LXXV.—*A Theory of the Mechanism of the Phytochemical Synthesis of certain Alkaloids.*

By ROBERT ROBINSON.

ALTHOUGH in recent years, largely owing to the investigations of Pictet and his collaborators, there has been a due recognition of the importance of the rôle played by formaldehyde in the production of alkaloids in plants, and although it is generally admitted (compare Winterstein and Trier, "Die Alkaloide," pp. 263–317) that the amino-acids and carbohydrates are the most probable starting points for the majority of phytochemical syntheses, yet little progress has been made in ascertaining the nature of these processes or even in the less ambitious task of formulating possible mechanisms based on laboratory analogies. The details of the

schemes which have been suggested, with but few exceptions, involve reactions for which little or no parallel exists in synthetical organic chemistry under conditions approximating to those obtaining in a plant. Thus Pictet's view of the mechanism of the synthesis of nicotine was founded on observations of pyrogenic reactions of pyrrole derivatives, and Winterstein and Trier seek to replace this hypothesis by another, according to which the base results from the oxidation of a mixture of pyridine and *N*-methylpyrrolidine (*loc. cit.*, p. 298). Similar ideas have been advanced by Windaus and Knoop (*Beitr. chem. Physiol. Path.*, 1905, **6**, 392) to explain the formation of xanthine by the oxidation of a mixture of carbamide and methylglyoxaline and of histidine by an analogous process applied to glycine and methylglyoxaline.

There has thus been a tendency to explain the results observed by the assumption that plants have at their command enormously powerful reagents that are able to cause substances, the properties of which have been investigated with considerable care, to undergo transformations which cannot be induced in the laboratory. To a certain extent, and especially in regard to oxidation and reduction, this must be true, but it is probable that this aspect has been exaggerated and that an equally important cause of the variety and complexity of syntheses in plants resides in the highly reactive nature of the substances which function as intermediate products.

The point of view reached in the present communication is due to a development of ideas which owed their inception to the hypothesis that the synthesis of tropinone recently described (this vol., p. 762), on account of its simplicity, is probably the method employed by the plant, and confirmation of this theory was sought and found in the structures of hygrine and cuschygrine, which stand to one another in the same relation as styryl methyl ketone (benzylideneacetone) to distyryl ketone (dibenzylideneacetone). Having found it desirable to proceed from ornithine in order to reach the bases of the pyrrolidine group, it was obviously interesting to inquire as to whether similar methods applied to the homologous lysine would lead to naturally occurring piperidine compounds. This proved to be the case, and the investigation was then extended to include the more important of the alkaloids the constitutions of which have been determined. In the schemes given in the sequel, linking of carbon to carbon is traced to two processes only, namely, the aldol condensation and the very similar condensation of carbinol-amines, resulting from the combination of an aldehyde or ketone and ammonia or an amine, and containing the group $\cdot\dot{\text{C}}(\text{OH})\cdot\dot{\text{N}}\cdot$, with substances containing the group $\cdot\dot{\text{C}}\text{H}\cdot\text{CO}\cdot$.

The latter reaction has been investigated chiefly in connexion

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with cotarnine and similar pseudo-bases, and the production of anhydrocotarnineacetone (I) may be cited as a typical example:

The condensing agent employed by Liebermann and Kropf (*Ber.*, 1904, **37**, 211) in this case is unnecessary, and the reaction proceeds to completion in aqueous solution and at the ordinary temperature. In fact, these pseudo-bases are substances which enter into a variety of condensations with the greatest facility, and a large number of substances have been prepared in this way, and in most cases in good yield.

Employing these admissible methods it is possible in each instance to obtain the alkaloid skeleton, and the further modifications are usually made by means of oxidations or reductions and by elimination of water with the formation of an aromatic nucleus or occasionally of an ethylene derivative. The more important starting points employed are ammonia and formaldehyde, ornithine (arginine) and lysine and degradation products of carbohydrates. Of the latter, citric acid is suggested as the source of acetone residues which it supplies in the form of acetonedicarboxylic acid as the result of oxidation. Seekamp has observed the formation of acetone (*Annalen*, 1893, **278**, 374) by the photochemical decomposition of a 5 per cent. aqueous solution of citric acid containing 1 per cent. of uranium oxide, and it can scarcely be doubted that the dicarboxylic acid was an intermediate product. The author does not, however, wish to emphasise unduly this theory of the source of the acetone residues, and it is interesting to note that Lippmann (*Ber.*, 1893, **26**, 3057) found that acetonedicarboxylic acid was obtained during the spontaneous decomposition of calcium trisaccharate. Further, a reactive acetone derivative may be found in diacetylacetone or other 'polyketen,' the formation of which in plants has been discussed by Collie (*T.*, 1893, **63**, 329; 1907, **91**, 1806), and in that case the acetyl groups would be removed by hydrolysis subsequent to the condensations. However, the occurrence of the carboxyl group in egonine suggests that in the synthesis of cocaine it is a carboxylated acetone derivative which is the forerunner of the alkaloid. Except in the cases of hygrine and tropinone, the carboxyl groups have been omitted from the acetone rests for the sake of simplicity in representation. As a starting point for both quinoline and isoquinoline bases, it has been found convenient to assume the intervention of acetylglycollaldehyde (II), or Δ^4 -butene- $\alpha\beta$ -diol- γ -one, a substance which has not yet been isolated. It may readily be derived from a pentose or

methylpentose by loss of water and oxidation, as shown below, and it is perhaps significant that a methylpentose, quinovose, occurs in a state of combination as quinovin in cinchona-bark.

The Pyrrolidine Group.

It has recently been demonstrated by Hess (*Ber.*, 1913, **46**, 4104 *) that the methylation of an amine with the aid of formaldehyde is accompanied by oxidation, amino-alcohols yielding methylaminoketones. The methylating and oxidising action of formaldehyde on ornithine might therefore yield a carbinol-amine of the pyrrolidine series in accordance with the equation

Naturally, the possibility is not excluded that the oxidation of the amino-acid † is preceded by the formation of a hydroxy-acid, and ammonia and alcohols may in all cases be intermediate between amines and the aldehydes obtained by oxidation.

Further oxidation accompanying methylation might attack both

* In which a complete list of references to earlier work by Eschweiler and others will be found.

† Dakin (*J. Biol. Chem.*, 1906, **1**, 171) has applied Fenton's method of oxidation by means of hydrogen peroxide and a trace of ferrous sulphate to the ammonium salts of the amino-acids, and has obtained aldehydes, ammonia, and carbon dioxide. Hurtle and Wootton (*T.*, 1911, **99**, 288) find that alloxan effects the same change which had already been observed in the particular instances of the conversion of alanine into acetaldehyde and of leucine into isovaleraldehyde by Strecker (*Annalen*, 1862, **123**, 363).

Quite recently Schweitzer (*Biochem. Zeitsch.*, 1916, **78**, 37) has shown that the tyrosinase from potatoes can oxidise glycine with the formation of formaldehyde, carbon dioxide, and ammonia. The reaction takes place in the presence of an alkali, preferably calcium hydroxide, and appears to be accelerated by chlorophyll.

* Succindialdehyde would be more readily obtained from a diamino adipic acid which does not, however, appear to have been isolated.

† The simplest substance produced on the cocaine model is probably arecoline, a comparison of the formula of which with that of cocaine shows that the only divergences, which it is necessary to postulate in the synthesis of the former from that of the latter, are the employment of two molecules of formaldehyde instead of one of succindialdehyde and loss of water instead of benzoylation.

Cocaine.

Arecoline.

Trigonelline.

Arecoline also closely resembles a hypothetical intermediate in the synthesis of nicotine. If it is oxidised, as was assumed for that more complex tetrahydropyridine, then the betaine trigonelline would be obtained.

The condensation product (VI), which forms the source of hygrine, may also be the progenitor of nicotine (VIII), and the reactions necessary involve condensation with formaldehyde and ammonia to a piperidone (VII) containing the nicotine skeleton, after which there are alternative ways of expressing the remaining stages.

The Piperidine Group.

Starting from lysine* (IX) and proceeding as illustrated above in the case of the lower homologue ornithine, the formation of the bases X and XI would be anticipated. The latter is the alkaloid ψ -pelletierine, isolated by Ciamician and Silber and by Piccinini from the root-bark of the pomegranate tree, and since tropinone has not yet been obtained from natural sources, the occurrence of its ring homologue is particularly valuable evidence. The base X has been synthesised by Hess, Merck, and Ubrig (*Ber.*, 1915, **48**, 1886), and later identified by Hess and Eichel (*Ber.*, 1917, **50**, 380) with a methylpelletierine occurring in small relative amount in the alkaloids of the pomegranate tree.

* Clearly the source through cadaverine of the piperidine rest which appears in piperine.

The frequent concurrence of closely related alkaloids, such as the pelletierines* or coniine and its associates, is probably to be explained by variations of some primary product due to alternate hydration and dehydration or by oxidation and reduction. In this connexion, a highly significant discovery has been reported by Hess, Eichel, and Uibrig (*Ber.*, 1917, **50**, 351), who find that the reaction between amino-alcohols and formaldehyde is reversible. The methylaminoketone (X), for example, is decomposed in alcoholic solution by semicarbazide acetate, with the formation of the demethylated amino-alcohol (XII) and formaldehydesemi-

* The imino-ketone pelletierine, containing one reactive methylene-group (Hess and Eichel, *loc. cit.*), has not yet been completely investigated, but, on the evidence so far recorded, and from analogy it should be the ketone corresponding with conhydrine or, more probably, the 3-piperidone obtained by addition of water to coniceine followed by oxidation. In either case it will fit into the lysine-acetone scheme.

carbazone. This suggests not only that oxidation accompanies *N*-methylation and *O*-methylation, but also that reduction is associated with *N*-demethylation. Coniine (XIII), *N*-methylconiine (XIV), conhydrine (XV), and coniceine (XVI) represent on this view modifications of the amino-alcohol (XII), and therefore of the normal product (X), from lysine, formaldehyde, and a reactive acetone derivative.

In the above, and also in some of the sections which follow, the reduction of alkylamines has been assumed, and it may be pointed out that there is evidence that these substances are reducible, the reaction probably depending on the intermediate formation of an unsaturated or cyclic ammonium hydroxide.

The Quinuclidine Group.

Condensations between formaldehyde, ammonia, and a reactive acetone derivative, such as acetonedicarboxylic acid, can explain in an astonishingly simple manner the formation of alkaloids containing the curious quinuclidine ring system. Ammonia, three molecules of formaldehyde, and the acetone derivative lead to the formation of the piperidone (XVII), two molecules of which enter another molecule of acetone derivative, producing XVIII. This, owing to the stability of the ring system produced, undergoes internal aldol condensation, and complete reduction then results in sparteine (XIX).

Sparteine thus appears as the reduction product of a substance obtained by condensation along normal lines of three molecules of an acetone derivative with six of formaldehyde and two of ammonia. In the presence of an excess of the acetone derivative, or with such a substance containing only one highly reactive methylene group, for example, acetoacetic acid, the reaction with formaldehyde and ammonia might take a different course, resulting in the formation of the diketone (XX), and this is believed to be

the origin of cinchonine and quinine. The quinoline derivative (XXI) enters the molecule in the manner assumed throughout, that is, by a carbinol-amine condensation, and the remainder of the reactions are of the type already formulated in the case of sparteine. An alternative for the later stages is presented in the scheme which is given below. It is possible that reduction of the diketone (XXII) produces, first, an internal pinacone (compare Kipping and Perkin, T., 1891, 59, 214), which, after further reduction, undergoes a transformation of the ring system accompanied by elimination of water.

With regard to the genesis of the quinoline derivatives required for cinchonine and quinine, it is natural to seek an explanation from the constitution of quinic acid (XXIII), which accompanies these alkaloids in the plant and is readily converted into quinol derivatives. The coincidence that quinine is also, in a sense, a derivative of *p*-aminophenol strengthens the conviction that quinic acid is the source of the quinoline half of the molecule. In any case, it would seem necessary that the acid should become oxidised to the ketone (XXIV), so as to provide the six-carbon system and admit the entry of the nitrogen atom. Further, a reactive

methylene group is so produced, enabling the occurrence of the condensation which closes the quinoline ring. This process is formulated below, and the heterocyclic nucleus is obtained by a reaction similar to that by means of which quinaldine may be synthesised from *o*-aminobenzaldehyde and acetone.

In the majority of the complex examples discussed, it is obvious that the order in which the reactions may be supposed to occur can be considerably varied without fundamentally altering the character of the suggested processes, and in the case of quinine there are several plausible variations of this kind, the most important of which is perhaps that the quinoline ring may be closed immediately after the appearance of an acetyl group in a modified carbohydrate, such as quinovose, and the product must then suffer further degradation by oxidation of the side-chain.

The isoQuinoline Group.

In the discussion of this large and important group, it will clear the ground to construct, in the first place, a table which it is considered represents the genetic relationships of the more important members.

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from ammonia, formaldehyde,* a reactive acetone derivative, and acetylglycollaldehyde, are represented below.

* In all cases where formaldehyde is supposed to enter into a carbinolamine condensation it is clearly equivalent to assume the intervention of glyoxylic acid or even of an aldehyde, $\text{R} \cdot \text{CHO}$, in which the group R is readily oxidisable to carboxyl after the condensation.

The amino-acids formed in such reactions must be α -amino-acids, and the elimination of carbon dioxide will therefore always be explicable. The

B. Formation of the Aromatic Compounds.—Simple dehydration of XXV and XXVI leads to 3:4-dihydroxyphenylethylamine (XXVII) and 3:4-dihydroxyphenylacetaldehyde (XXVIII), and attention is directed to the peculiarity of the constitution of the hydroaromatic substances, which renders it extremely improbable that an orientation in the benzene derivatives other than that observed could result from the process. Oxidation of XXV would, however, produce a pyrogallol derivative, and this oxidation might be the result of methylenation of the two adjacent hydroxyl groups preventing the removal of oxygen from the ring. The dihydrobenzene so obtained would then be oxidised to XXIX.

C. Elaboration of the Morphine Sub-group.—The hydroaromatic aldehyde (XXVI) condenses with the hydroaromatic base (XXV), producing XXX, XXXI, and XXXII by a carbinol-amine condensation, an internal aldol condensation, and by elimination of water. At this stage, in order to obtain morphine it is necessary to assume the only reduction which is encountered in the whole group. The hydroxyl group marked (a) is in a position with respect to the nitrogen atom which renders plausible syntheses of histidine, tryptophane, and tyrosine probably involve reactions of this type. In the case of histidine the complete representation would be the following :

In general, the group $\cdot\text{CO} \cdot \text{CH}_3$ becomes $\cdot\text{CO} \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{CO}_2\text{H}$, and the carbonyl group can then take part in aldol condensations leading to cyclic structures, whilst the carboxyl group may be eliminated or the amino-acid be oxidised to an aldehyde. The adoption of such a view in the case of the forerunner of the isoquinoline alkaloids is favoured by the author, but the simpler suggestion is retained in the text in order to avoid undue complexity of the formulæ.

the assumption of the formation of a cyclic ammonium hydroxide and after the reduction morphine (XXXIII) is obtained by *N*-methylation and elimination of two molecules of water. *O*-Methylation, in addition, provides codeine, and thebaine is the result of still further methylation, accompanied by loss of two atoms of hydrogen.

D. *The Aromatic Phenanthrene Sub-group*.—The compound XXXII, by symmetrical elimination of three molecules of water, yields the phenol derivative (XXXIV), which by *N*-methylation and methylation of two phenolic hydroxyl groups becomes isothebaine (XXXV), which Klee (*Arch. Pharm.*, 1914, **252**, 211) has shown accompanies thebaine in *Papaver orientale*.

If the hydroaromatic ring of XXXII becomes oxidised, as may well happen simultaneously with the *N*-methylation of formaldehyde, one of the $\cdot\text{CH}(\text{OH})\cdot$ groups becoming $\cdot\text{CO}\cdot$, then elimination of water leads to XXXVI, which by methylation and methylenation provides numerous alkaloids of the corydalis-phenanthrene type, such as bulbocapnine (XXXVII) (Gadamer and Kuntze, *Arch. Pharm.*, 1911, **249**, 598).

In glaucine (XXXVIII) and dicentrine (Asahina, *Arch. Pharm.*, 1909, **247**, 201; Gadamer, *ibid.*, 1911, **249**, 680) the orientation of the catechol ether groups suggests that these bases are the result

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of condensation of the aromatic aldehyde (XXVIII) with the hydroaromatic base (XXV), and the condensation which closes the phenanthrene ring may then produce a 4:5-substituted catechol derivative. Apart from this, the reactions necessary will entirely resemble those required for bulbocapnine.

E. *Norlaudanosine and the Products obtained from it by the Action of Formaldehyde.*—Norlaudanosine (XXXIX) is the result of condensation of XXVII and XXVIII, as illustrated below (compare Winterstein and Trier, *loc. cit.*, p. 307):

Norlaudanosine is subject to attack by formaldehyde at six points, and the nature of the substances produced largely depends on the amount of oxidation which accompanies the methylations.

(a) *Laudanosine*,

Complete methylation of phenolic hydroxyls and of the imino-group unaccompanied by internal oxidation.

(b) *Papaverine*,

Methylation of phenolic hydroxyl and oxidation of the tetrahydroisoquinoline ring.

(c) *Xanthaline (papaveraldine)*,

(d) *Hydrastine*,

The essential reaction here is a "Lederer-Manasse" synthesis, introducing the group $\cdot\text{CH}_2\cdot\text{OH}$ into the benzene ring. The product then becomes simultaneously methylated and oxidised, as indicated below:

(e) *The Berberine Sub-group.*

The establishment of a bridge between the nitrogen and the benzene ring produces norcanadine (XL), and the reaction is, of course, that which Pictet and Gams (*Compt. rend.*, 1911, **153**, 386; *Ber.*, 1911, **44**, 2480) devised for the synthesis of tetrahydroberberine:

From norcanadine the following are obtained by the action of formaldehyde:

(a) *Canadine*,

Methylation of two phenolic hydroxyls and methylenation of two more.

(β) *Berberine*,

The same processes as with canadine, using the oxygen for the conversion of the tetrahydroisoquinoline derivative into a true alkylisoquinolinium hydroxide.

(γ) *Protopine*,

Complete methylenation of norcanadine yields XLI, and the action of formaldehyde on this substance may produce protopine (XLII) (Perkin, T., 1916, **109**, 875).

This is a reaction of a more hypothetical character than any other introduced in this communication, but since a ring-scission in this direction of tetrahydroberberine methohydroxide has been established by Pyman (T., 1913, **103**, 828) and since these results have been paralleled in the *isotetrahydroberberine* series in connexion with derivatives of cryptopine (Perkin, *loc. cit.*, p. 841) there appears to be little improbability in the assumption, and the details of the process may follow the partial scheme:

(δ) *Cryptopine* (Perkin, *loc. cit.*, p. 831),

This would result from norcanadine by methylation and methyl-

enation to form an *isotetrahydroberberine*, which might yield the base by the further action of formaldehyde as with protopine.

F. *Narcotine and Narceine*.—3:4-Dihydroxyphenylacetaldehyde (XXVIII) and the base XXIX are supposed to condense with formation of the methylene ether of hydroxy-*N*-methylnorlaudanosine (XLIII), which is converted into narcotine (XLIV) in precisely the manner employed above in the case of hydrastine. The ring-scission of narcotine with the formation of narceine is similar to the production of protopine and cryptopine, except that the further methylation of the nitrogen is not accompanied by internal oxidation:

G. *Corydaline*.—Notwithstanding the observation of Gadamer (*Arch. Pharm.*, 1915, **253**, 274) that corydaline loses its optical activity when it is oxidised to didehydrocorydaline, and that therefore the two asymmetric carbon atoms should be contiguous, an alteration in the accepted formula of the alkaloid cannot be considered. Especially is the position of the methyl group clearly proved by the arguments of Dobbie and Lauder (T., 1902, **81**, 154) relating to the methylpyridinetricarboxylic acid obtained by them from corydic acid, although a slight modification of the constitution of the latter substance would now be made so as to represent it as a true pyridine derivative and as a betaine (compare Perkin, *loc. cit.*, p. 836).

Corydaline accordingly appears as a methylated norlaudanosine with an ethylidene bridge between the nitrogen atom and the aromatic nucleus, a structure produced by the intervention of acetaldehyde instead of formaldehyde. Attention may be again directed to the possibility that what may be termed the hemipinic orientation may result from aldol condensation with the hydroaromatic progenitors of these alkaloids, whilst the meta-hemipinic orientation is to be expected if the condensations are subsequent to the conversion of the hydroaromatic compounds into catechol derivatives by loss of water.

H. *The Conditions affecting the Production of the isoQuinoline Bases.*—The problem may be put in the form of a question: Why do not alkaloids assumed as above to have a common origin always occur together in the plant? Why, for example, does not morphine occur in *Hydrastis canadensis*? It is reasonable to expect some answer to this, but not, in the circumstances, a complete one. In the particular case mentioned the scheme shows that the molecule must suffer reduction before morphine can be obtained. That there are reducing conditions is clear also from the formation of laudanosine. On the other hand, the formation of hydrastine and of berberine follows such a course that all the oxygen available from the methylations is used internally, and powerful reducing agents would therefore appear to be absent during the formation of these bases. This would be sufficient to account for the non-production of morphine. Among other circumstances that may affect the nature of the end-products are the stereochemical relations of the hydroaromatic substances, the rapidity with which these lose water with the formation of aromatic compounds, the stage at which *N*-methylation occurs, the concentration of formaldehyde and other reagents, the presence or absence of enzymes and other catalysts, all of which are without doubt connected with the needs of the plant itself. If these varying conditions are taken into account the objection that the simplicity of the schemes proves too much cannot well be sustained.

Some of the more remarkable coincidences encountered in the development of the foregoing suggestions may now be noted in summary and conclusion. In the pyrrolidine group hygrine, cuschygrine and tropinone are related by their method of formation, and by introducing a piperidone ring into hygrine by means of a reaction entirely similar to that required for sparteine it is seen that an explanation is provided of the β -position of the pyrrolidine complex in the pyridine nucleus of nicotine. In the piperidine group the methods are homologous with those of the pyrrolidine group and the nature of the reduced pyridine derivatives

which have been obtained from plants is quite in harmony with the origin from lysine. In particular, the α -propyl chain of coniine is explicable on the assumption that it represents a reduced acetone residue. In the quinuclidine group the bridged rings of sparteine and quinine are produced by similar methods, the application of which fixes the position of the connecting methylene group of sparteine and the vinyl group of quinine. Substances accompanying quinine and cinchonine in cinchona-bark have been found to be suitable starting points for a synthesis of the quinoline-half of the molecules of these alkaloids. In the *isoquinoline* group it is noteworthy that one and the same hypothetical hydroaromatic substance derived in part from a carbohydrate degradation product also required for quinine, suffices for the production of the whole of the bases of the group the constitutions of which have been elucidated. It is hoped that it will prove possible to employ this theory as a working hypothesis in several directions.

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