SOME STUDIES IN THE BIOGENESIS OF PLANT PRODUCTS

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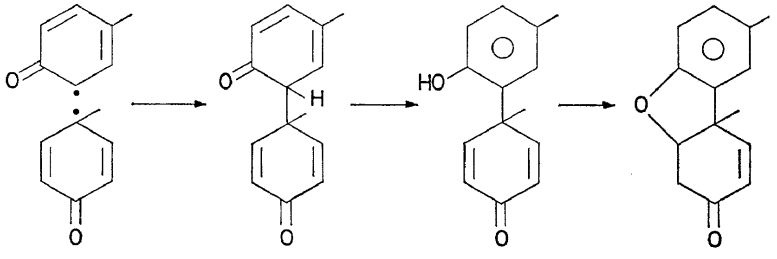
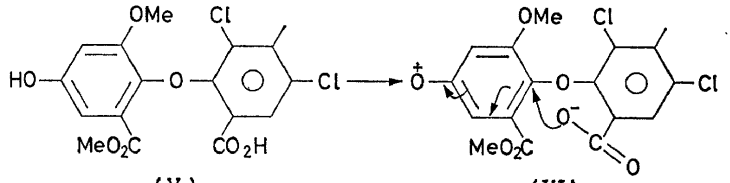
The concept that certain natural products are constructed by Nature through the coupling of phenolate radicals has been discussed on many occasions. We may cite, for illustration, the work of Erdtman which dates from 1933[1] and which has been summarized together with relevant comment[2]. Our own interest in the coupling of phenolate radicals was first aroused by the need for revision of the structure proposed for "Pummerer's ketone", the crystalline oxidation product of *p*-cresol. We showed[3] that "Pummerer's ketone" is correctly formulated as (IV) being derived from the union of two *p*-cresolate radicals (I) to give the intermediate (III) which by intramolecular tautomerism (β-addition of phenolate anion) affords the stable ketone (IV). In this scheme we note that, for clarity of expression, two different canonical forms of the *p*-cresolate radical are written, although the radical really has the odd electron spread over oxygen as well as over the two *ortho* carbon atoms and the *para* carbon atom. There must also be a further intermediate (II) in the scheme. Since this is a "ketonic" tautomer of a phenol we may readily accept its essentially instantaneous tautomerism to (III). In the sequel we shall assume that such tautomerisms occur with equal rapidity and that, therefore, it is not necessary to write in for every case the analogues of (II). The revised constitution (IV) for "Pummerer's ketone" provided a model for the biogenesis of several important natural products. It also provided the inspiration for a particularly simple synthesis of usnic acid[3]. In the present context we need, however, only consider the implication of formula (IV) as a model for the biogenesis of certain alkaloids. The treatment given in the sequel was initiated in a general survey of the significance of phenolate radical coupling in the biogenesis of alkaloids[4]. For the sake of brevity we shall consider here only two groups of alkaloids.

Of course, the mere fact that a biogenetic scheme based on the coupling of phenolate radicals can be written for an alkaloid, and even the demonstration that the "theoretical" phenolic precursors are actually involved in the biosynthesis, is not a proof that the coupling of phenolate radicals is really involved in Nature. Phenolate radicals certainly exist[5] and dimerize when the radical concentration is sufficiently high[6, 7]. In Nature, however, the same bonds can be formed, in principle, by radical coupling or by the union of phenolate anions with phenoxonium ions. At least one case[8], which could be regarded as intramolecular coupling of phenolate radical with carboxylate radical, must surely be written as the union of phenoxonium ion with carboxylate ion. Thus, oxidation of geodin hydrate (V) with

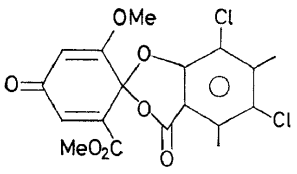
ammonium ceric sulphate or with lead dioxide affords the dienone geodoxin (VII). Since carboxylic acids like (V) are not readily oxidized to radicals under such conditions it appears irrational to formulate a radical coupling process. No doubt the phenolic hydroxyl is oxidized first to the phenolate radical and then to the phenoxonium ion (VI), which cyclizes by addition of carboxylate anion to give the final product (VII).



(I) (II) (III) (IV)



(V) (VI)

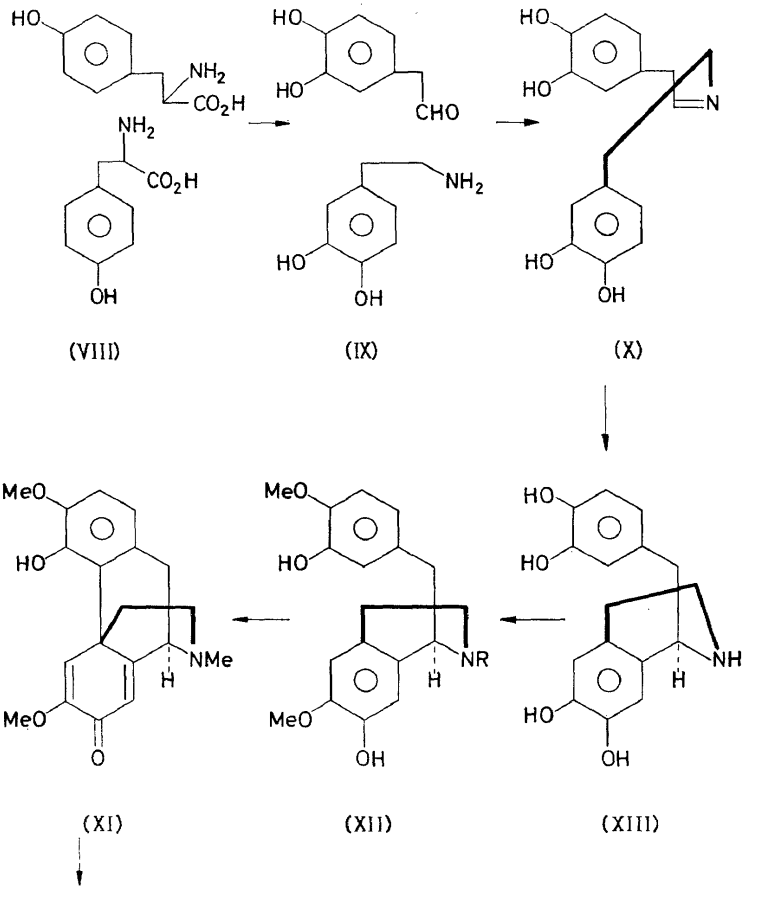


(VII)

With these reservations made we can proceed to consider the application of the theory of phenolate radical coupling to the biogenesis of the morphine alkaloids[4]. The insight of Robinson[9, 10] that norlaudanosoline (XIII) should be the precursor of morphine led to the correct formulation (XVII) for this important alkaloid. The actual manner of coupling has, however, been the subject of much speculation. On the basis of the correct structure (IV) for Pummerer's ketone the biogenesis can be stated[4] in unambiguous terms. Thus the diphenol (XII, R = Me) should on oxidative coupling give the dienone (XI). In our original discussion[4] it was assumed that dienone (XI) would tautomerize (*cf.* (III) and (IV) above) to an $\alpha\beta$-unsaturated ketone (XX) which, by reduction to the alcohol (XXI) and dehydration, would afford thebaine (XV). Thebaine should then be the

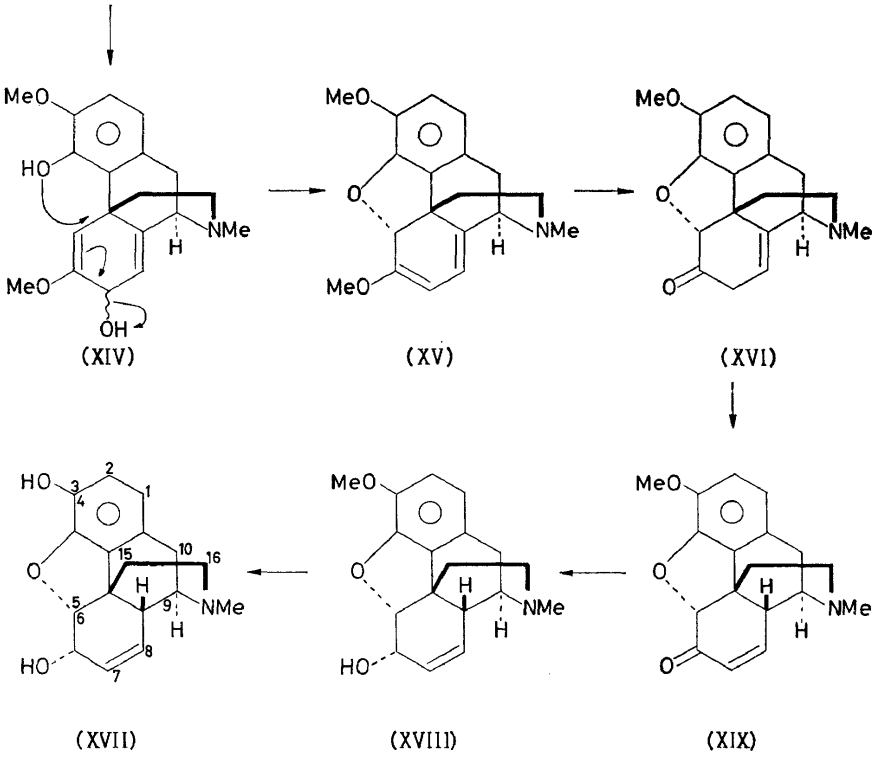
precursor of codeine and morphine, a view contrary to earlier opinion. An important variant of this scheme was proposed by Battersby[11, 12] and by Ginsburg[13]. These authors suggested that the dienone (XI) is reduced to the dienol (XIV) rather than cyclized to (XX). Dehydration of (XIV) coupled with cyclization would then furnish thebaine (XV).

At the present time we can state that there is now powerful tracer evidence for the correctness of the scheme (VIII) through (XVII) as the correct path of biosynthesis of morphine alkaloids. 2-Labelled tyrosine (VIII) gives morphine labelled at positions 9 and 16[14]. Although the two positions are approximately equally labelled the morphine molecule is, in fact,



constructed from two different moieties. 1-Labelled 3,4-dihydroxy-2-phenylethylamine gives morphine labelled only at position 16[15]. The results are best explained if the morphine molecule is constructed from one molecule of the phenylamine and one molecule of 3,4-dihydroxyphenylacetaldehyde (see IX) giving the Schiff's base (X). By rearrangement the latter would afford norlaudanosoline (XIII) which has been proven to be an efficient precursor of morphine[16].

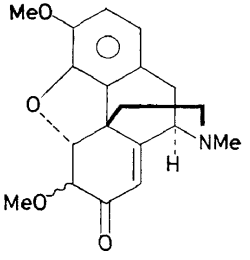
The key derivative (see above) of norlaudanosoline for morphine biosynthesis should be the diphenol (XII, R = Me). This compound is a natural product known as reticuline and has been synthesized on several occasions[17]. We have prepared reticuline with five different labels (see (XXII)) and have studied its incorporation into thebaine[18]. It was especially important to label both of the methoxy groups and the *N*-methyl group in



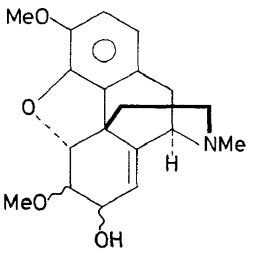
reticuline (XII, R = Me) in order to show that all these labelled methyl groups appeared unaltered in thebaine. After feeding the multi-labelled reticuline (XXII) to *Papaver somniferum* (var. Noordster) multi-labelled thebaine (XXIII) was isolated with the labels in essentially the correct ratios for intact incorporation of (XXII)[20]. This provides a firm proof that reticuline is really the precursor of thebaine. Earlier work from our group[21] with only *N*-methyl and tritium labelling was also in accord with this conclusion.

The supreme importance of the dienone (XI) (or its equivalent tautomer (XX)) as an intermediate in morphine biosynthesis has already been stated. It, therefore, became essential to synthesize this compound which at the time was unknown. The synthesis was accomplished in the following way. Thebaine was reduced with sodium in ammonia to give "phenolic dihydrothebaine" (XXIV, R = H)[22]. The acetate (XXIV, R = Ac) of

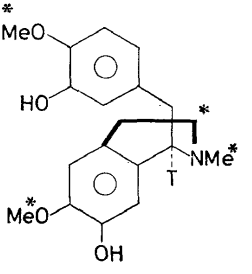
this compound was oxidized with selenium dioxide and then with manganese dioxide to furnish the dienone acetate (acetate of XI). On mild alkaline hydrolysis this afforded the dienone (XI), which existed exclusively in the open form as written. There was no tautomerism with (XX). After the appearance of our preliminary communication[23], Barnes (Universidade do Brasil, Rio de Janeiro, Brasil) noted a similarity between our dienone (XI)



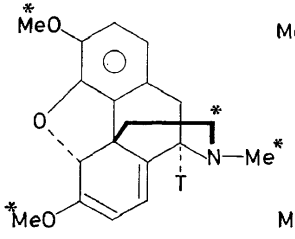
(XX)



(XXI)



(XXII)



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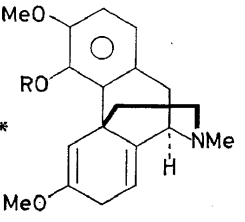
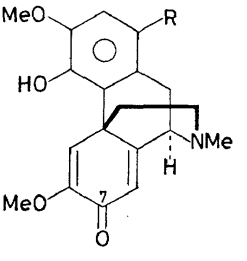


(XXIV)

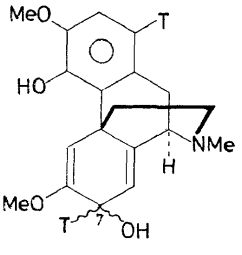


(XXV)

and a new alkaloid (salutaridine) that he had isolated from a Brazilian cource. An exchange of specimens confirmed identity. We propose for convenience to use the name salutaridine for (XI) in the sequel. Salutaridine does occur in *Papaver somniferum* but in very low concentration. Reduction of salutaridine with sodium borohydride gave two alchols, salutaridinols —I and —II (XIV). Both of these alcohols gave thebaine (XVI) in reasonable yield merely on incubation at pH 3–4 at room temperature. The chemical feasibility of the Battersby-Ginsburg steps ((XI) → (XIV) → (XV)) was thus demonstrated.

By base-catalysed tritium exchange[24], which is specific for unsubstituted positions *ortho* and *para* to phenolic hydroxyl of the phenol (XXIV), labelled salutaridine (XXV; R = T) was prepared. Reduction of this with sodium borotritiide gave salutaridinols —I and —II, both doubly labelled with tritium (XXVI). Tritium-labelled salutaridine (XXV) and salutaridinol-I (XXVI) were both incorporated in *Papaver somniferum* (var. Noordster)

in very high yield (*ca.* 7 per cent) into thebaine (XXVII). The retention of the labels in the correct positions and in the correct ratio was confirmed[25] in the following way. Reconversion of the thebaine into salutaridine gave the amount of tritium at position 7. Bromination of salutaridine then gave inactive 1-bromosalutaridine (XXV, R = Br) thus confirming the position and amount of the other tritium label. Salutaridinol-II was also converted



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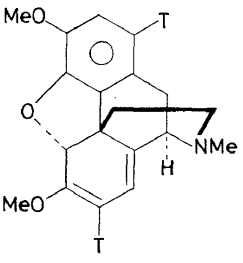
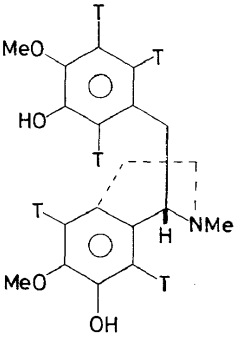
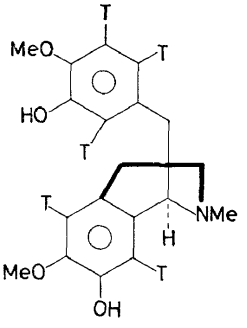


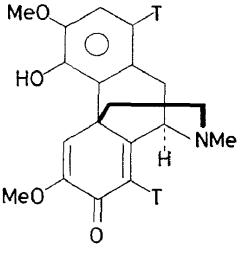
(XXVII)



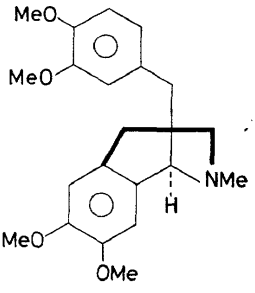
(XXVIII)



(XXIX)



(XXX)



(XXXI)

into thebaine. However, the efficiency of incorporation for salutaridinol-I relative to salutaridinol-II was nearly 30 to one. In a buffer at pH 3–4 both alcohols are converted at approximately the same rate into thebaine. There is no question then, that we have really been studying an enzymatic reaction and not a purely *in vitro* process.

The sequence thebaine (XV) → codeine (XVIII) → morphine (XVII), predicted in our original discussion of the morphine alkaloids[4], has been firmly established[26]. It is reasonable to add other intermediates in this sequence. Thus neopinone (XVI) and codeinone (XIX) should be real intermediates between thebaine (XV) and codeine (XVIII).

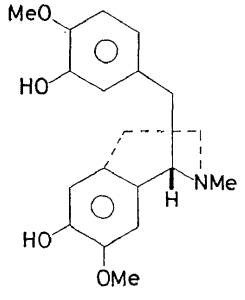
Many unsuccessful attempts have been made to duplicate the oxidative coupling step which converts the benzylisoquinoline into the morphine skeleton[27, 28]. With supplies of reticuline (XII, R = Me) and salutaridine

(XI) available it was possible to study the critical coupling step ((XII, R = Me) → (XI)) in some detail[29]. Oxidation of (±)-reticuline labelled with tritium only (as in (XXII)) with manganese dioxide gave, after dilution with unlabelled salutaridine, a radiochemical yield of salutaridine of about 0·01 per cent[23]. This yield, equivalent to a yield of about 0·02 per cent of racemate, was confirmed by conversion to thebaine of the same specific activity. Since the presence of trace radioactive impurities can vitiate claims of radiochemical synthesis it was important to confirm our findings. The simplest method, the isolation of (±)-salutaridine from the oxidation of unlabelled (±)-reticuline, was precluded by the low yield and by our finding that salutaridine is oxidized faster then reticuline by phenol oxidizing reagents. An alternative procedure was, therefore, adopted. (±)-Reticuline was resolved into its (+)- and (−)- forms by the method of Battersby[30]. The two forms of reticuline were tritiated under acid catalysis which affords substantially the isomers (XXVIII) and (XXIX)[24], an assignment based on preliminary deuteration experiments coupled with nuclear magnetic resonance observations. The isomer (XXVIII) represents (+)-reticuline, the isomer (XXIX) (−)-reticuline[31]. Each form of reticuline was oxidized with potassium ferricyanide (two mols.) in aqueous solution containing sodium hydrogen carbonate. Dilution with unlabelled (+)-salutaridine and crystallization to constant activity gave a radiochemical yield of about 0·0044 per cent for the oxidation of (−)-reticuline and essentially a 0 per cent yield from (+)-reticuline. These yields are calculated allowing for a one-fifth loss of tritium in the conversion of (−)-reticuline (XXIX) into (+)-salutaridine (XXX). The numerical data were confirmed by conversion of the specimens of (+)-salutaridine into thebaine. Oxidation of (±)-reticuline under exactly the same conditions gave (+)-salutaridine in 0·0021 per cent yield. The results not only prove the correctness of our synthesis, which amounts to a further total synthesis of morphine[32], but also provide a direct confirmation of the absolute configuration of benzylisoquinoline[31, 33] relative to morphine alkaloids.

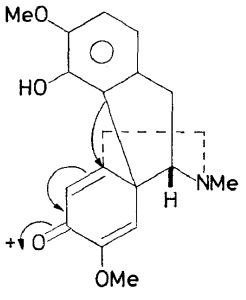
A further direct correlation of reticuline with salutaridine was achieved in the following way. Treatment of salutaridine with sodium hydride and methyl tosylate in dimethylformamide gave the corresponding 0–Me ether. Reduction of this compound with sodium and liquid ammonia[34] afforded a mixture of non-ketonic products which on methylation with diazomethane and careful chromatography afforded (−)-laudanosine (XXXI) in low yield. The identity of the isolated (−)-laudanosine was rigorously established by repetition of the experiment using tritium-labelled (+)-*O*-methylsalutaridine (*O*-methyl ether of (XXV, R = T)). The purified (−)-laudanosine had the same specific molar activity as the starting material and retained a proportionate activity after dilution with authentic unlabelled (±)-laudanosine and repeated recrystallization.

The interesting Japanese alkaloid simonenine (XXXVII)[35] has been considered to be derived from "protosinomenine" (XXXII)[28]. If this is correct then the theory of oxidative coupling requires that the dienone (XXXIII) should be an intermediate. By acid-catalysed rearrangement this dienone (see (XXXIII)) should afford the carbonium ion (XXXIV) which by direct, or indirect, reduction would afford sinomenine (XXXVII).

We have, however, advanced the view[4] that the position of the enolic methoxyl group in sinomenine is misleading and that (+)-reticuline is the true precursor. Thus, oxidation of (+)-reticuline would furnish (−)-salutaridine (enantiomer of (XI)). Reduction to the corresponding dienol (XXXVI, R = H), methylation to the methyl ether (XXXVI, R = Me),



(XXXII)



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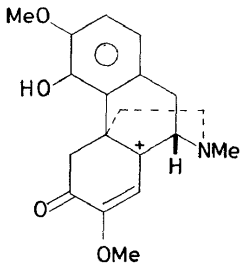
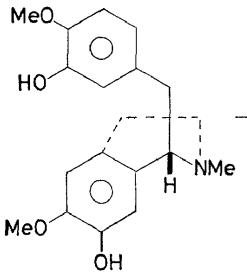
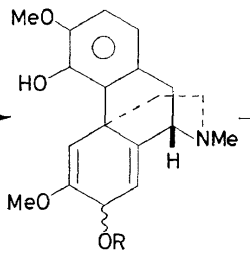


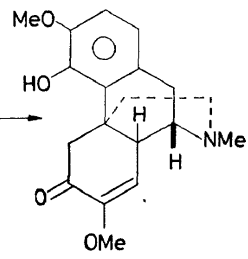
(XXXIV)



(XXXV)



(XXXVI)

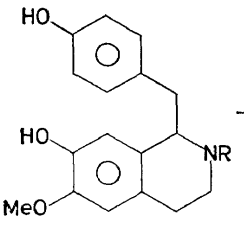


(XXXVII)

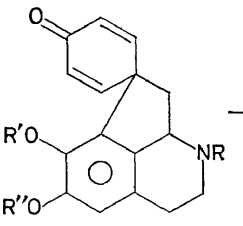
hydrolysis of the vinylic methyl ether and conjugation of the ethylenic linkage from the $\beta\gamma$-position would then furnish sinomenine (XXXVII). In preliminary experiments with 2-labelled (±)-tyrosine we have shown[36] an incorporation of 0·08 per cent into sinomenine in *Sinomenium diversifolius*[37]. Experiments on the incorporation of tritium-labelled "protosinomenine" (XXXII) and reticuline are in hand and the results will be reported as soon as the vagaries of the English summer permit.

As has been appreciated for many years aporphine alkaloids are formed in Nature by phenol oxidation. In considering the biogenesis of the apparently abnormal alkaloids anonaine (XLII, R = H) and roemerine (XLII, R = Me), it was proposed[4] (for convenience we have revised this scheme to take account of our recent discovery of the mode of biosynthesis of the methylenedioxy-group[38]) that the precursors (XXXVIII, R = H

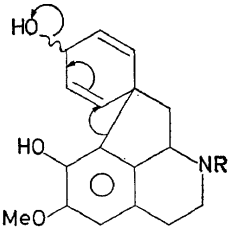
and R = Me respectively) were initially oxidized to dienones (XXXIX, R = H and R = Me respectively, R′ = H, R″ = Me). Reduction of these dienones to the corresponding dienols (XL, R = H and R = Me respectively) followed by acid-catalysed rearrangement (see XL, arrows) would then furnish anonaine (XLIII, R = H, R′ = R″ = $\frac{1}{2}CH_2$) and roemerine (XLIII, R = Me, R′ = R″ = $\frac{1}{2}CH_2$). The later discovery of the dienol–benzene rearrangement made such speculation much more acceptable.



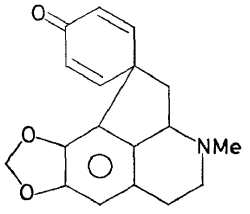
(XXXVIII)



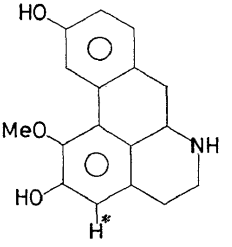
(XXXIX)



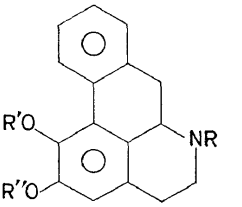
(XL)



(XLI)



(XLII)

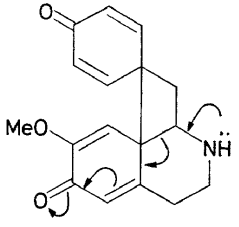


(XLIII)

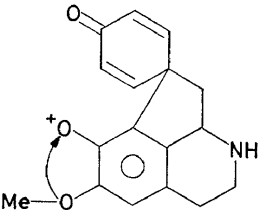
In the last year the correctness of the general scheme has been placed almost beyond doubt by the discovery of a new class of alkaloids of the general type (XXXIX). Thus crotonosine, from *Croton linearis* Jacq.[39], was shown to be either (XXXIX, R = R′ = H, R″ = Me) or (XXXIX, R = R″ = H, R′ = Me)[40] and pronuciferine, from *Nelumbo nucifera* Gaertn., was demonstrated to be (XXXIX, R = R′ = R″ = Me)[4]. Another alkaloid of this class must be fugapavine from *Papaver fugax* Poir.[42] which should have the constitution (XLI)[43]. The sequence from the dienones to the corresponding aromatic compounds can be carried out readily in the laboratory[34, 40–42], though not yet proven to take place in the plant. We have experiments in hand using *Anona reticulata* and other appropriate plants.

In so far as prior work on the biosynthesis of *Amaryllidaceae* and morphine alkaloids has confirmed that methylation of phenolic hydroxyl is employed in

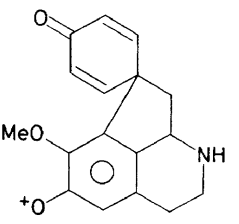
Nature in order to direct the sites of phenolic coupling we, at first, favoured the constitution (XXXIX, R = R′ = H, R″ = Me) for crotonosine. However, we have recently discovered that base-catalysed deuteration of apocrotonosine (XLIV) results in loss of the proton signal at 3·5τ which is characteristic of the isolated aromatic hydrogen (asterisk in XLIV). Crotonosine must,



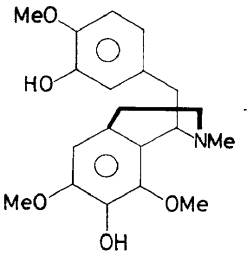
(XLIV)



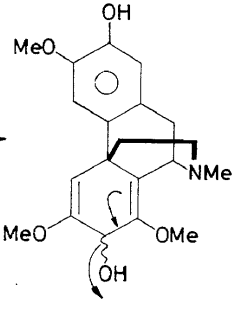
(XLV)



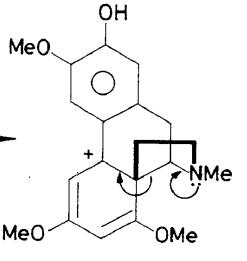
(XLVI)



(XLVII)



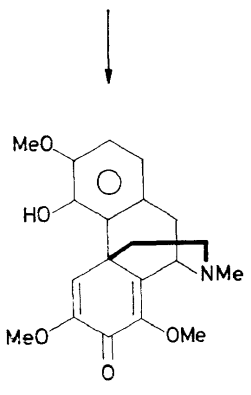
(XLVIII)



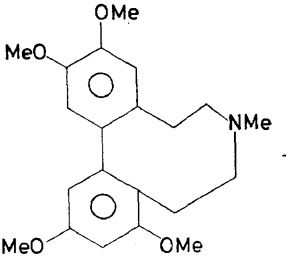
(XLIX)

therefore, be (XXXIX, R = R″ = H, R′ = Me). One must, at a first consideration, conclude that either the intermediate bis-dienone (XLIV) is involved, with a dienone-phenol as well as a dienol-benzene rearrangement taking place subsequently, or that a removable protective group is used prior to oxidation in the sense already discussed by Barton and Cohen[4]. The methylation of the catechol (XXXIX, R = R′ = R″ = H), or equivalent intermediate would then provide the *O*-methyl group. The existence of the intermediate (XLIV) seems most improbable, especially as such a compound should rearrange rapidly in another sense (XLIV, see arrows) to that already discussed. The second explanation is quite possible, but rather uninteresting. A third, and novel, possibility[44] would be if the first product of coupling of (XXXVIII, R = H), namely "isocrotonosine" (XXXIX, R = R′ = H, R″ = Me) could "rearrange" to crotonosine (XXXIX, R = R″ = H, R′ = Me). Some preliminary evidence that this

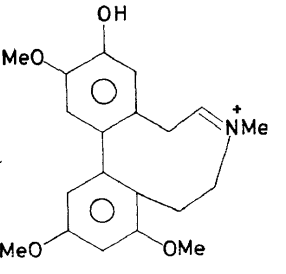
is not inconceivable is the fact that (±)-coclaurine (XXXVIII, R = H), labelled with tritium *ortho* to its phenolic hydroxyl groups, is incorporated into crotonosine in 0·53 per cent yield[45]. The tritium is found in the crotonosine at only the α-positions to the ketone as shown by catalytic hydrogenation to the tetrahydro-series followed by base-catalysed removal of *all* the tritium. The mechanism for the rearrangement of the methyl group *could* be through the corresponding phenoxonium ion (*cf.* above). Thus oxidation of (XXXIX, R = R′ = H, R″ = Me) to (XLV) *could* provoke methyl migration to (XLVI) which by reduction would give



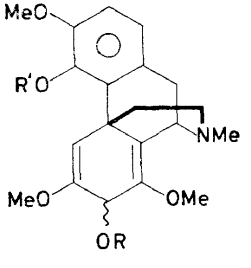
(L)



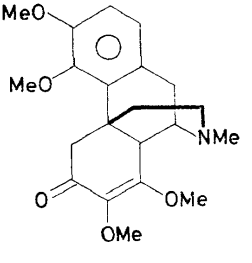
(LI)



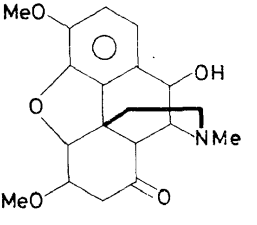
(LII)



(LIII)



(LIV)



(LV)

crotonosine (XXXIX, R = R″ = H, R′ = Me). Further experiments are in hand to establish if this methyl migration really occurs or not. Another alkaloid which presents the same problem is nornuciferine to which constitution (XLIII, R = R′ = Me, R″ = H) has been assigned[46].

The dienol-benzene rearrangement can also be invoked to explain certain abnormal oxygenation patterns in aporphine alkaloids[12]. We consider that some of the interesting constitutions found in *Stephania* alkaloids must be explained by analogous considerations. Thus protostephanine[47]

(LI) would be derived by the sequence (XLVII) → (XLVIII) → (XLIX) → (LII) → (LI), or its equivalent. Similarly hasubanonine[48] could be derived from an alternative coupling of (XLVII) to give the dienone (L). Reduction to the dienol (LIII, R = R′ = H), methylation to (LIII, R = R′ = Me) and selective hydrolysis as in the case of sinomenine (see above) would then furnish hasubanonine (LIV). The structure (LV) tentatively proposed for metaphanine[49] could be readily derived from (LIII, R = R′ = H) with appropriate 10-hydroxylation. Studies on the biosynthesis of the alkaloids of *Stephania japonica* from these theoretical points of view are currently in progress.

It is clear that biogenetic studies with alkaloidal compounds are at the very interesting stage of development where hypothesis and experiment can be synergistically combined. In this connection we would add that very much more has been omitted fron this lecture than has been included. No reference has been made to the stimulating speculations of Wenkert or to the pioneering investigations of Marion, Leete, and others on other types of alkaloids simply because of lack of relevancy to the specialized topic here discussed.

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