Synthesis in Biochemistry.

THE FIFTH PEDLER LECTURE DELIVERED BEFORE THE CHEMICAL SOCIETY ON MAY 28TH, 1936.

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No pupil of Perkin could approach the task that lies before me to-day without recalling the memory of the first Pedler lecturer and of that fascinating account of pioneering synthetical work which he presented to the Society on May 30th, 1929, in his inimitable, lucid style.

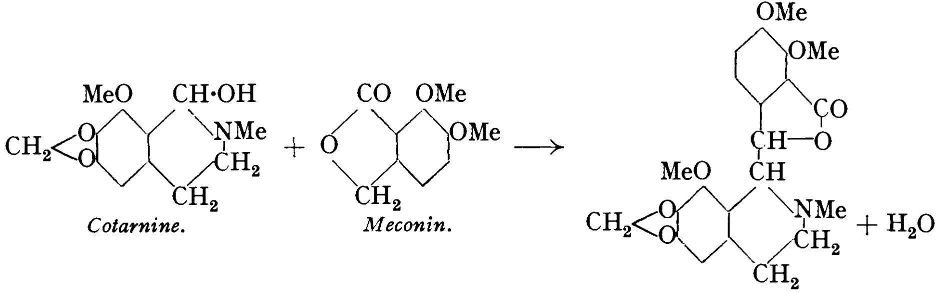
Arriving in the research laboratory at Manchester toward the end of the period of terpene synthesis,* the main impression one received was of the conclusiveness of these achievements in relation to molecular structure and their complete lack of contact with biology. The very success of Perkin's labours served to throw the laboratory processes and those occurring in the living cell into sharp contrast. In spite of the seemingly insuperable obstacles confronting the explorer of this region it became an object of investigation to attempt imitations of biosynthesis, however far from the mark such attempts might eventually prove to have been.

There was, and is, a further inducement to probe these mysteries in the circumstance that, marvellously adaptable as the methods of the classical organic chemist have proved to be, his successor encounters many synthetical problems of such intrinsic difficulty that the only hope of a solution appears to lie in the use of Nature's key. It may be only a skeleton key and a good deal of fumbling may be necessary before it can be made to work. Thus the elucidation of the course of biosynthesis, always a preoccupation of the physiological chemist, is also an interest of the pure organic chemist whose aim it must be to find the synthetic reactions which can be effected in aqueous solution at the ordinary temperature and with the help of mild reagents only.

Furthermore, comparisons and analysis of the molecular structures of the more complex plant products have revealed in many cases the architectural plan and have given clear indications of the nature of the units used in the building. This is particularly true of the alkaloids, the colouring matters, and the terpenes and polyterpenes.

I can attempt no complete account of the approaches that laboratory syntheses have made to those occurring in plants, and will mention only a few aspects of the topic which happen to have interested me. In any case it must be confessed that only a beginning has been made towards the realisation of our ambitions and I am more interested in advocating a point of view than in recording achievements that may be credited to those who have adopted it. Hence I may perhaps be allowed to follow the thread of some personal experiences, including many disappointments, so that the standpoint may be made clear.

In 1910 the synthesis of *dl*-narcotine was effected in poor yield by the condensation of cotarnine and meconin [1] and in connection with the subsequent improvements of the process the opportunity was taken to study more closely the facile condensation reactions of cotarnine and other pseudo-bases.[2]



Cotarnine. *Meconin.* *Gnoscopine* (dl-*narcotine*).

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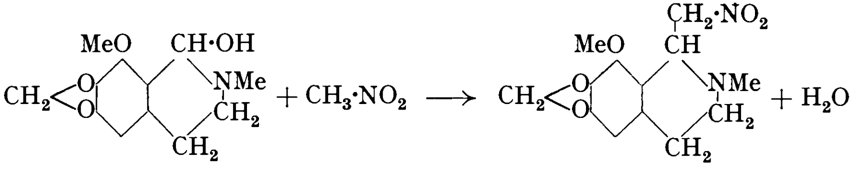
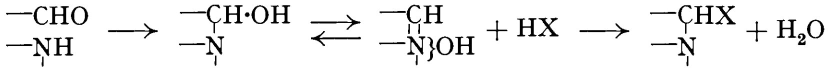
* The term " synthesis " in this lecture always connotes synthesis of natural products. It is not used generally to include, for example, synthesis of dyes, drugs, etc.

In this matter we were following Liebermann's lead, but some of the new condensations that were encountered proceeded with striking ease and it was natural to speculate on the mechanism of the processes involved as well as on the possible rôle of analogous reactions in Nature. An example is the formation of anhydrocotarninenitromethane, which goes to completion in a few seconds in cold alcoholic solution; the reaction may also be conducted in aqueous solution.



Other substances with which cotarnine readily condenses are hydrogen cyanide, alcohol, mercaptan, acetone, acetophenone, ethyl malonate, phenylacetonitrile, 2 : 4-dinitrotoluene, indene, fluorene, isatin, and many others.

Professor A. Lapworth saw in these rapid condensations a clue to the mechanism of the Knoevenagel reaction (catalysis by secondary bases), and he recognised the cation of the unsaturated ammonium hydroxide form as the reactive condition of the system :



$$\begin{matrix}\text{—CHO}\\ \text{—NH}\end{matrix} \longrightarrow \begin{matrix}\text{—CH·OH}\\ \text{—N}\end{matrix} \rightleftarrows \begin{matrix}\text{—CH}\\ \text{—N\}OH}\end{matrix} + \text{HX} \longrightarrow \begin{matrix}\text{—CHX}\\ \text{—N}\end{matrix} + H_2O$$

Carbinol-amine. *Unsaturated ammonium hydroxide.* *Condensation product.*

In the Knoevenagel reaction there is a further stage in which the secondary amine is regenerated, but in the cotarnine condensations the ring structure has a stabilising influence and this elimination does not supervene.

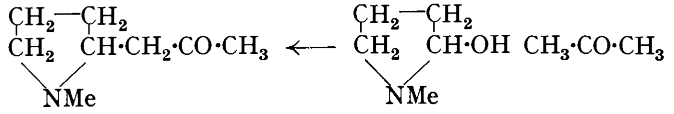
The next step was the attempt to find further analogies for the cotarnine condensations in the behaviour of much simpler pseudo-bases; I say further analogies because the formation of the nitrile of an α-amino-acid from an aldehyde and ammonium cyanide is obviously similar to that of cyanohydrocotarnine from a cotarninium salt and a cyanide.

Thus cotarnine reacts with alcohols and mercaptans, and McLeod and (Mrs.) G. M. Robinson[3] were able to show that a mixture of a secondary base and formaldehyde, which doubtless contains the carbinol-amine, $NR_2·CH_2·OH$, likewise condenses with alcohols and mercaptans, affording the new acetal-like types $NR_2·CH_2·OR$ and $NR_2·CH_2·SR$.

Mannich has made further applications of the same fundamental idea in coupling substances containing the ketomethylene group with aldehydes (especially formaldehyde) and secondary bases;[4] for example,

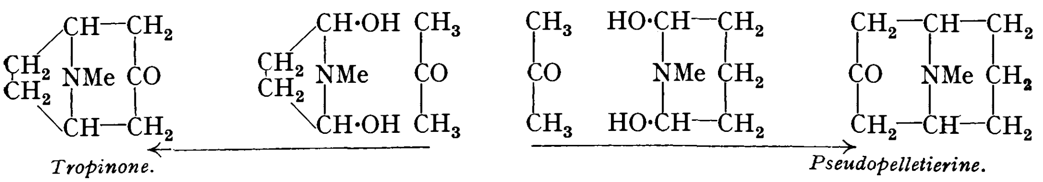
$$CH_3·CO·CH_3 + CH_2O + NHEt_2 \longrightarrow CH_3·CO·CH_2·CH_2·NEt_2$$

which is analogous to the formation of anhydrocotarnineacetone. The possible significance of the carbinol-amines in phytochemical processes was not overlooked and it was noted that the alkaloid hygrine could be dissected by imaginary hydrolysis reversing a presumed synthesis :[5]



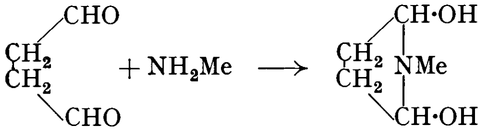
Hygrine.

Tropinone and pseudopelletierine were also recognised as of similar possible construction :

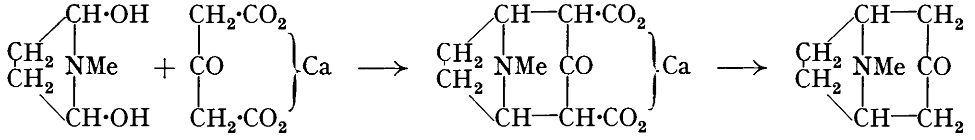


Tropinone. *Pseudopelletierine.*

It is only recently that it has been found possible to realise this type of synthesis in the case of hygrine,* but the validity of the tropinone and pseudopelletierine dissections was easily demonstrated. The carbinol-amines in these cases are evidently those derivable from methylamine, succindialdehyde, and glutardialdehyde respectively,

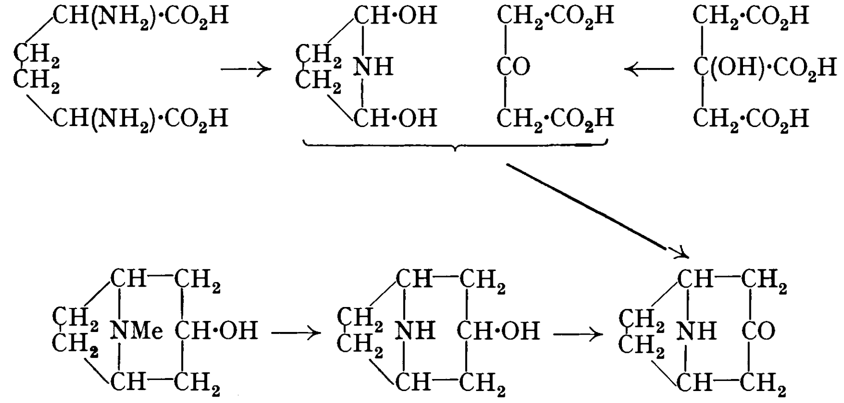


and it was found that tropinone could actually be obtained by condensation of succindialdehyde, methylamine, and acetone. The yield was very unsatisfactory, but could be greatly improved by the use of a reactive derivative of acetone, especially acetonedicarboxylic acid : [6]

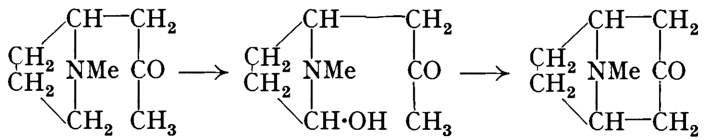


Pseudopelletierine, unlike tropinone, is a naturally occurring base and it was synthesised by substituting glutardialdehyde for the succindialdehyde in the above scheme.[7]

A still closer approach to a possible phytochemical synthesis was realised in the joint oxidation of the ammonium salts of Sörensen's $\alpha\alpha'$-diaminoadipic acid and citric acid by means of hydrogen peroxide in aqueous solution. The product was *nor*tropinone, which is accessible from tropine by successive oxidations with acid permanganate and chromic acid. The yield was small, but was a little better when ready-formed acetonedicarboxylic acid was employed. Ornithine could not be used instead of diaminoadipic acid, and experiments on the oxidation of hygrine to tropinone in the hope of realising the annexed scheme have been fruitless up to the present.



Tropine. nor*Tropine.* nor*Tropinone.*



Hygrine. *Hypothetical oxidation product.* *Tropinone.*

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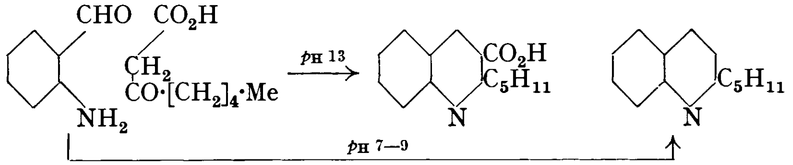
* It is hoped that an account of experiments on the products of oxidation of various mixtures of an amino-acid with a reactive derivative of acetone will shortly be submitted to the Society. A synthesis of *dl*-hygrine on these lines has proved feasible.

It is not very venturesome to predict that such transformations as that of hygrine to tropinone will eventually be realised, but in spite of the attractive nature of the hypotheses connecting ornithine with tropinone and lysine with pseudopelletierine, the assumption of biogenesis from the diaminoadipic and diaminopimelic acids is certainly in better accord with the experimental models. The constitutions of the alkaloids of *Lobelia*, worked out by Wieland and his co-workers, are of much significance in this connection because they afford clear indications of the occurrence of chains longer than that of hexane in the amino-acid section of the molecules.[8] It may be necessary to revise the view that lysine represents a modified hexose unit and to adopt the working hypothesis that it arises from two molecules of a triose and formaldehyde (or equivalents of these substances) as shown below :

$$CH_2(OH)\cdot CO\cdot CH_2\cdot OH + CH_2O + CH_2(OH)\cdot CO\cdot CH_2\cdot OH \longrightarrow$$
$$CH_2(OH)\cdot CO\cdot CH(OH)\cdot CH_2\cdot CH(OH)\cdot CO\cdot CH_2\cdot OH \longrightarrow$$
$$CO_2H\cdot CH(NH_2)\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot CO_2H \longrightarrow$$
$$CH_2(NH_2)\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot CO_2H$$

In the case of diaminoadipic acid and ornithine the two molecules of the triose would be coupled by oxidation instead of by condensation with formaldehyde, or alternatively a hexose might be oxidised and transformed. It must again be emphasised that all such schemes are regarded as too simple in the detail and that they are only advanced in broad outline.

Striking advances in this field are due to Professor C. Schöpf of Darmstadt, who has studied the effect of varying the p_H of the solution on the nature of the products and the yields in aldol condensations, Friedländer quinoline syntheses, the tropinone synthesis, and related carbinol-amine condensations. Schöpf and Lehmann found that 2-*n*-amylquinoline, which is one of the minor alkaloids of angostura bark, could be directly obtained in 70—75% yield by the condensation of *o*-aminobenzaldehyde with *n*-hexoylacetic acid at p_H 7—9. This decarboxylation is remarkable and does not occur at p_H 13.[9]



It may be noted that *n*-hexoylacetic acid is the β-oxidation product of *n*-octoic acid and that the ketone obtained on decarboxylation, namely, methyl *n*-amyl ketone, has been recognised as a constituent of certain essential oils. The tropinone and pseudopelletierine syntheses also proceed directly at the appropriate p_H, and the tables show the yields of these bases obtained as the result of spontaneous decarboxylation. A citrate buffer was employed.[10]

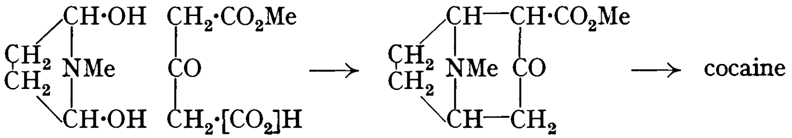
M/40-Succindialdehyde, *M*/25-methylamine, *M*/25 (at p_H 5, *M*/12)-acetonedicarboxylic acid, *M*/10-buffer; 3 days; 20°.

p_H	3	5	7	9	13
Yield of tropinone, %	38	90	73	70	3

M/80-Glutardialdehyde, *M*/40-methylamine, *M*/40-acetonedicarboxylic acid, *M*/30 buffer; 8 days; 25°.

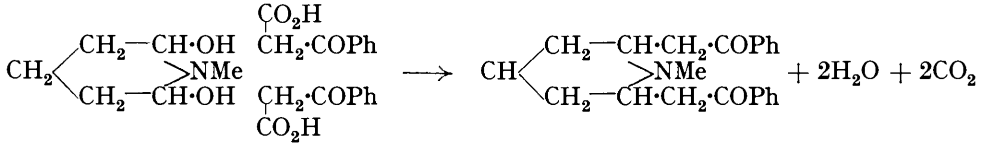
p_H	3	5	7	9	11	13
Yield of pseudopelletierine, %	65	74	76	40	37	54

It is significant that the optimum p_H is a little on the acid side of neutrality, a condition satisfied by the cell sap of most plants. A further point is that the cocaine group of bases probably arises from a protected acetonedicarboxylic acid and most plausibly from methyl hydrogen acetonedicarboxylate in view of the carbomethoxy-group occurring in the alkaloids.



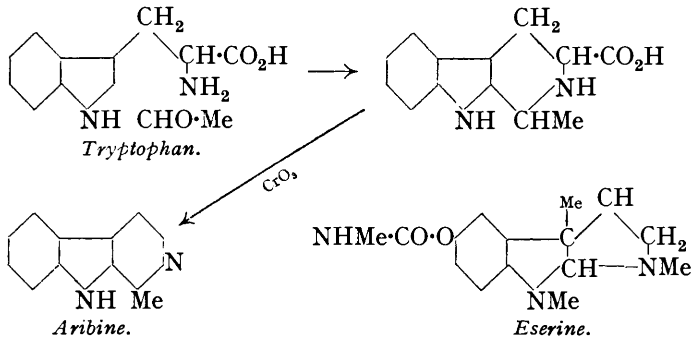
In the pseudopelletierine synthesis at p_H 7 it was possible to raise the yield to 95% of that theoretically possible by working in more concentrated solutions ($M/12$ of dialdehyde).

A further very interesting development was the synthesis of lobelanine from glutardialdehyde, methylamine, and benzoylacetic acid at p_H 4. The yield was 55%, but was only 1% at p_H 2 and no product was obtained at p_H 9.



The base isolated was the naturally occurring *cis*-isomeride.

Another alkaloid which has been synthesised by a method probably analogous with the natural process is aribine (harman), but this statement only applies to the later stages because we use ready-made tryptophan, which can be artificially prepared but only in the old brutal way. And here it must be said that one of the most serious gaps in our knowledge of biosynthesis is in connection with the aromatic nuclei. It is easy to imagine schemes for the condensation of hexose units to benzene rings, but the transformations have only been carried out in the laboratory in isolated instances. The most successful and significant practical efforts in this direction are still represented by the pioneering work of J. N. Collie on the so-called polyketens, and their conversion into a variety of aromatic substances.[11] Reverting to aribine, this base was obtained by the oxidation of the condensation product of acetaldehyde and tryptophan.[12] The intermediate has recently been isolated by Jacobs and Craig.[13] Here again a closer approach to natural conditions can be made and aribine was obtained by the oxidation of a mixture of tryptophan and alanine.

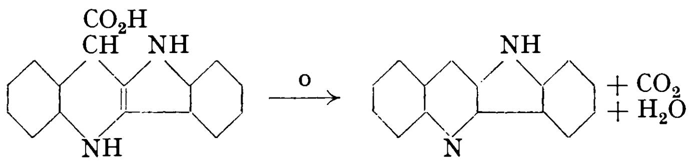

Tryptophan.

Aribine.

Eserine.

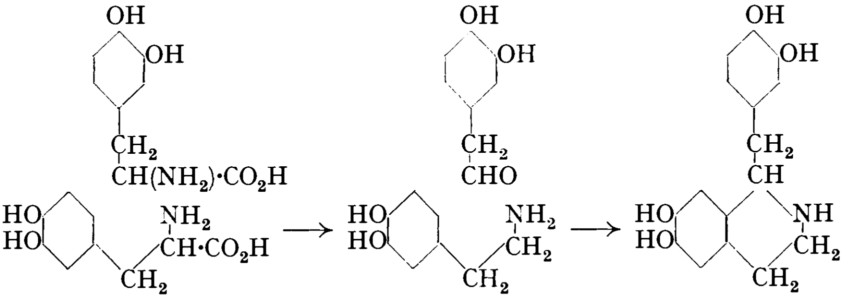
(The constitution of eserine is figured above in order to illustrate its relation to tryptophan. Evidently the NH·C:C of the indole-amino-acid can be *C*-methylated in Nature and the process resembles that responsible for the introduction of the characteristic methyl group of corydaline. Doubtless the latter group owes its presence to *C*-alkylation of the system N·C:C in a base of dihydroberberine type. Both natural *C*-methylations can be closely paralleled in the laboratory, but we cannot identify the natural reagent, although it is possibly formaldehyde and a reducing substance.)

The loss of the carboxyl group in the above processes is in accord with analogy. Thus dihydroflavindine affords quindoline when its alkaline solution is shaken with air :

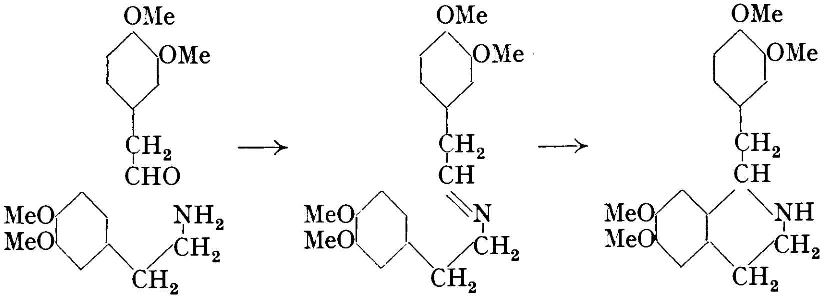


Dihydroflavindine. *Quindoline.*

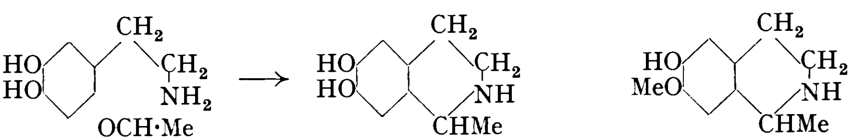
Very similar in principle are the attempts that have been made to provide experimental models for Winterstein's view of the biosynthesis of the *iso*quinoline alkaloids which is represented below.



Späth and Berger [14] realised the following scheme :

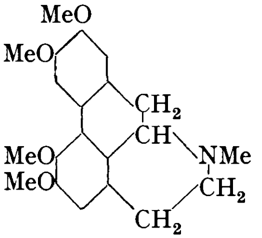


They worked, however, in strongly acid solution and heated the mixtures on the steam-bath; hence interest attaches to similar experiments of Hahn and Schales,[15] who used the methylenedioxy-analogues in dilute aqueous solution at 25° and p_H 5. They isolated the bis(methylenedioxy)benzyltetrahydro*iso*quinoline in 5% yield. High yields (up to 83%) are claimed by Schöpf and Bayerle in the synthesis of *nor*salsoline (*nor*carnegine) at 25° in dilute aqueous solution at p_H 5.[16]

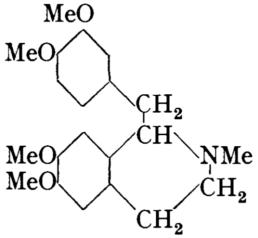


nor*Salsoline.* *Salsoline.*

It must be admitted that the main lines of these biosyntheses have been correctly identified, but many difficult problems remain. Thus inspection of the constitution of glaucine and its analogues of the aromatic phenanthrene sub-group of the *iso*quinoline alkaloids certainly suggests a simple dehydrogenation of the laudanosine type.

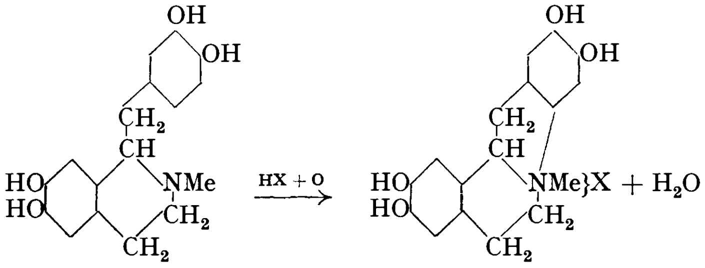


Glaucine.



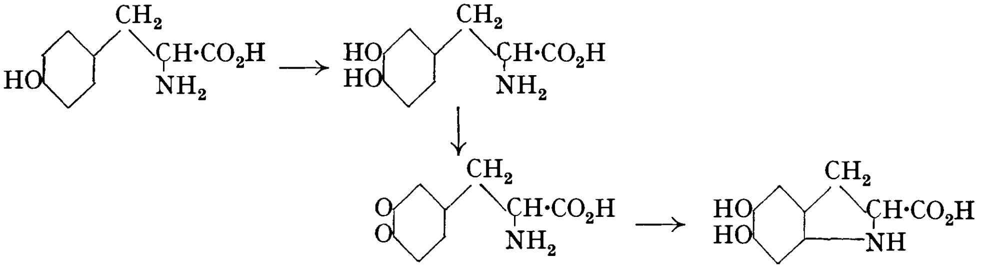
Laudanosine.

This will surely be realised in due course, but in the meantime we have found that laudanosoline (the tetrahydric phenol corresponding to laudanosine) is oxidised by chloranil in the presence of an acid in an entirely different manner.[17]



A little later Schöpf and Thierfelder published their independent work on the same subject; they used tetrabromo-*o*-benzoquinone as the oxidising agent, alternatively platinum as dehydrogenating agent, and attributed the same constitution to the product.[18]

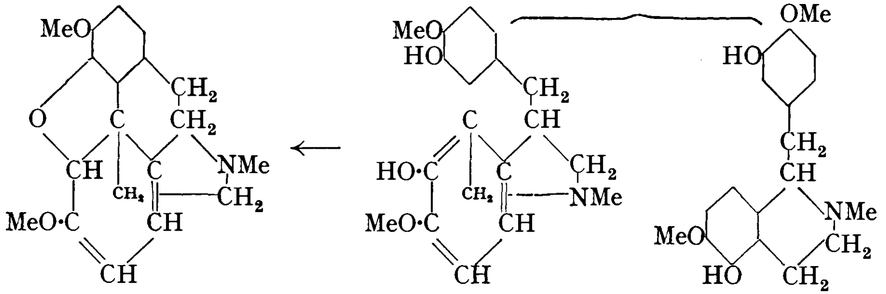
These results recalled the work of Raper on the oxidation of tyrosine and dihydroxyphenylalanine in the presence of tyrosinase in which a similar formation of an indole nucleus was observed: [19]



We need not be too much discouraged by our failure to find the appropriate specific oxidising agent, and it would be premature to abandon the search for it.

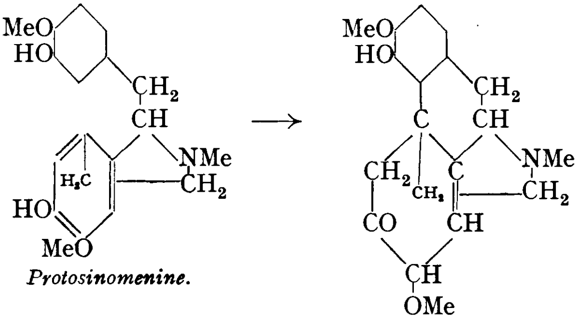
Not wholly unexpected lack of success has also attended attempts to copy what we conceive to be Nature's way of constructing the morphine–thebaine ring system. Inspection of the thebaine molecule leads to the conviction that it must be derived from a base of laudanosine type by dehydration, and a coupling of the two aromatic nuclei analogous to polymerisation of unsaturated substances. A certain doubt is engendered, however, by the circumstance that the orientation of the substituents in the laudanosine-type base is unusual, and in view of the prevalence of molecular rearrangements in this region of chemistry we elected to test a case in which the substituents are normally situated.

This is provided by the alkaloid sinomenine, a knowledge of the constitution of which we owe to Kondo and Ochiai and to Goto.[20] The so-called protosinomenine was



Thebaine. *Laudanosine-type base.*

synthesised [21] and experiments on its possible conversion into sinomenine are still in progress.



Protosinomenine. *Sinomenine.*

This unfinished work is mentioned in illustration of the conviction that the most difficult synthetical problems can be solved only after an attentive study of the probable way in which the different parts of the molecule have been fitted together.

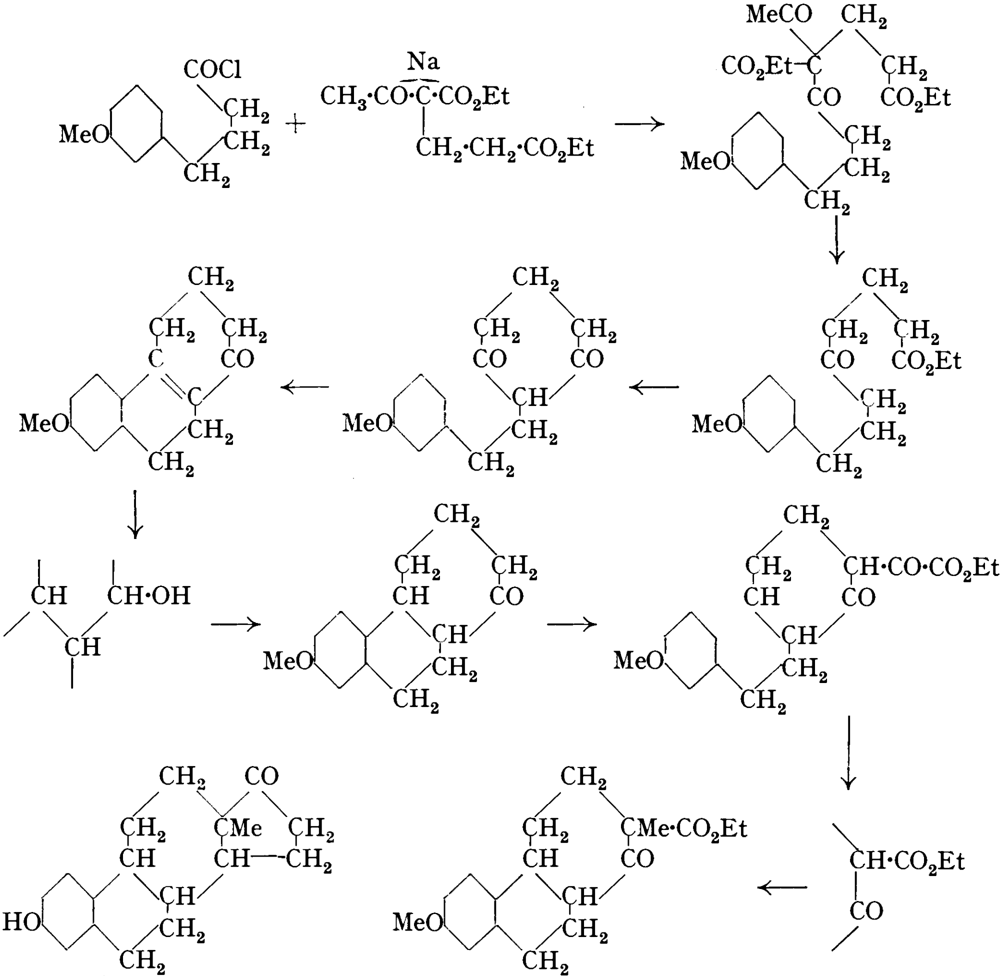
This brief sketch of the attempts which have been made to follow Nature's methods in the alkaloid field must end here, but not without acknowledgment of the parallel investigations in other branches of the chemistry of natural products. Especially interesting are the experiments on the polymerisation (and hydration) of isoprene from Tilden to Ruzicka and Wagner-Jauregg, and on the condensations of unsaturated aldehydes such as crotonaldehyde to normal chains from Smedley-Maclean to Kuhn and F. G. Fischer.

We have travelled far since 1828, and the interest formerly attached to " total synthesis " has disappeared. The point of a total synthesis is no longer the demonstration that the natural product can be artificially prepared; it is confined to the proof afforded of a molecular structure. The recent brilliant researches of Ruzicka [22] and of Butenandt [23] on the transformations of the sterols into hormones and on the modifications of the sex hormones themselves are outstanding examples of the value of part syntheses starting with substances of known constitution, although not yet artificially prepared.

Apart from the confirmation of molecular structure, the synthesis of natural products has other valuable functions in biochemistry. It is useful, for example, in confirming physiological activity, because the observed properties, say, of a specimen thought to be a pure hormone or vitamin *may* be due to traces of intensely active impurities. From this point of view a synthesis of linoleic acid is desirable. Again, syntheses such as those of the anthocyanins give possession of standards which can be used in the examination of further plant material. Another example is afforded by the long-chain aliphatic substances, because in this instance pure synthetic specimens are absolutely necessary in order to standardise cryoscopic behaviour and the spacings of crystal lattices as determined by *X*-ray diffraction. Chibnall's recent studies of the constituents of waxes represent the most complete survey that has been made on this basis.[24] But no attempt can be made even to summarise all the manifold applications of synthesis in biochemistry, and I will turn to a problem very much in the minds of many of us at this moment, namely, the contribution that synthesis may make to our knowledge of the sterols and sex hormones.

One might regard this as the present-day task of the organic chemist of the classical tradition; it lies well within his scope and, taking into consideration the ever-increasing realisation of the physiological importance of the group, it may be thought a worthy object of investigation in spite of the undoubted fact that it must take time and absorb energy that can ill be spared. It is hardly open to question that the classical organic chemist with his battery of Grignard, Friedel–Crafts, and other non-biological reactions will ultimately overcome the obstacles presented by the two angle-methyls of the sterols and by their stereochemical relations and general complexity, and it is certain that the sterols and sex hormones will be synthesised if the present interest is maintained. Nevertheless, the game will only be worth the candle if it leads to an enrichment of our knowledge of organic chemistry itself, commensurate with the prodigious effort which will be required.

At the Dyson Perrins Laboratory we have adopted a dual policy. The relatively simple problem of the female sex hormone is being attacked by the usual methods and as the result of the work of E. Schlittler and J. Walker the following processes have been realised : [25]

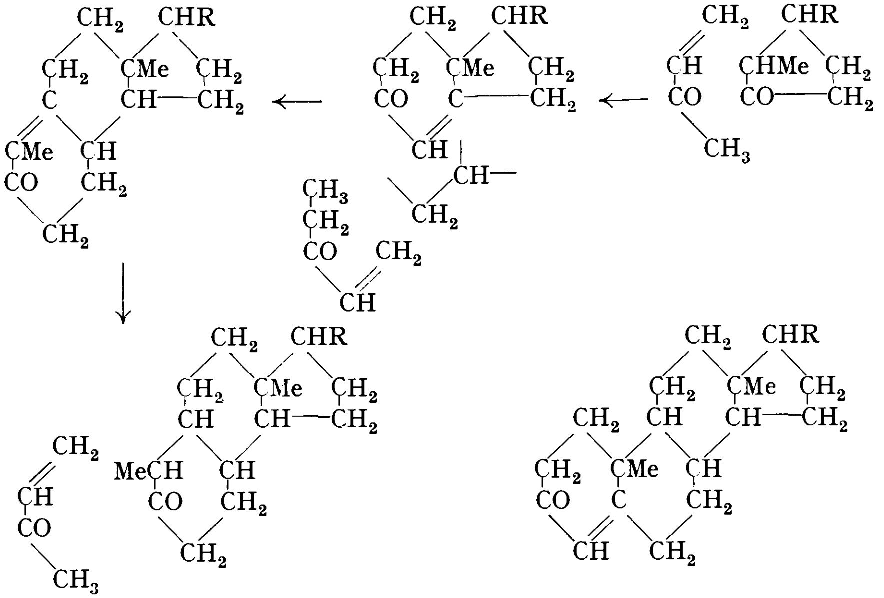


Oestrone.

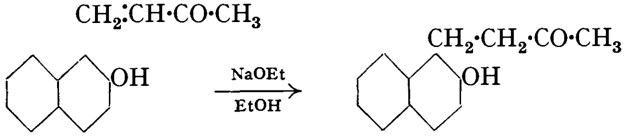
The rings appear to be fused in the *trans*-position, so that the completion of the synthesis depends on the isolation of the ester last-figured in the correct stereoisomeric form. After this the building on of the *cyclo*pentane ring will involve a final stereochemical forking of the roads.

The syntheses of the systems of the sterols and of the male sex hormones are being attempted from a somewhat different standpoint. As in the alkaloid group, we have tried to find some common factors in the sterol molecule with the object of following up the suspected plan of organisation in our synthetical operations. At first we thought only of the *iso*pentane units, but plausible as this hypothesis of the origin of the sterols is, one must perform some very arbitrary loppings of methyl groups in order to make it feasible.[*] Furthermore, the side chains of ergosterol and stigmasterol neutralise the effect on our minds of the very terpenoid cholesterol side chain.

An alternative mechanism which we noted more than two years ago has not been developed as a full biosynthesis, because it cannot be used for the construction of a *cyclo*pentane nucleus, but, given this unit, it presents a remarkable coincidence and represents our working hypothesis for synthetical experiments in the sterol group. Starting with a methyl*cyclo*pentanone derivative, we propose a series of *cyclo*hexenone syntheses with reduction of the intermediates. The unsaturated ketones applied are successively methyl vinyl ketone, ethyl vinyl ketone, and methyl vinyl ketone, and the product ought to contain the sterol system complete with angle-methyl groups, because (a) the group $\cdot CHMe\cdot CO\cdot$ should be attached in preference to $\cdot CH_2\cdot CO\cdot$ (compare the αα-dialkylation of cyclic ketones), and (b) β-decalones should be reactive in the α- rather than in the β′-position. This scheme, a *paper* synthesis indeed, is illustrated below :



The group R might be the cholesterol side chain or carbethoxyl, in which case it could be replaced by amino and then hydroxyl, giving testosterone. In an attempt to realise this scheme the first problem was to find conditions for the *cyclo*hexenone synthesis. Methyl vinyl ketone could be condensed with β-naphthol in alkaline solution,[26]



but the reaction could not be extended to *cyclo*hexanone.

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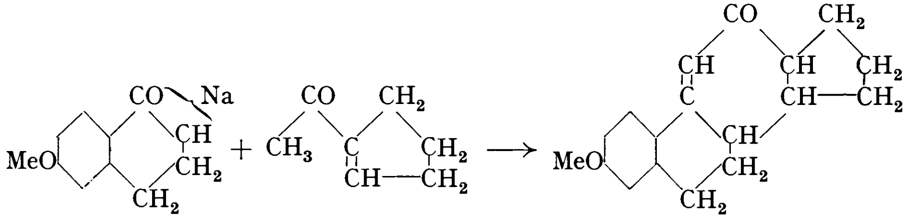
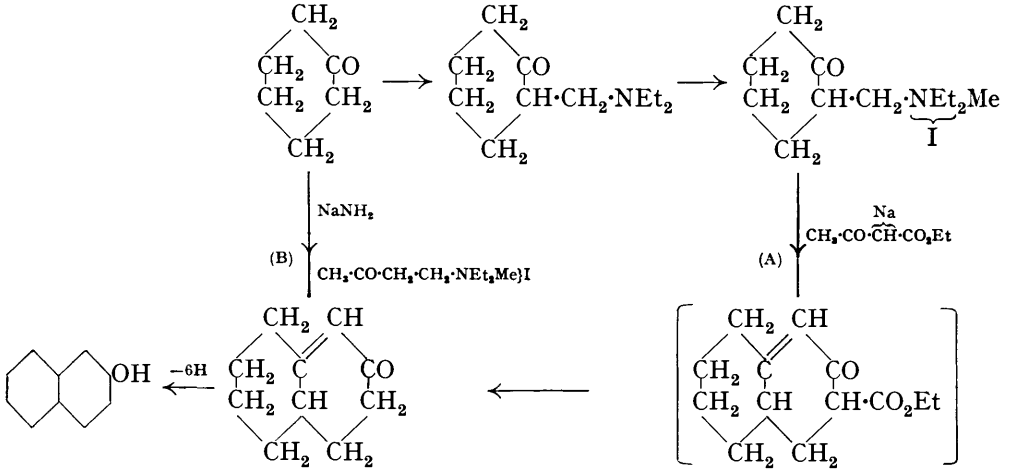
[*] Nevertheless the statement of Lettre and Inhoffen (" Über Sterine Gallensäuren und verwandte Naturstoffe," F. Enke, Stuttgart, 1936) that the isoprene hypothesis cannot be used in connection with the four-ring skeleton is incorrect if the extrusion of three carbon atoms from the molecule is permissible.

We were encouraged to proceed, however, by the discovery of the condensation of acetyl*cyclo*hexene and acetyl*cyclo*pentene with the sodio-derivatives of cyclic ketones and by the favourable yields often obtained in these reactions. The products are hydrochrysene or hydro*cyclo*pentanophenanthrene derivatives and may be constitutionally allied to the sex hormones.[27]

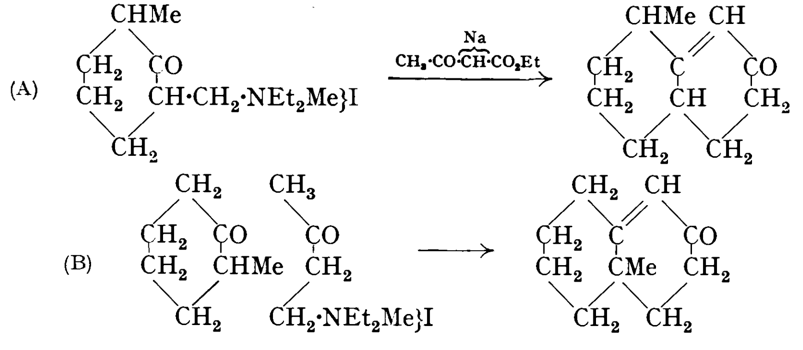


Nevertheless, our trials with methyl vinyl ketone and methyl *iso*propenyl ketone were all but fruitless; the yields were hopelessly low as the result of polymerisation. We therefore turned our attention to the use of substances which can yield the simple unsaturated ketones on decomposition. Dr. J. Walker had successfully employed methyl β-chloroethyl ketone for the synthesis of piperitone,[28] but we found that it loses the elements of hydrogen chloride too easily and the resulting methyl vinyl ketone is polymerised in the attempted condensation with the sodio-derivatives of cyclic ketones.

The problem appears to have been solved by the use of quaternary ammonium salts derived from the Mannich bases already mentioned, and these compounds have been applied in two distinct ways illustrated in the scheme below : [29]



When routes (A) and (B) are applied to 2-methyl*cyclo*hexanone, different methyloctalones are obtained. The isomeride from route (A) can be dehydrogenated to a methyl-



β-naphthol, whereas that from route (B) resists dehydrogenation by means of palladised charcoal but affords β-naphthol in poor yield when it is heated with selenium. Hence we consider that a model for the last stage of the *paper* sterol synthesis has been realised and one of our two assumptions (a; *v. supra*) appears to have been justified.

Turning from our present preoccupations, it may be useful to attempt to define some of the main problems awaiting solution in the near future. Much more must be done in the direction of probing and imitating Nature's methods of manufacture of the simple molecules, and even the sterols, heart poisons, morphine, and strychnine must be included in this category, but so far as we can see now the chemists of the future must concentrate on the study of polymerisation. The work of Staudinger, Carothers, and others has laid a sound foundation, but the type of polymerisation hitherto studied is very different from that occurring in a plant. There the units, which themselves await identification, are evidently marshalled under the direction of surface forces and probably of templates consisting of ready-formed polymerides.

We already know that diketopiperazines can be used to extend the peptide chains, and cycloids with a larger number of amino-acid residues than two should be still more prone to form long polypeptide chains. Plans have been made to undertake this investigation in Oxford, and I am glad to have this opportunity of acknowledging the stimulus provided by Dr. D. M. Wrinch, who has elaborated an elegant scheme of protein pattern based on a cycloid containing six amino-acid residues in the simplest case.[30]

The structure and orientation of natural products of high molecular weight can only be ascertained as the result of the labours of both analytical-organic and physical chemists, but it is safe to predict that in this field the synthetical chemist also will play his part, and that, as in other branches of structural chemistry, the final decisions will be made by him.

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[20] Numerous papers from 1923. Cf. H. Kondo and E. Ochiai, *Annalen*, 1929, **470**, 224. [21] R. Robinson and S. Sugasawa, J., 1933, 280. [22] Cf. L. Ruzicka, *Naturwiss.*, 1935, **23**, 44, and many papers in 1935, 1936. [23] A. Butenandt and H. Dannenberg, *Ber.*, 1936, **69**, 1158; A. Butenandt and B. Riegel, *ibid.*, p. 1163, and many other papers. [24] *E.g.*, A. C. Chibnall, S. H. Piper, A. Pollard, E. F. Williams, and P. N. Sahai, *Biochem. J.*, 1934, **28**, 2189. [25] J., 1935, 1288; this vol., p. 192. [26] S. A. Miller and R. Robinson, J., 1934, 1535. [27] W. S. Rapson and R. Robinson, J., 1935, 1285; D. A. Peak and R. Robinson, this vol., p. 759. [28] J., 1935, 1585. [29] With E. C. du Feu and F. J. McQuillin; an account will shortly be submitted to the Society. [30] *Nature*, 1936, **137**, 411.