The iso*Quinoline Alkaloids.*

CENTENARY LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT THE UNIVERSITY, EDINBURGH, ON TUESDAY, APRIL 27TH, 1954, AND AT BURLINGTON HOUSE ON THURSDAY, MAY 6TH, 1954.

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I DO not propose to give a chronological account of the chemistry of *iso*Quinoline Alkaloids but I cannot refrain from noting two dates. The first is 1817 when Robiquet isolated narcotine from opium, and this is, for good reasons, the birth of alkaloid chemistry. The second landmark was 1885 when Hoogewerf and van Dorp isolated *iso*quinoline from coal-tar distillates. In terms of progress in the sciences as of to-day this interval of sixty-eight years between the above two events is indeed a long one, particularly since no real progress could be made in the elucidation of the structure of an *iso*quinoline alkaloid until the structure of the *iso*quinoline nucleus was clear We, who sometimes determine the structure of an alkaloid in a single day, should pause before we bask in complacency. If we had to determine not only the positions of the methoxyl groups in hemipinic acid but also the relative positions of the carboxyl groups our progress would indeed be much slower, and if in addition to these formidable difficulties we were not very certain of atomic weights we should probably leave the structure of a new alkaloid to the mercies of posterity.

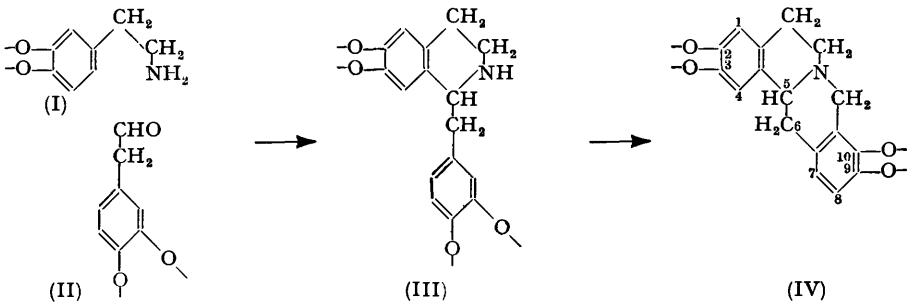
I have made these observations to show you that I am not unmindful of the skill of our predecessors and if I should appear to give short notice to a great work I do so only because I must make haste and may not tarry too long in any one paradise.

The *iso*quinoline nucleus can be conceived as the nucleus formed by the fusion of a benzene and a pyridine nucleus although there are no chemical reactions which can accomplish such a union with the necessary loss of two carbon atoms. In Nature the nucleus is invariably substituted and in all examples save papaverine the hetero-ring is in the tetrahydro-form. The oxygen-substituents and the four hydrogen atoms furnish a clue to the biogenetic origin of the compounds, and indeed there is a strong hint that the building blocks used by the plant and by the chemist are at least formally similar. Without the *O*-substituents the benzene nucleus lacks activated positions and ring closure becomes practicallly impossible *in vitro* and presumably also *in vivo*. Consequently the benzene portion of the *iso*quinoline of natural origin carries an *O*-substituent in the position *para* to that of ring closure and generally one and sometimes two more oxygen atoms. By extrapolating backward it is possible to recognize dihydroxyphenylalanine or its decarboxylated derivative as one of the main precursors of *iso*quinolines. This important compound has long been known as a product of plant anabolism, and ample evidence is now available that at least the animal cell can prepare tyrosine from phenylalanine by hydroxylation.[1] The added oxygen always enters *ortho* to the one already present and it is therefore not surprising that the lignins have the oxygens in the 3 : 4- (or vanillin) and in the 3 : 4 : 5-positions. There is here a suggestion that the alkaloids and the lignins have common ancestors and that tyrosine or a near relative is that ancestor. There is a sufficiency of examples of the co-presence of alkoxyarylethylamines and the corresponding alkoxy*iso*quinolines in the same plant to lend conviction to the hypothesis that the latter are derived from the former.

The exact mechanism by which this synthesis takes place is open to speculation. Certainly the plant cell does not cause an aroyl halide to react with the amine in the presence of strong alkali and then treat the resultant amide with phosphoric oxide in boiling toluene. Nor does it then treat the resultant base with methyl iodide and reduce the product with zinc dust in glacial acetic acid. The early suggestion by Robert Robinson and the later work of Schöpf [2] and of Hahn [3,4,5] and their associates have shown that the dihydroxyamino-compounds react with aldehydes, under conditions of pH and temperature probable in a plant, to give *iso*quinolines in excellent yields. That enzymes also play a rôle, though not necessarily an

[1] A. R. Moss and R. Schoenheimer, *J. Biol. Chem.*, 1940, **135**, 415.
[2] C. Schöpf and H. Bayerle, *Annalen*, 1934, **513**, 190.
[3] G. Hahn and H. Wassmuth, *Ber.*, 1934, **67**, 696.
[4] G. Hahn and O. Schales, *Ber.*, 1935, **68**, 24.
[5] G. Hahn and F. Rumpf, *Ber.*, 1938, **71**, 2141.

important one, is shown by the almost universal optical activity of the *iso*quinolines when an asymmetric carbon is present. The subsequent alkylation of oxygen and nitrogen offers no problem and is common to many vital processes. It is therefore possible to state with reasonable certainty that plants elaborate 1-substituted *iso*quinolines by condensing 2-dialkoxyarylethylamines (I) or their progenitors with dialkoxyarylacetaldehydes (II) or their progenitors. The ease with which small carbon moieties are bandied about by the living cell does not at present enable us to distinguish between an amino-acid or a pyruvic acid and their decarboxylated derivatives, namely, the corresponding amine or aldehyde respectively. Indeed, if we give credence to the full possible resources of living cells we may find it difficult to distinguish between an amine or its possible progenitors, namely, an aldehyde, ammonia, and a reducing agent.

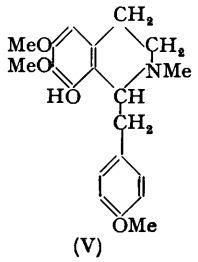


That 1-benzyl*iso*quinolines (III) are not ends in themselves and the ultimate product of plant metabolism is not only to be expected *a priori* but is observed in fact. These compounds are genuine 2-arylethylamines and as such should be susceptible to further condensation with aldehydes. There can be little doubt that the biosynthesis of the protoberberines (IV) proceeds *via* the benzyl*iso*quinolines, but the necessary reagent to bring about this condensation has eluded us. That it is not formaldehyde is fairly certain because formaldehyde has never been found in plant cells. There is however another reason why formaldehyde is not the reagent and this is an indirect one. The 1-alkyl*iso*quinolines have either no substituent or a methyl group, so that if formaldehyde were the reagent in one instance it would be expected that acetaldehyde would be the reagent in the second. Alkaloids of type (IV) however have never been found with a methyl group in the new position so that the reagent which brings about the formation of (IV) seems to be one which does not have a naturally occurring homologue, and glyoxylic acid may be such a substance. It has the further merit that it is known to be present in plants. Some interesting problems however emerge at this point. The ring closure to (III) takes place at a position *para* to the hydroxyl group with one exception (where it takes place *ortho* to a hydroxyl group) [6] whereas the ring closure from (III) to (IV) takes place *ortho* to a hydroxyl group with one exception (where it takes place *para*). It seems either that the reagents concerned in the two ring closures are different, or that the mechanisms are different. The second of the exceptions noted above is the alkaloid coreximine in which the *O*-substituents are in the 8 : 9-positions—positions which are assumed when (III) is digested *in vitro* with formaldehyde and hydrochloric acid! There is a benzyl*iso*quinoline (V) which, quite by accident, has given strong positive evidence that benzyl*iso*quinolines are indeed intermediates in the synthesis of protoberberines although the evidence itself is of a negative kind. This benzyl-*iso*quinoline is the only one found in the entire subfamily Fumarioideæ, and it occurs in a plant, *Corydalis aurea*, Willd.,[8] notable for the abundance of protoberberines. Since, however, the possible position of ring closure is neither *ortho* nor *para* to an alkoxyl group, ring closure cannot take place and therefore the alkaloid survives as such.

It should not be assumed however that protoberberines are the final anabolic products of alkaloid biogenesis in spite of their abundance. They afford a number of positions of attack, particularly by oxidizing agents, and these oxidation products can be very interesting. If for instance the hydrogen at position 5 is replaced by a hydroxyl group there results a carbinolamine which, if methylated in ketonic form, gives rise to the protopine type of base (VI). An

[6] A. Pictet and T. Q. Chou, *Ber.*, 1916, **49**, 370.
[7] R. H. F. Manske and W. R. Ashford, *J. Amer. Chem. Soc.*, 1951, **73**, 5144.
[8] R. H. F. Manske, *ibid.*, 1952, **74**, 2864.

alternative, and more pleasing, hypothesis for the formation of (VI) is a preliminary hydroxylation at position 6. This is the position of the hydroxyl group in ophiocarpine [9] as well as in the phthalide*iso*quinolines (VIII), and when such a compound is hydrated and *N*-methylated it gives rise to (VII) which need only lose water to yield (VI). Furthermore, there are two possible ways in which it may be dehydrated, resulting in compounds in which the carbonyl is either at position 5 or at position 6. In the latter case the alkaloid could be cryptocavine and the presence of the two types of ketonic alkaloids in the same plant can scarcely be fortuitous.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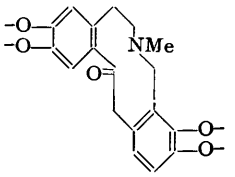
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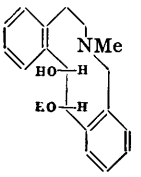
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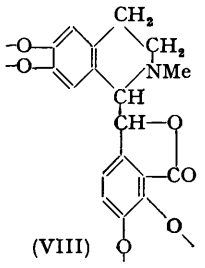
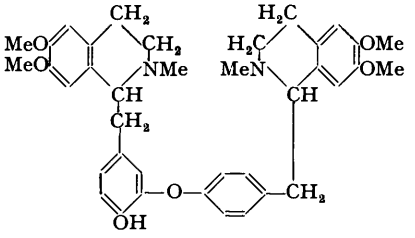

(VIII)

The further oxidation of a 6-hydroxylated protoberberine at position 11, to yield a carboxyl group, and the subsequent methylation of the NH group are sufficient to account for the genesis of the phthalide*iso*quinolines (VIII). It is evident that there are a number of pathways down which the protoberberines may be led and that the nature of the ultimate products is determined by the genetic nature of the plant. The presence of a methyl group at position 6 in a number of protoberberines and protopine-type alkaloids is explicable with some assurance if it is borne in mind that the methyl group in arylacetic acids is potentially already present in tropic and atropic acid, and its introduction in the molecule of (II) before its further assimilation is therefore not without analogy.

While the saga of the protoberberines is not yet exhausted we can return to the benzyl*iso*quinolines. The simplest of their possible transformations, though leading to the most complicated products, is the oxidative coupling of two molecules to yield the so-called biscoclaurine alkaloids, the simplest of which is dauricine. Since the benzyl group has no activated position *ortho* or *para* to a hydroxyl group at which to form a unimolecular condensation product, two molecules must combine if coclaurine is to be changed at all. Plants which elaborate this type of alkaloid (mostly those of the Menispermaceae family) seem to have a one-track mechanism that must form diphenyl ethers at all costs. This process may be repeated until no less than three ether bridges are formed in the one molecule, but the method of forming these bridges is always the same, namely, removal of two hydrogen atoms, one from the phenolic hydroxyl and the other from a position activated by a hydroxyl group.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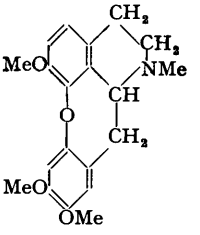
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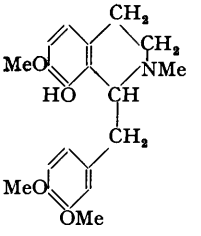
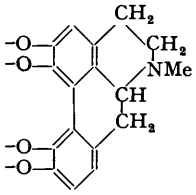

(XI)

A modification of this diphenyl ether formation is the alkaloid cularin (X).[10] This is unique in two respects—it is the only unimolecular diphenyl ether alkaloid and it is the only alkaloid in which the original *iso*quinoline ring closure proceeded *ortho* to an *O*-substituent. There can be no reasonable doubt that the precursor of cularine is the unknown benzyl*iso*quinoline (XI). The spatial arrangements of the atoms in the seven-membered hetero-ring are such that there is very little strain.

Benzyl*iso*quinolines may undergo still another transformation and this is perhaps the

[9] *Idem, Canad. J. Res.*, 1939, **17**, *B*, 51.
[10] *Idem, J. Amer. Chem. Soc.*, 1950, **72**, 55.

simplest of all. If two hydrogen atoms are removed, one from the 8-position and one from either the 2′- or the 6′-position, and the resulting radicals are coupled, two different aporphines (XII) and (XIII) may result. Until some twenty years ago only one type was found in any one plant, but there have been a number of recent examples in which one plant has elaborated both types. It is philosophically more satisfactory to assume one precursor for both types than to assume separate precursors for each.



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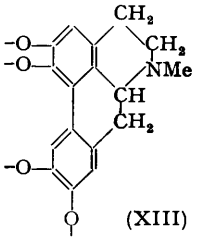
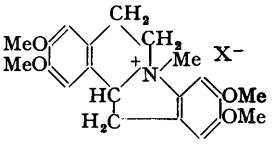


(XIII)

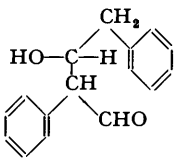


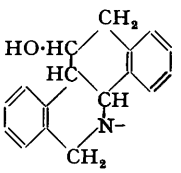
(XIV)

Another and somewhat unexpected dehydrogenation product of a benzyl*iso*quinoline was recently recognised in the alkaloid cryptaustoline (XIV) [11, 12] which was shown to be a partly methylated dehydrolaudanosoline. The oxidative ring closure has brought about quaternization of the nitrogen atom, presumably *via* some type of quinone. This oxidation of laudanosoline and the structure of the product had already been exhaustively studied by Robinson and Sugasawa [13]—tetrachlorobenzoquinone was the oxidizing agent.

To conclude, mention should be made of a group of *iso*quinoline alkaloids which are not derivable from benzyl*iso*quinoline, namely, the 1 : 2-benzophenanthridines. Nevertheless, their precursors are almost certainly identical at least in part with the precursors of the benzyl-*iso*quinolines with which they occur in the same plants. Let two molecules of an aryl-acetaldehyde condense to form the aldol (XV). This by reaction first with ammonia and then

(XV)





(XVI)

with formaldehyde would lead to a compound which by a double ring closure would give the sought-after alkaloids (XVI). The great merit of this scheme is that the hydroxyl group is in the correct place and that one of the possible intermediates is almost certainly analogous to the possible intermediate concerned in the formation of β-phenylnaphthalene from phenyl-acetaldehyde.

[11] J. Ewing, G. K. Hughes, E. Ritchie, and W. C. Taylor, *Nature*, 1952, **169**, 618.
[12] *Idem*, *Austral. J. Chem.*, 1953, **6**, 78.
[13] R. Robinson and S. Sugasawa, *J.*, 1932, 789.