complex.

As pyridin is the compound from which most of the alkaloids are derived, it may be well to speak of it somewhat in detail.

It consists, according to Körner, whose view has been generally accepted, of a benzene ring in which a methin group has been replaced by a trivalent nitrogen atom.

Piperidin $C_5 H_{11} N$ bears a close relation to pyridin and following up the researches of Cahours, Hofmann, by the action of bromine on the former compound, converted it into a substance having the empirical formula, $C_5 H_3 NO Br_2$, which he held to be a brominated pyridin derivative. That there was a close connection between these two substances was shown by the oxidation of piperidin to pyridin by means of sulphuric acid.

The full synthesis of piperidin was accomplished by Ladenburg by the dry distillation of penta menthylendiamin hydrochloride. The relation between these three substances may be shown by the following scheme:



The next synthesis which was effected was that of coniin, the alkaloids of conium maculatum. It was of interest also because it belongs to the somewhat restricted group of alkaloids which contain no oxygen, and Liebig, Gerhardt, Kekulé and Hofmann submitted it to close investigation without elucidating its constitution. It was Hofmann who, in 1881, proved that it was a compound closely related to piperidin but his conclusions, drawn from experiments with methyl and dimethyl piperidin as to its exact constitution. were unfounded.

Koenigs, after the conclusion of Hofmann's investigation came to the view that coniin must be a propyl piperidin. This view found a convincing proof in the work of Hofmann, who, by the distillation of coniin with zinc dust, discovered a base conyrin, which was not as expected, a reduction. but an oxidation product of coniin, and which stood in the same relation to it that pyridin does to piperidin, and

that it was a homologue of pyridin was shown by its yielding on further oxidation and pyridin carboxylic acid.

From these considerations Ladenburg was induced to take up the synthesis of coniin. The difficulties which he encountered, owing to the uncertainty of a change not occurring in the propyl group which he introduced, cannot be taken up in this place. He was, however, successful in his endeavours by condensing α picolin with paraldehyde to äthyl pyridin. This unsaturated compound on reduction gave inactive, normal α propyl pyridin. On combination of this base with dextro tartaric acid he was enabled to separate the inactive compound into dextro and lerorotatory modifications, the former of which proved in every way to be identical with the natural alkaloid. Some years later Engler condensed calcium picolinate with calcium propionate and obtained after the well known reaction α äthyl pyridyl keton and subsequent reduction of this to α äthyl piperyl alkin, which, on continuous reduction, yielded coniin. Thus has coniin been produced in two ways.

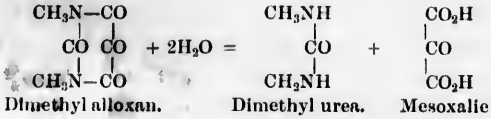
Next in order were three less important alkaloids synthesised whose production was not of interest from a technical point of view, but of great scientific worth. These were trigonellin, the alkaloid of trigonella, fœnum græcum by Hantzsch, and arekaidin, and arekolin from the areca nut by Jahns.

Piperin, the original alkaloid of pepper, was partially synthesised at first by Rügheimer in 1882, by the condensation of piperinyl chloride with piperidin. The piperinic acid from which the acid chloride was obtained was not made until Fittig had, by extremely beautiful work, shown its constitution, and afterwards Ladenburg and Scholtz effected its synthesis from proto-catechuic aldehyde.

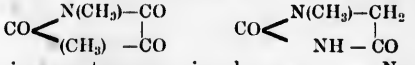
The next two compounds are of more than theoretical interest, as one plays a large technical *rôle* and both are of interest from their relation to some important physiological processes. These are caffein and theophyllin. These do not, as before mentioned, belong to the pyridin group of alkaloids, but their history is closely bound up with uric acid and urea. Although the acid was discovered by Scheele so long ago as 1776, its connection with caffein was not established till Emil Fischer began his wonderful researches on the uric acid series, which have yielded splendid results.

The decomposition products of caffein belong to a series of compounds which contain the grouping $C<^{N-C}_{N-C}>C$ and which can well be supposed to be formed by the union of urea with dibasic acids. Caffein on oxidation with chlorine yields dimethyl alloxan, which, on

treatment with alkalies, forms dimethyl urea and mesoxalic acid, which contains the grouping above mentioned.

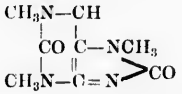


Dimethyl alloxan. Dimethyl urea. Mesoxalic acid.

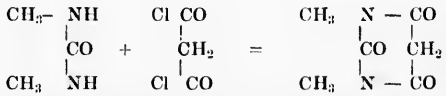
There is also formed at the same time mono-methyl urea. In both these we have groupings which are present in caffein and the question arises: In which way are they joined together in the alkaloid? This has been found by other decomposition products, *e.g.*, cholestrophan and methyl hydantoin, 

both of which contain the ring system previously mentioned. 

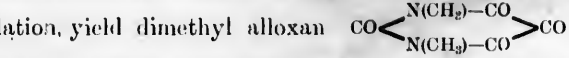
The breaking up of caffein into mono methyl urea and dimethyl alloxan is a proof also of the fact that of the ten hydrogen atoms, nine are contained in the molecule as methyl groups, the tenth being peculiar in being replaceable by chlorine, bromine, hydroxyl, or amido groups. Further, the addition of two atoms of bromine clearly shows an unsaturated carbon bond. Fischer from these considerations suggested the formula



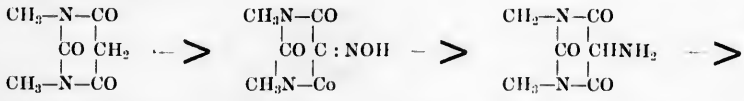
for caffein. Thirteen years after this it fell to Fischer and Ach's lot to synthesise this compound from the consideration of the investigation of Mulder on the reaction between the dimethyl urea and malonic chloride



by which was obtained dimethyl barbituric acid; from this he obtained by means of nitrous acid, dimethyl violuric acid which gave on reduction dimethyl uramil. A. v. Baeyer had at the same time submitted the unsubstituted compound uramil to the action of cyanic acid, expecting to obtain uric acid by the reaction, and had obtained not that body but a pseudo uric acid, in which the second ring system was not closed. On treating dimethyl uramil with melted oxalic acid Fischer and Ach split off the molecule of water and produced dimethyl uric acid. By the action of phosphorus penta chloride on this compound, they obtained a substance which was also obtained on treating theopyllin, a second alkaloid in tea extract with the same

reagent. Now theophyllin has a methyl group less than caffein, and, as both on oxidation, yield dimethyl alloxan  it is clear that the third methyl group does not belong to the alloxan ring; so that theophyllin must be represented by formula VI., in which chlorine is replaced by a methyl group.

Theophyllin can be changed to caffein by the action of methyl iodid on its silver salt. This is one of the prettiest examples of a compound being synthesised by purely scientific considerations. The following formulæ show the relation between the different compounds which led up to it:

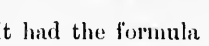


I. Dimethyl alloxan. II. Dimethyl violuric Acid. III. Dimethyl uramil.

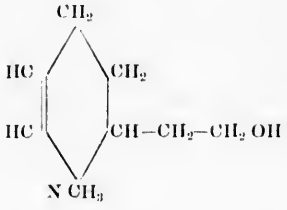
IV. Dimethyl pseudo uric acid cyanate. V. Dimethyl uric acid.

VI. Chlortheophyllin. VII. Caffein.

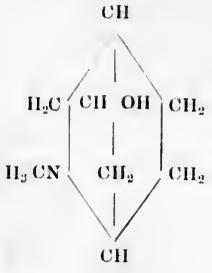
Partial Synthesis.

Atropin—The synthesis of atropin has not been a complete one, yet much successful work has been done in this direction since Liebig determined that its formula was $C_{17}H_{23}NO_3$. Ladenburg, after Kraut and Lossen had split it into two of its components, tropin and atropaic acid, combined these two to form the alkaloid. Investigating the latter product, he found it had the formula  and determined it thus to be α phenyl hydracrylic acid, and the first synthesis of this acid, starting from acetophenon, was due to these observers working in conjunction with Rügheimer. They treated phenyl methyl ketone with phosphorus penta chloride, obtaining the ketone chloride, this treated with alcohol and potassium cyanide the compound  which on saponification after the well-known method with baryta water yields a saturated acid, atrolactic acid, the äthyl ester of which, with strong sulphuric acid, splits off

äthyl alcohol, giving the unsaturated atropaic acid. By treatment of this with hypochlorous acid, the chlorinated acid is obtained, which on treatment with nascent hydrogen gives tropaic acid. The acid part of atropin having been synthesised, Ladenburg, on the ground of some cleavage products of tropin, has suggested the formula I, which has been changed by Merling, with the consent of many chemists, to formula II.



I.

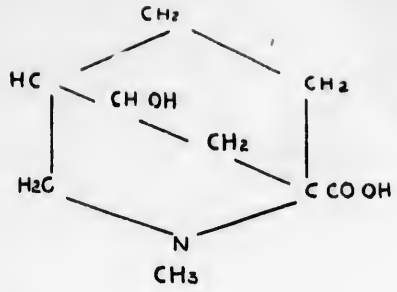


II.

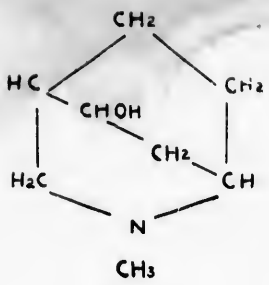
Although neither of these compounds has as yet been completely synthesised, yet, tropin has been built up again from one of its decomposition products which, according to Merling's formula, must be dihydro benzyl dimethylamin. This latter is a derivation of tropidin methyl ammoninm hydrate, which is, in its turn, derived from tropin by dehydration. Now Merling showed that the monocyclic compound, the α methyl tropin, combined with two molecules of hydrochloric acid to hydrochlor α methyl tropin hydrochloride, which, with sodinm hydrate, gave the base hydrochlor α methyl tropidin. This changed to tropidin methyl ammonium chloride, which broke up by distillation into tropidin and methyl chloride. The transformation of tropidin into tropin was previously accomplished by Ladenburg.

The next alkaloid, which is of great importance medically, is cocain. This compound bears a close relation structurally with the foregoing as Wilstätter showed, and also with the alkaloid α tropin found in Javanese coca leaves.

Cocain, on saponification, splits up into ecgonin benzoic acid and methyl alcohol. From this decomposition one may infer that ecgonin contains an acid and a hydroxyl group, of which the latter one is benzoylated and the former methylated in cocain. Ecgonin is very similar to tropin, and Einhorn has been able from the former body to prepare the latter. By dehydration ecgonin yields an hydro ecgonin which gives off carbon dioxide air on suitable treatment yielding tropidin. The relation between tropin and ecgonin, according to the newer formulæ, may be easily seen by comparing the two formulæ.



Ecgonin.

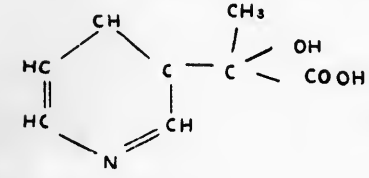


Tropin.

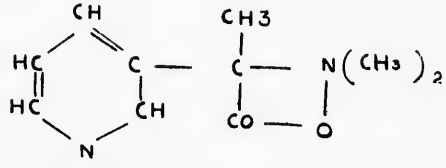
Ecgonin on treatment with benzoic anhydride and methyl iodide gives cocain. Taking into account the previous work on tropin one may say that the synthesis of cocain is far advanced towards completion.

Pilocarpin has also engrossed the attention of many observers. According to Hardy and Calmels it consists of a pyridin nucleus combined with a betain group in the β position.

Pilocarpin, on boiling with water, breaks up into trimethylamin and an acid of the formula $C_8N_9NO_3$. The barium salt of this acid on distillation yields C_7H_9NO, which on oxidation gives β pyridyl methyl keton hydrate, which can be prepared synthetically. The first named of these compounds is from these considerations a β pyridyl, α lactic acid, and from the splitting of pilocarpin into this acid and trimethylamin it may be assumed to have the formula



β pyridyl α lactic acid.

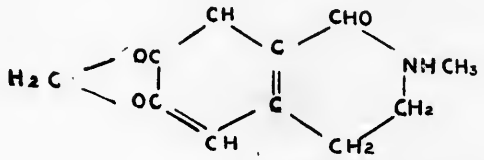


Pilocarpin.

Hardy and Calmels endeavoured to synthesise pilocarpin from its decomposition products. By treating β pyridyl α lactic acid with phosphorus dibromide and heating the bromo acid so obtained with dimethylamin, pilocarpidin was obtained. This when heated in methyl alcohol solution with methyl iodide and potash gave pilocarpinic acid. This on oxidation and dehydration with permanganate of silver yields pilocarpin. According to Herzig and Meyer pilocarpin contains but one group attached to nitrogen, but owing to the extremely unsuitable state in which the various compounds are obtained, it is too early

to form a definite opinion as to which is the precise constitutional formula.

The work of Schmidt and Freund has done much to clear up the constitution of hydrastin, the alkaloid of hydrastis canadensis, and we may be said now to have a fully formed idea of its constitution. The work which led up to the views of its formula would require a somewhat lengthy statement, which cannot be given here. One of its decomposition products (hydrastinin) has been shown to have the formula



This has been prepared synthetically, but the transformation into hydrastin has not been effected. Neither has the formation of opianic acid been completed, so that these two steps are lacking to the preparation of the original alkaloid itself.

I may mention that much of the data given here are to be found in the admirable work of Scholtz "Die Kunstliche Aufbau der Alkalöide," and those wishing to pursue the subject further will find in it references to the original papers, which contain fuller accounts of the work done in this interesting field.