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Isoquinoline Alkaloid Biosynthesis

Speculations on some unsolved problems

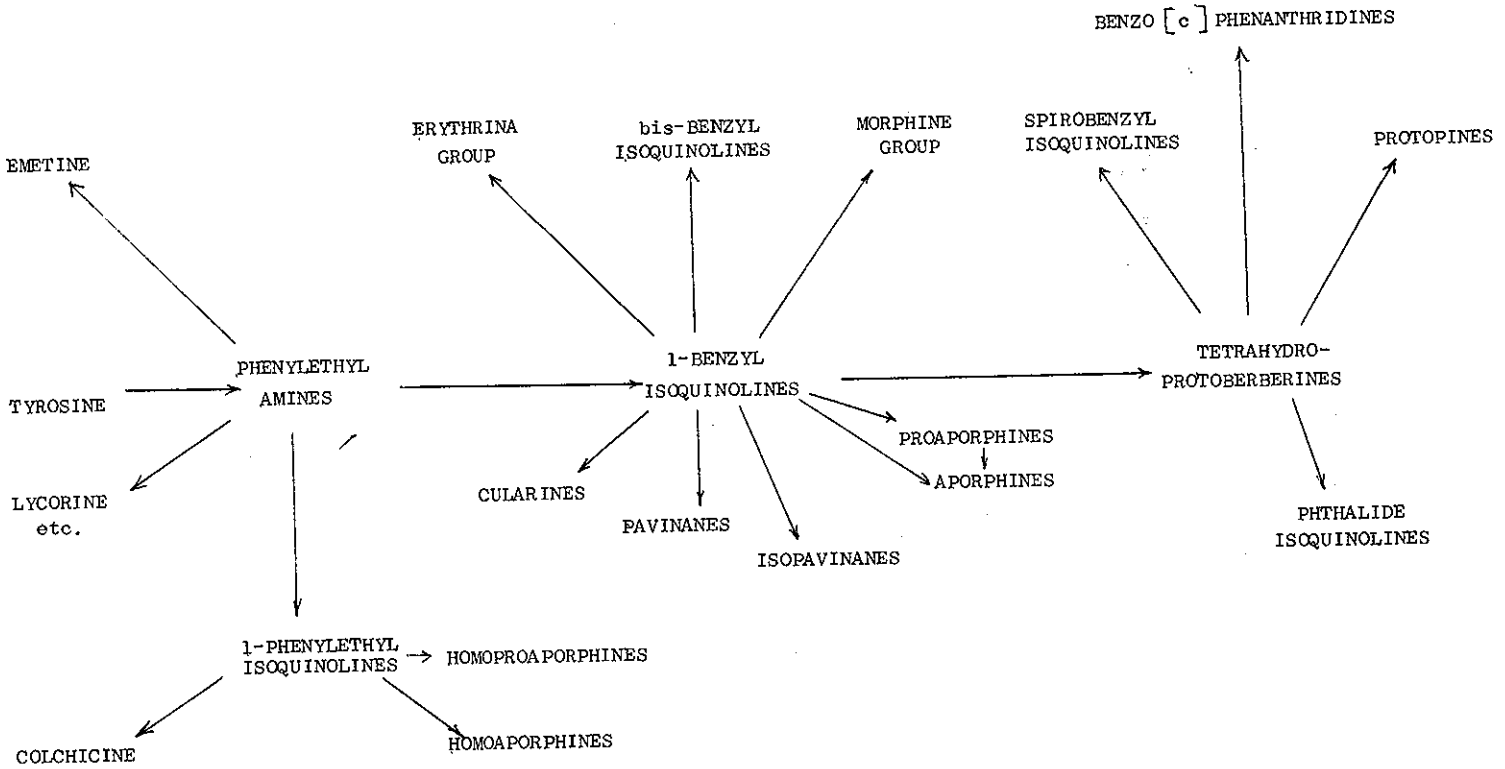
by

S.F.DYKE

School of Chemistry, University of Bath,
Bath BA2 7AY, England

Introduction

It is now generally accepted that the 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids arise in Nature from tyrosine, and thence 3,4-dihydroxyphenylalanine (DOPA), approximately in accordance with the scheme outlined in 1910 by Winterstein and Trier[1]. Once formed, these isoquinoline derivatives are the precursors of a large array of polynuclear structures (Scheme I). An enormous amount of effort has been expended over the last 20 years or so to establish these interrelationships[2-6]. The methods used[7] have involved feeding the plant with a postulated precursor to the alkaloid(s) under examination, suitably labelled with ^{14}C, ^{15}N, ^{2}H or ^{3}H atoms at specific sites. More recently some very elegant work has shown how the enzyme systems of plants are used to generate, stereospecifically, asymmetric centres, especially from prochiral methylene groups[8]. The concept of phenol oxidation[9-16] has proved to be of supreme importance for a clearer understanding of the individual steps in the biosynthetic pathways.

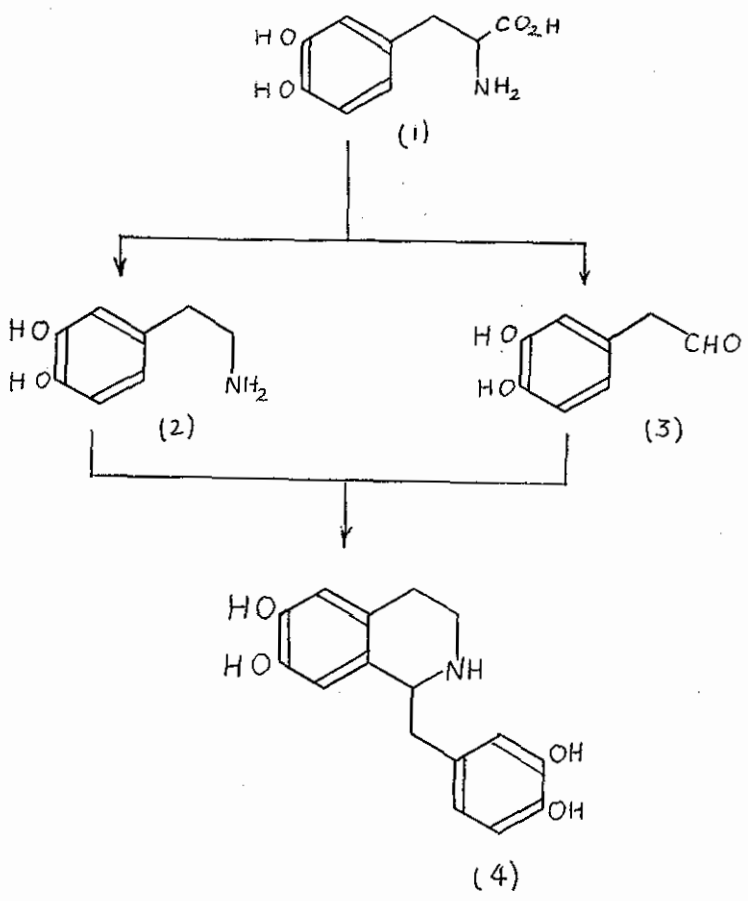

BENZO [c] PHENANTHRIDINES
ERYTHRINA GROUP
bis-BENZYL ISOQUINOLINES
MORPHINE GROUP
SPIROBENZYL ISOQUINOLINES
PROTOPINES
EMETINE
PHENYLETHYL AMINES
TYROSINE
1-BENZYL ISOQUINOLINES
TETRAHYDRO-PROTOBERBERINES
LYCORINE etc.
CULARINES
PAVINANES
ISOPAVINANES
PROAPORPHINES
APORPHINES
PHTHALIDE ISOQUINOLINES
1-PHENYLETHYL ISOQUINOLINES
HOMOPROAPORPHINES
COLCHICINE
HOMOAPORPHINES

Despite this vast body of knowledge there are some intriguing problems still outstanding. Among these are (a) the mechanism of formation of the 1-benzyltetrahydroisoquinolines, especially the decarboxylation of tetrahydroisoquinoline-1-carboxylic acids, (b) the dehydrogenation of the nitrogen-containing ring to the fully aromatic state present in such structures as papaverine, berberine and sanguinarine, (c) the biosynthesis of the pavinane and isopavinane alkaloids, (d) the mechanism of phenol oxidation in vivo and (e) some unusual oxygenation patterns.

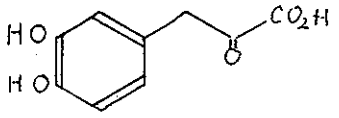
Formation of 1-benzyl-1,2,3,4-tetrahydroisoquinolines

In their original scheme[1], Winterstein and Trier postulated that DOPA (1) is converted into dopamine (2) by decarboxylation, and into 3,4-dihydroxyphenylacetaldehyde (3) by decarboxylation and deamination (Scheme II), followed by a Pictet-Spengler type of condensation to give rise to norlaudanosoline (4). It was shown[17] that in vitro high yields of 1-benzyltetrahydroisoquinolines could be obtained from (2) and (3) under so-called "physiological conditions". It has been postulated that DOPA is converted into the pyruvic acid (5), rather than the aldehyde (3), and that condensation with (2) provides norlaudanosoline-1-carboxylic acid (6), which subsequently undergoes decarboxylation to (4)[18]. This proposal has the great merit that both dopamine and (5) are normal products of α-amino acid metabolism. Hahn, et al.[18] showed that the condensation reactions occur in vitro in high yield under "physiological" conditions, but the 1-benzyltetrahydroisoquinoline-1-carboxylic acids proved to be very resistant to decarboxylation under conditions even remotely similar to those existing in the plant cell. However, these proposals have been

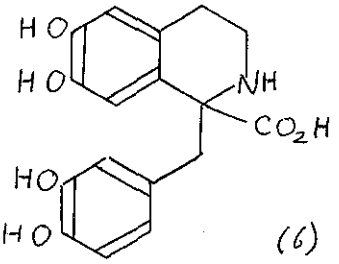
SCHEME 2



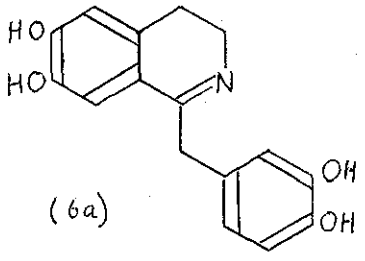
revived recently[19,20], especially since the isolation of peyoxylic acid (7) and peyoruvic acid (8) from cacti[21]. It was established[22] that these acids are efficiently incorporated into anhalanine (9) and anhalonidine (10), when fed to the appropriate plants. Further, it was reported[22] that when peyoruvic acid (8) was incubated with fresh



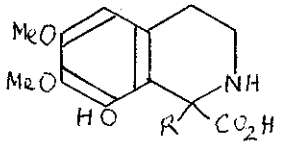
(5)



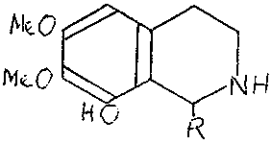
(6)



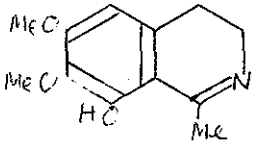
(6a)



(7), R = H
(8), R = Me

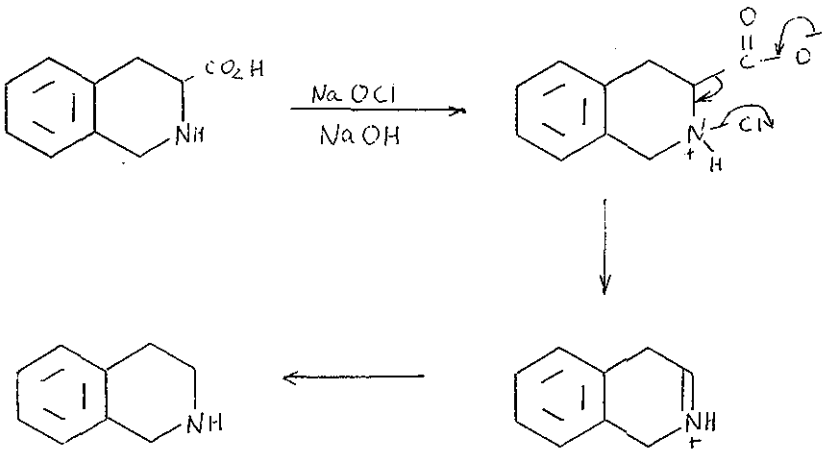


(9), R = H
(10), R = Me



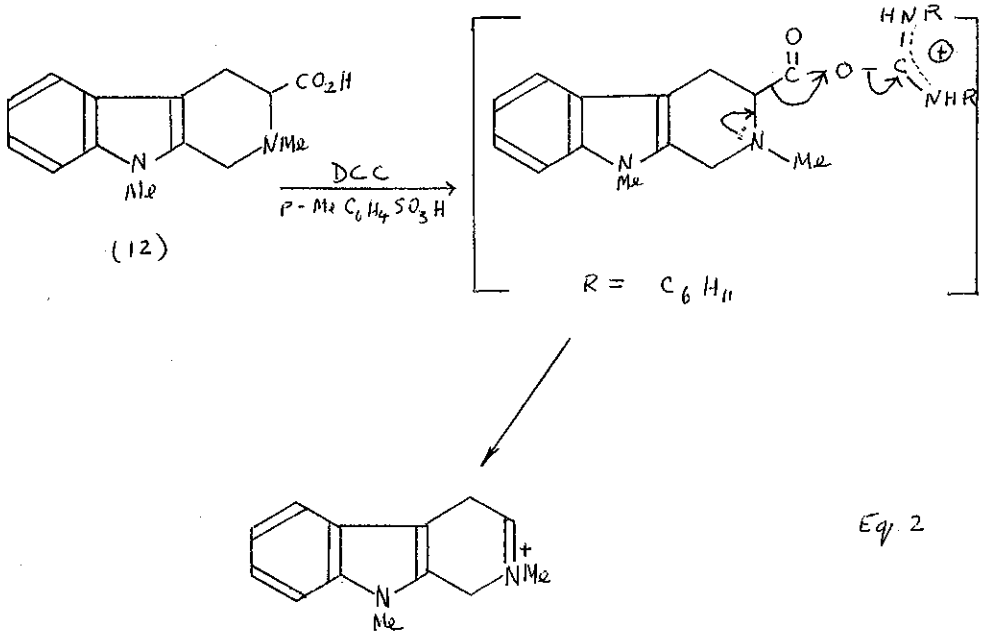
(11)

cactus slices, the corresponding 3,4-dihydroisoquinoline (11) was produced. This observation suggests that the decarboxylation of a tetrahydroisoquinoline-1-carboxylic acid to the tetrahydroisoquinoline may be a two-step process involving oxidative decarboxylation to the 3,4-dihydroisoquinoline, by processes discussed below, followed by a (stereospecific) reduction[23,24]. Some recent results using Papaver orientale[20] and P.somniferum[25] have shown conclusively that (6) is formed from DOPA and that (6a) is probably an intermediate between (6) and (4). Some time ago the oxidative decarboxylation of tetrahydroisoquinoline-3-carboxylic acid, using sodium hypochlorite, (equation 1) was studied as a biosynthetic model, but the results were inconclusive[26]. More recently[27]



.... Eq. 1

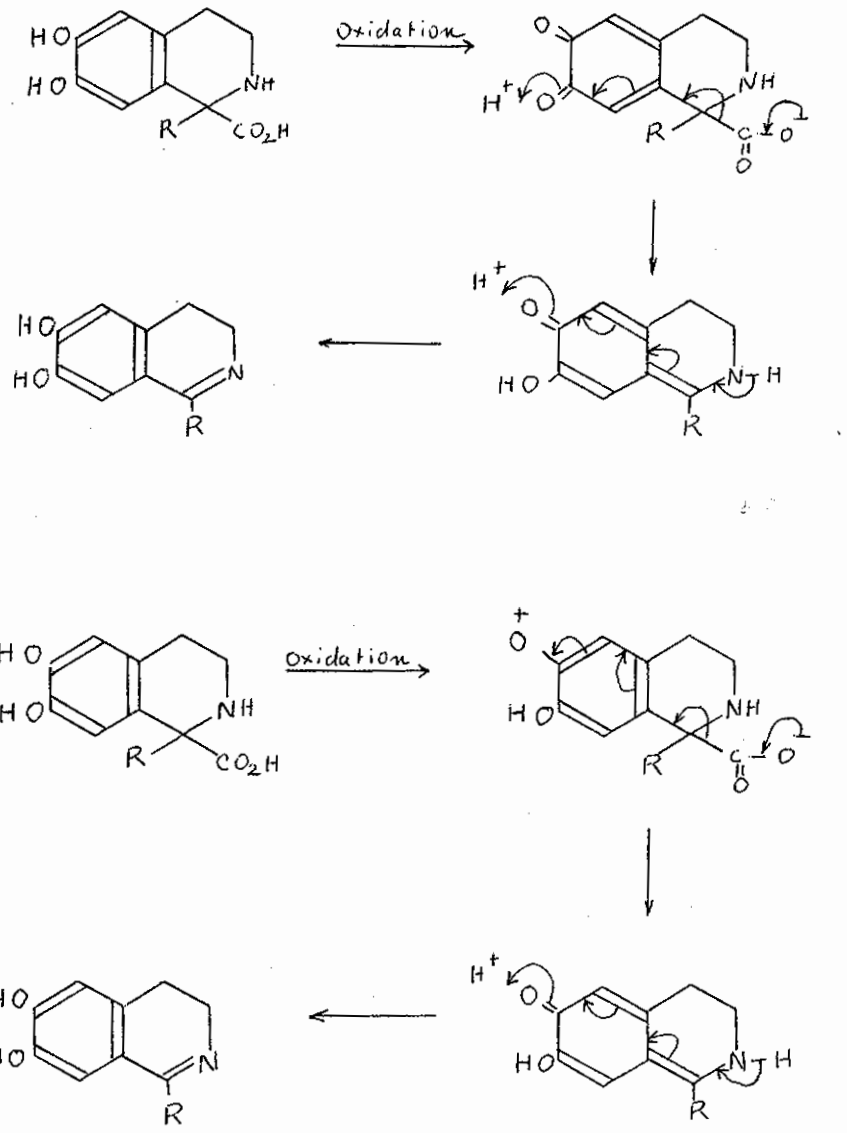
it has been found that decarboxylation of (12) can be achieved by treatment with dicyclohexylcarbodiimide (equation 2). The method of generation of the imminium ion was used in a synthesis of ajmaline.



Eq. 2

However, Bobbitt and Cheng[23] have suggested that the phenolic hydroxyl group of, for example (4), rather than the nitrogen atom, might be the point of oxidation that triggers the loss of carbon dioxide. Several mechanisms could be written for such a process; one showing the intermediate formation of an o-quinone and another involving a phenoxy cation (see later) are represented in Scheme III. It has been found[23,24] that anodic oxidation of the tetrahydroisoquinoline-1-carboxylic acids (13) give the 3,4-dihydroisoquinolines in a reaction that involves a single, two-electrons wave at a potential at which phenol oxidations

SCHEME III


HO
HO
NH
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CO2H
Oxidation
O
H+
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NH
R
C
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HO
HO
N
R
HO
HO
NH
R
CO2H
Oxidation
+
O
HO
NH
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H+
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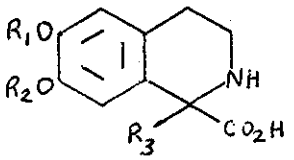
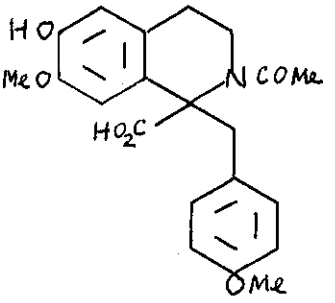
are known to occur. When the phenolic isoquinoline derivative (14) was



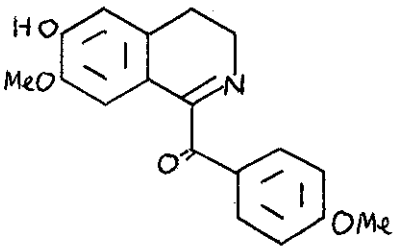
(13)

	R_1	R_2	R_3
a	H	Me	p-MeOC$_6$H$_4$CH$_2$
b	H	Me	Me
c	Me	H	C$_6$H$_5$CH$_2$

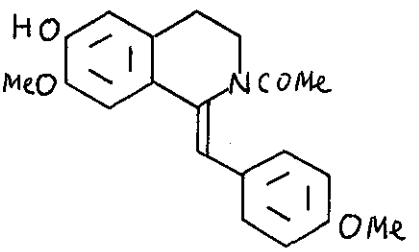


(14)

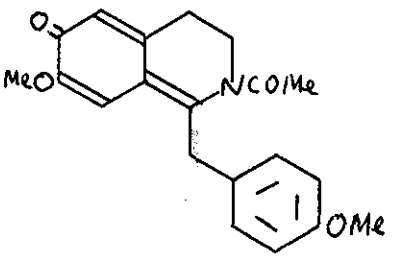
oxidised electrolytically[23,24], the major product was (15), together with some (16) and (17). The product (16) could be isomerised to (17) with acids.



(15)

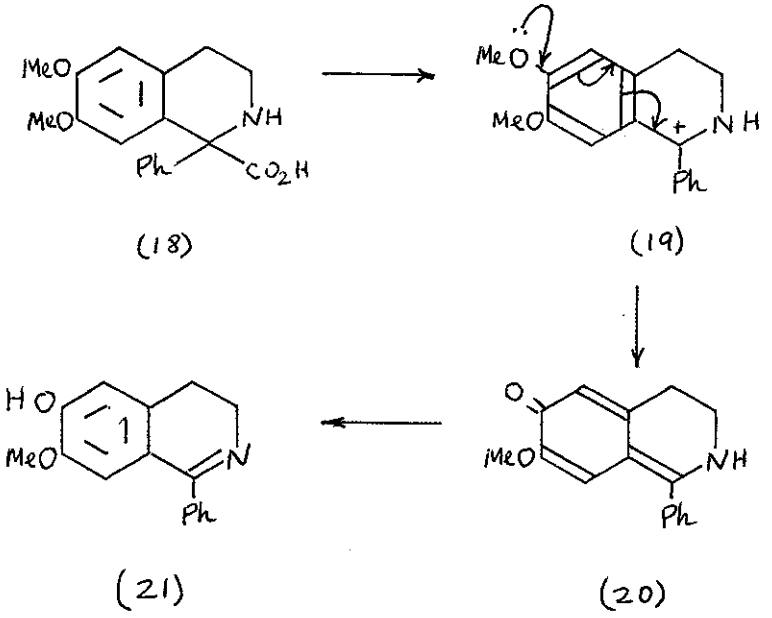


(16)



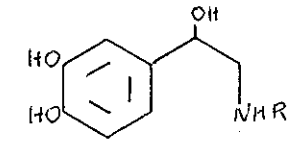
(17)

When the amino acid (18) was oxidised with periodic acid, the product was (21) and since the amount of oxidant consumed was exceptionally high, it was proposed[28] that the reaction proceeded via (19) and the quinone methide (20).

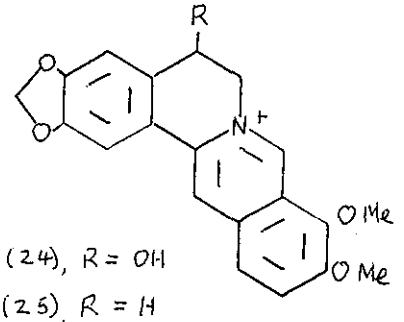


Alkaloids Derivable from 4-Hydroxylaudanosoline

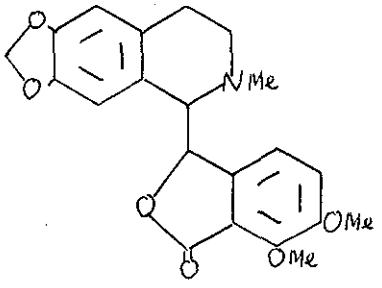
Noradrenaline[22] and adrenaline[23] are normal constituents of mammalian tissues; they are biosynthesised from tyrosine by way of DOPA and dopamine[29]. Noradrenaline has also been detected in a number of plant species[30] and probably is formed by a route similar to that in mammalian tissues. It has been shown that noradrenaline is the precursor of berberastine[24] in Hydrastis canadensis[31,32]. When dopamine-1-^{14}C ($3,4\text{-}(OH)_2C_6H_3CH_2\overset{*}{C}H_2NH_2$) was fed to the plant, radioactive berberastine (24),



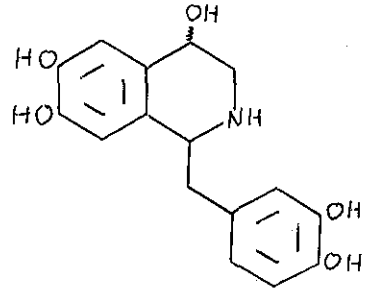
(22), R = H
(23), R = Me



(24), R = OH
(25), R = H



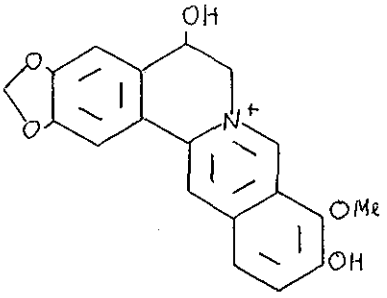
(26)



(27)

berberine (25), canadine (tetrahydroberberine) and hydrastine (26) were isolated. Degradations revealed that the berberine was specifically labelled at C_5. It is

possible that (24) arose by hydroxylation of berberine, but this is unlikely since berberastine had a higher specific activity than berberine or canadine. When (±)-noradrenaline-2-^{14}C was fed to H.canadensis high levels of incorporation into berberastine were found; incorporations into berberine and canadine were only one-sixth of those achieved with dopamine-1-^{14}C. It was concluded that norlaudanosoline (4) cannot be the precursor of berberastine, since it had been established[33,34] that (4) is the specific precursor for berberine, and 4-hydroxynorlaudanosoline (27) seems to be the logical precursor; the stereochemistry of (27) at C_1 and C_4 have not been discussed.



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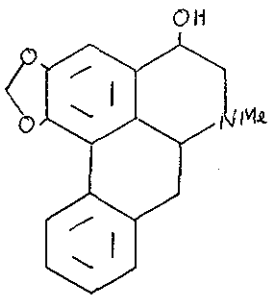
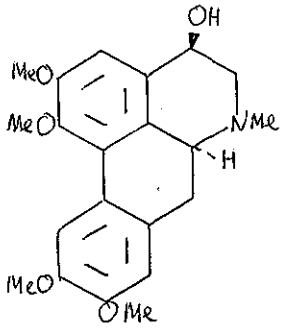


(29)



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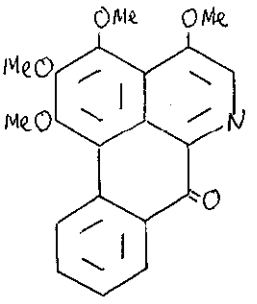
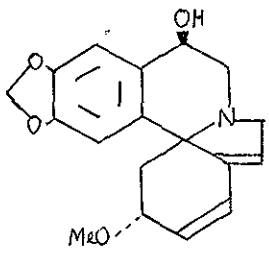


(31)

The intriguing possibility arises that 4-hydroxynorlaudanosoline is the starting point for a range of alkaloids in parallel to the large number of structural types derivable from norlaudanosoline itself (Scheme I). This concept is supported by the characterisation of compounds such as thalidastine (28)[35], tetrahydroberberastine[31], stephorphine (29)[36], cataline (30)[37], imenine (31)[38], erythrinine (32)[39] and erythistemine (33)[40].



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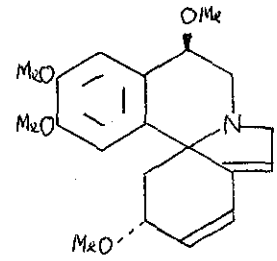
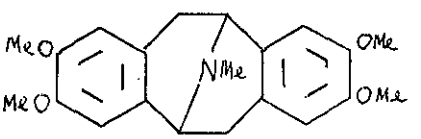


(33)

It has always been supposed[41,42] that the pavinane alkaloids, such as argemonine (34), are biosynthesised from reticuline (35). However, when ^{14}C-labelled reticuline was fed to Argemone mexicana L., the argemonine was not radioactive[42], but this may be due to the fact that only very small amounts of (34) are present in this plant[43]. It was



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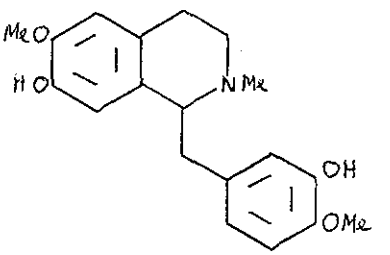
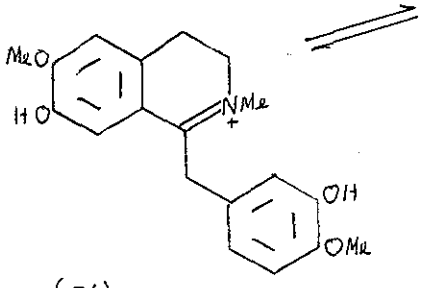
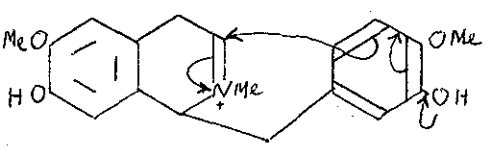


(35)

postulated by Stermitz and Seiber[43] that, in view of the known[44] dehydrogenation of reticuline to (36) (which probably occurs via the N-oxide and then the pseudobase), the 3,4-dihydroisoquinoline (36) could isomerise to (37), which might then undergo cyclisation to the pavinane system.



(36)



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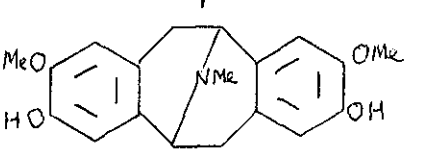
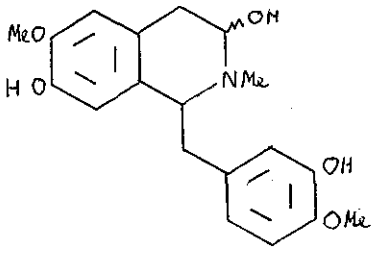


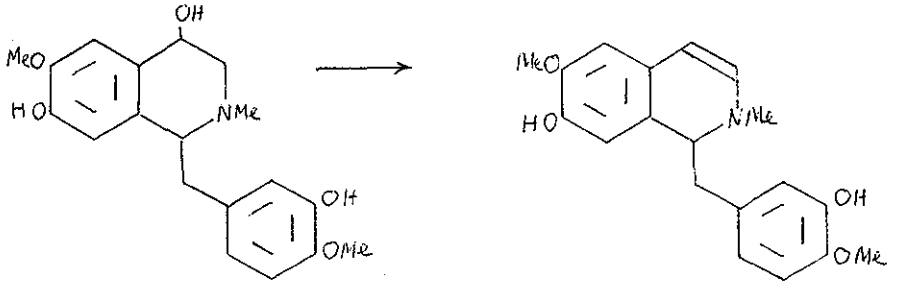
(34)

If, on the other hand, reticuline can[41] be hydroxylated enzymatically to (38), conversion to (37) is easily visualised.

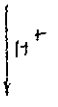


(38)

A very attractive alternative possibility[45] is that the precursor of the pavinanes is 4-hydroxynorlaudanosoline (27) which becomes partially methylated, probably to 4-hydroxyreticuline (39), which then undergoes dehydration to the enamine (40) and protonation to yield (37). It has been



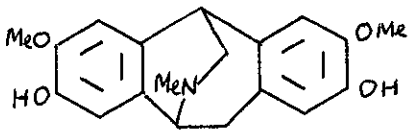
(39) (40)



(37)

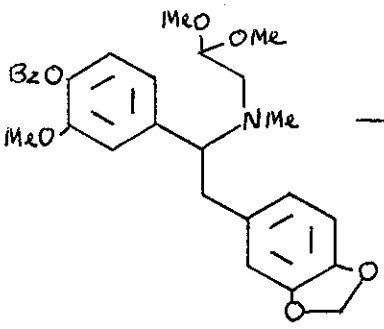
known for some time[46] that enamines such as (40) are cyclised to pavinanes under acid conditions. Since such enamines are also known[47,48] to undergo rearrangement into 3-benzyl-3,4-dihydroisoquinolines under mild acid conditions, it may be anticipated that 3-benzylisoquinoline derivatives should occur as natural products, although none have been reported so far.

This scheme for the biosynthesis of pavinanes has the great merit that the genesis of isopavinanes is also readily explained by the cyclisation of the 4-hydroxy-1-benzyltetrahydroisoquinoline derivative, for example (39) → (41). Acid-catalysed cyclisations of this type *in vitro* are well

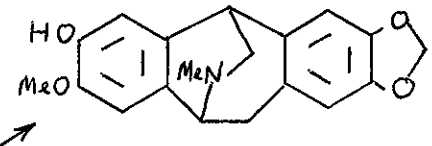


(41)

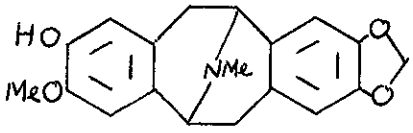
known[49]; more significantly it has been found[49] that when the acetal (42) is treated with 2N HCl at room temperature the isopavinane (43) *and* the pavinane (44) are produced. It is also significant that the pavinane and



(42)



(43)

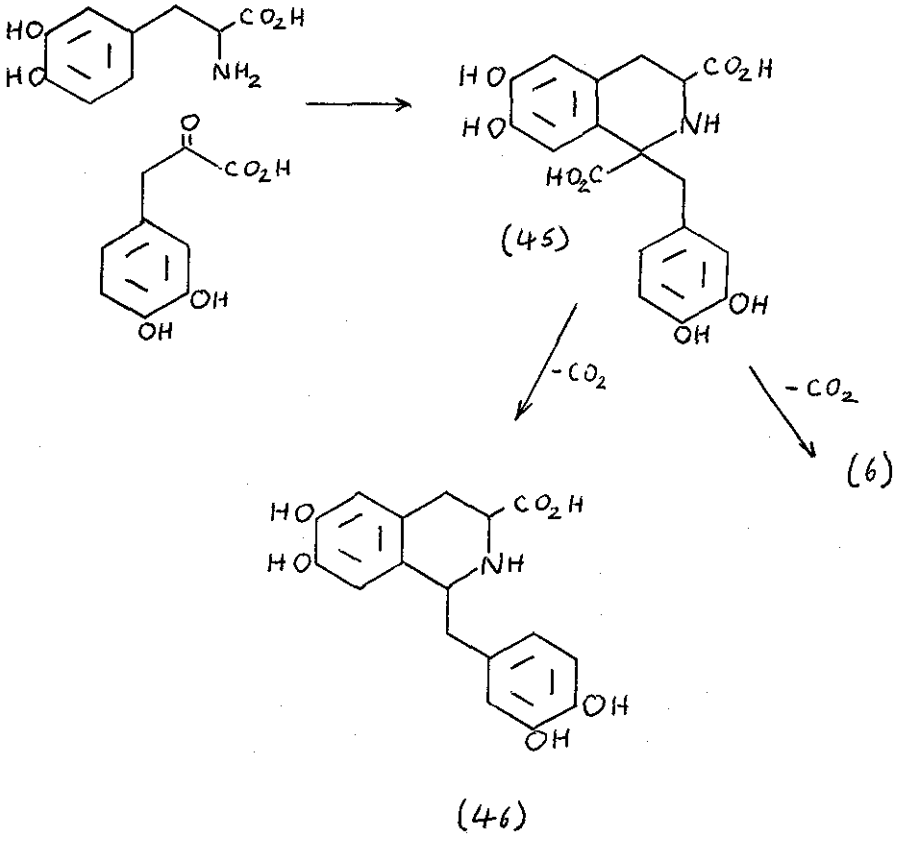


(44)

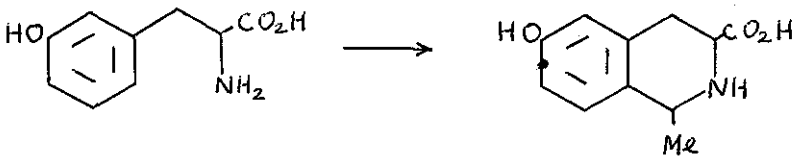
isopavinane alkaloids possess the same absolute configuration[50].

It is generally accepted that in the biosynthesis of the isoquinoline ring, DOPA is first decarboxylated to dopamine, and it is known that when ^{14}C-labelled dopamine is fed to plants that produce alkaloids of the isoquinoline group, the products are specifically labelled. Nevertheless it is still possible that DOPA, and not dopamine is condensed with the α-keto acid (5), to give rise to a tetrahydroisoquinoline-1,3-dicarboxylic acid (45). It is then possible for this to lose one carboxyl group to yield (6) or (46) (Scheme IV).

SCHEME IV

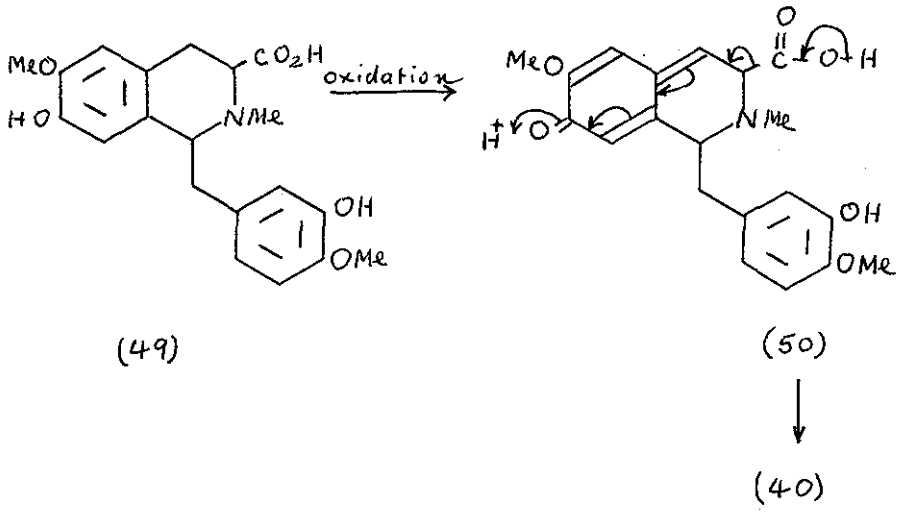


When (±)-m-tyrosine-2-^{14}C (47) is fed to Euphorbia myrsinites, the alkaloid (48) can be isolated, specifically labelled[51].



(47) (48)

An alternative mode of biosynthesis of pavinanes that does not involve 4-hydroxynorlaudanosoline (27) can then be considered in which a 1-benzyltetrahydroisoquinoline-3-carboxylic acid, for example (49), undergoes oxidative decarboxylation via (50) and thence to the enamine (40). However, to explain the formation of isopavinanes it would be necessary to postulate hydration of

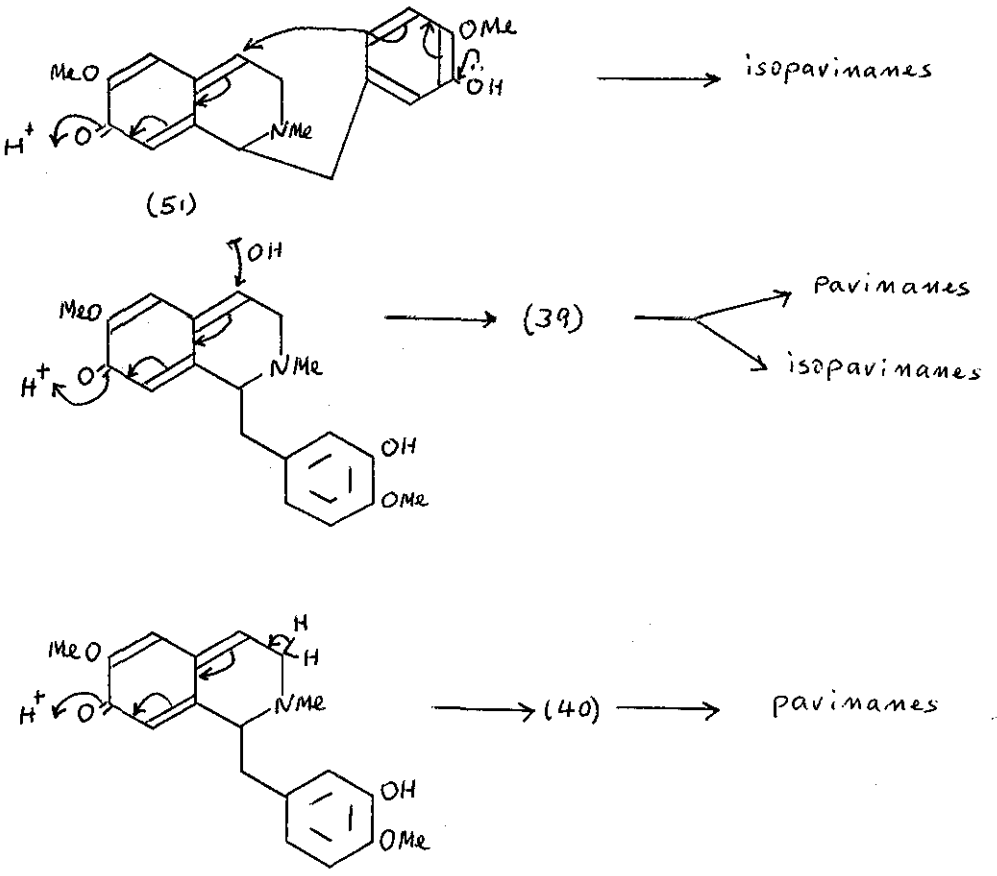


(49) (50)

(40)

(40) to give (39). This reaction is known <u>in vitro</u>[52]. Of course both pavinanes and isopavinanes could arise from reticuline if initial oxidation to the quinone methide (51) is assumed to occur (Scheme V) followed by cyclisation, or hydroxylation to (39), followed by further reactions as discussed above. Examples of C_4-hydroxylation of 7-hydroxytetrahydroisoquinolines <u>in vitro</u> are known[53] involving oxidation with lead tetraacetate.

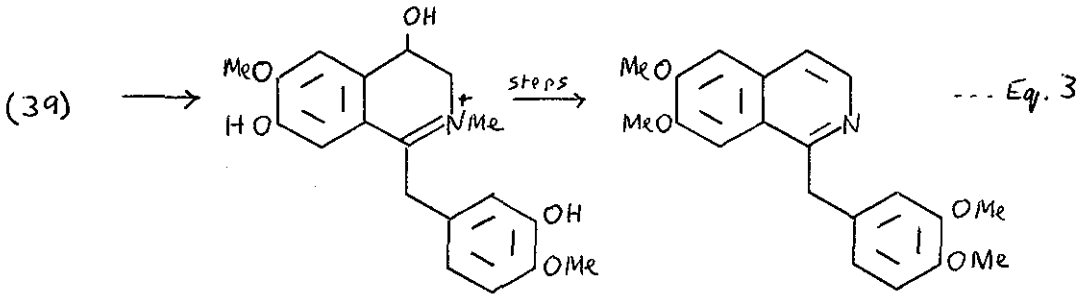
SCHEME V



One of the many developments of this reaction concerned the synthesis of an isopavinane from a 1-benzyl-7-hydroxytetrahydroisoquinoline derivative[54].

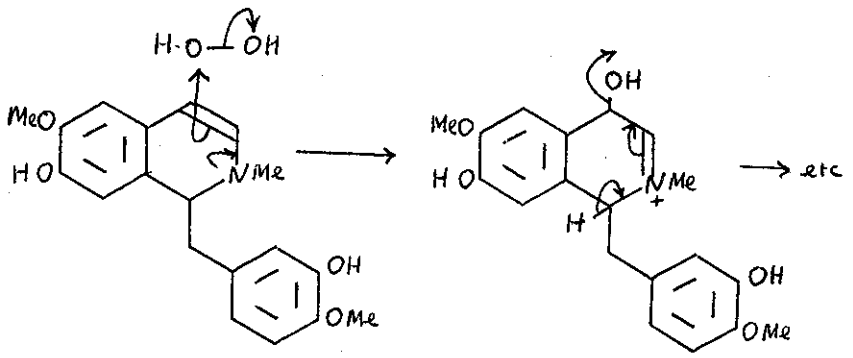
Dehydrogenation to Fully Aromatic Isoquinolines

The actual pathway adopted in vivo for the dehydrogenation of a 1,2,3,4-tetrahydroisoquinoline into the fully aromatic state, for example in papaverine, is largely unknown, but several possibilities can be considered. Thus, if it is assumed that 4-hydroxyreticuline can be dehydrogenated to the 1,2-dehydro compound, by analogy with the known[44] similar reaction with reticuline, aromatisation is easily understood (equation 3) and laboratory analogies for this process do exist[55]. Of



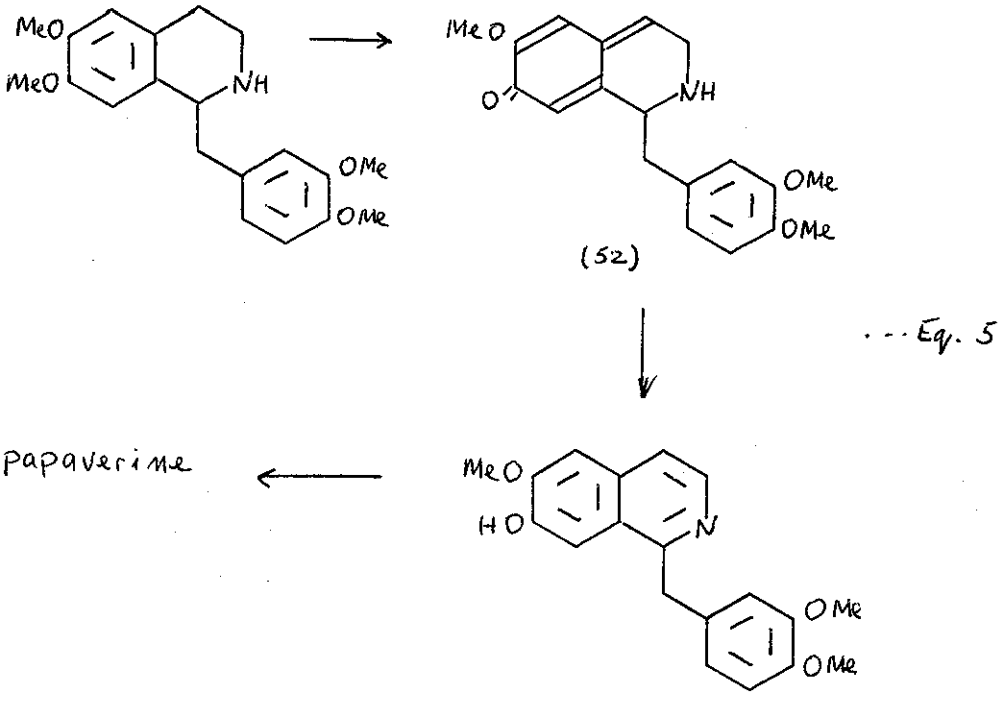
--- Eq. 3

course the quinone methide (51) is equivalent to (39) and tautomeric shift would give the enamine (40), which could then be dehydrogenated as outlined in equation 4. It is possible to envisage the formation of the fully aromatic isoquinoline by successive oxidative decarboxylations of a tetrahydroisoquinoline-1,3-dicarboxylic acid. However, in the opium poppy at least, it has been shown[56] that tetrahydropapaverine is the immediate



..Eq 4

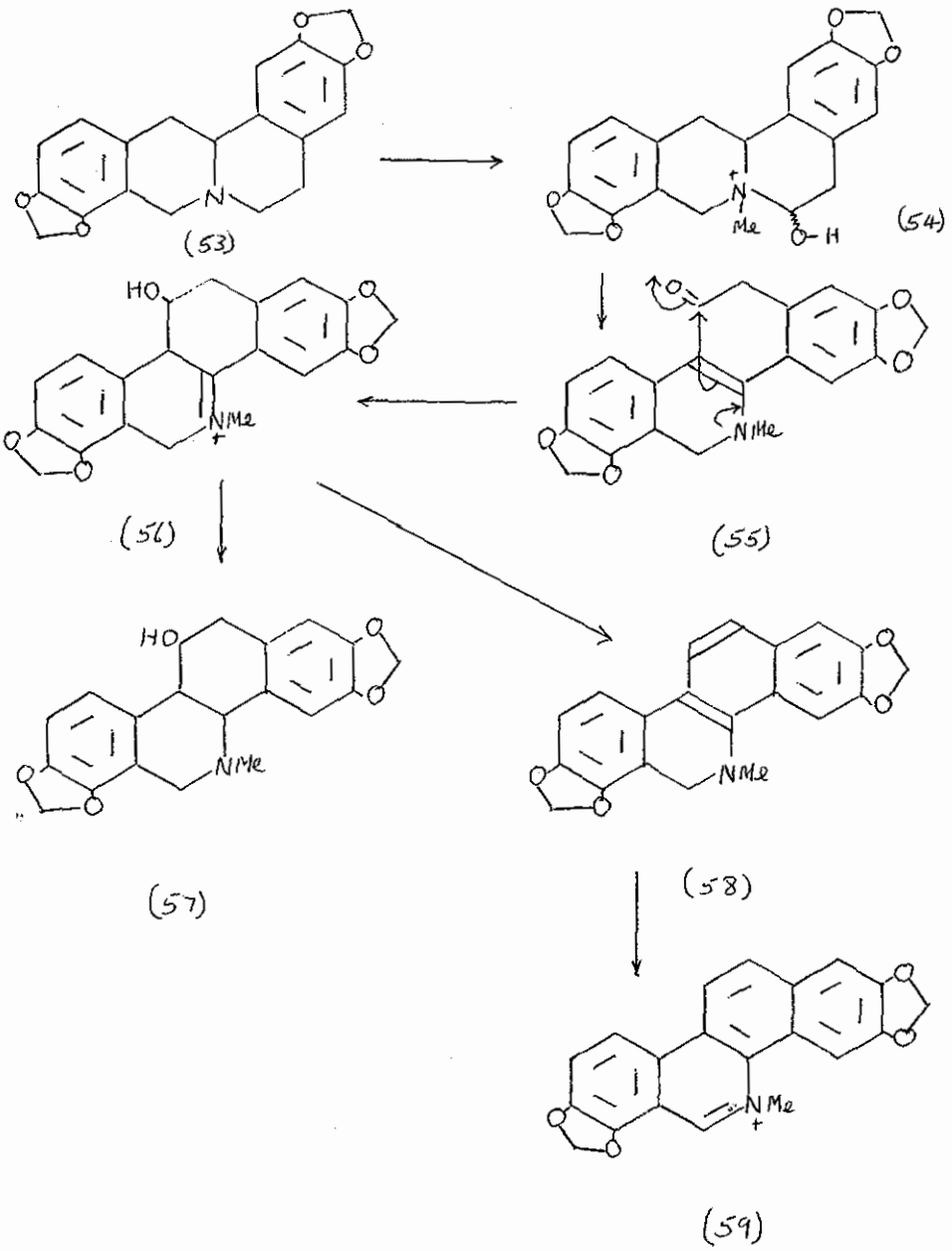
precursor of papaverine. The data are not inconsistent with a demethylation-remethylation sequence which would be necessary if a quinone methide (52) were an intermediate (equation 5).



...Eq. 5

It has been established[57] that in Chelidonium majus chelidonine (57) is derived from (±)-stytopine (53); the intermediates between them probably are (54), (55) and (56) (*Scheme VI*). It is possible that sanguinarine (59)

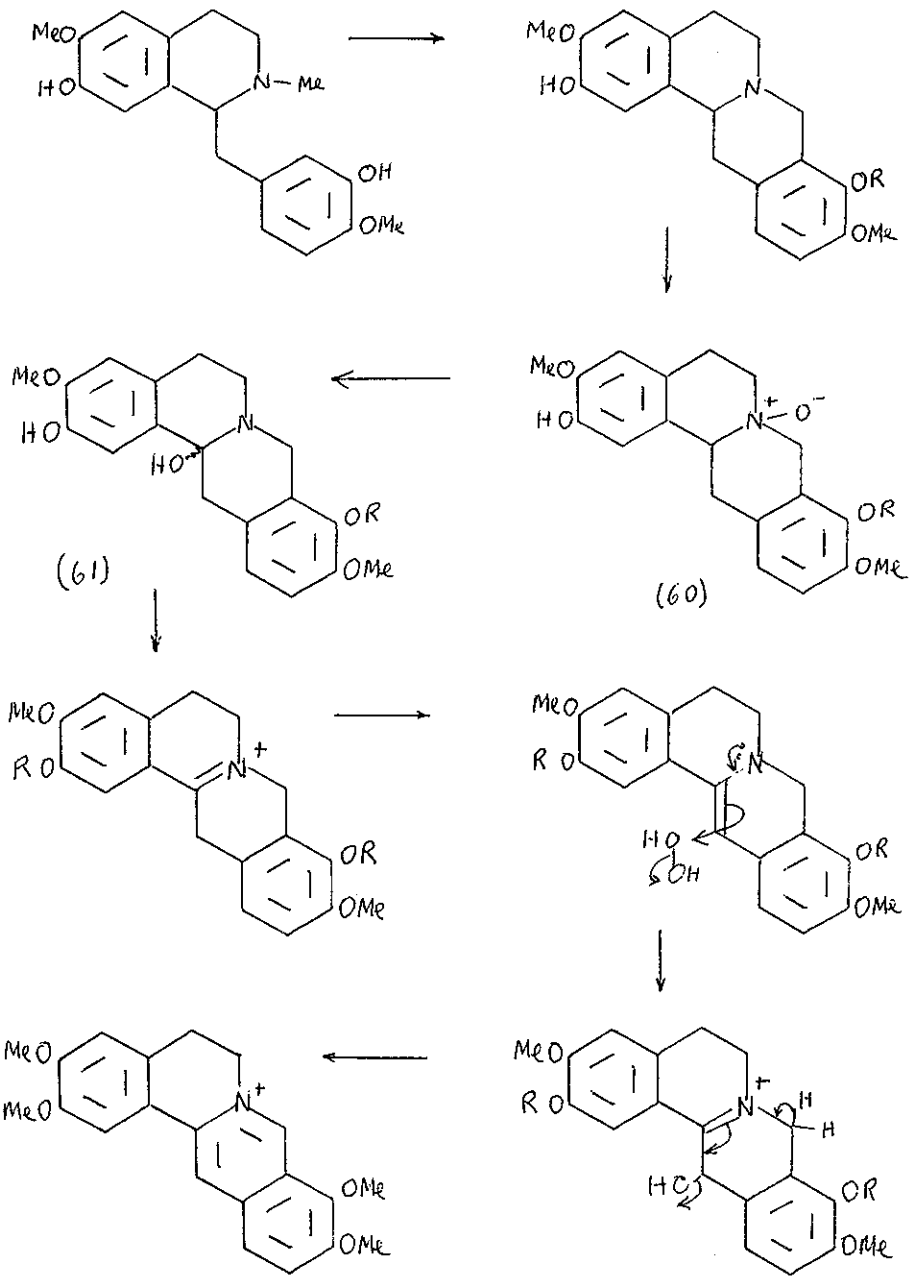
SCHEME VI



is the product from further transformation of chelidonine, but, alternatively, it may arise from an intermediate such as (56), via dihydrosanguinarine (58). Thus, aromatisation of the nitrogen ring in this case is a particularly favoured process.

The formation of protoberberines from the initially formed tetrahydroprotoberberines might involve the initial formation of the N-oxide (60) as depicted in Scheme VII. It is known[58] that tetrahydroprotoberberine N-oxides can be rearranged *in vitro* to the carbinolamine structure (61).

SCHEME VII


MeO
HO
N–Me
OH
OMe
MeO
HO
N
OR
OMe
MeO
HO
N
O⁻
OR
OMe
(60)
MeO
HO
N
HO
OR
OMe
(61)
MeO
RO
N
OR
OMe
MeO
RO
N
HO
OH
OR
OMe
MeO
MeO
N
OMe
OMe
MeO
RO
N
H
H
HC
OR
OMe

Phenol Oxidation

The role of phenolic oxidation in the biosynthesis of many groups of natural products in general, and of alkaloids of the isoquinoline group in particular, cannot be overemphasised. The subject has been reviewed on a number of occasions[4,5,9,10,12-16,59]. Until recently it was assumed[9,10] that the oxidative coupling of phenols involves the generation and pairing of radicals (equation 6), but in a preface to a book on oxidation in organic

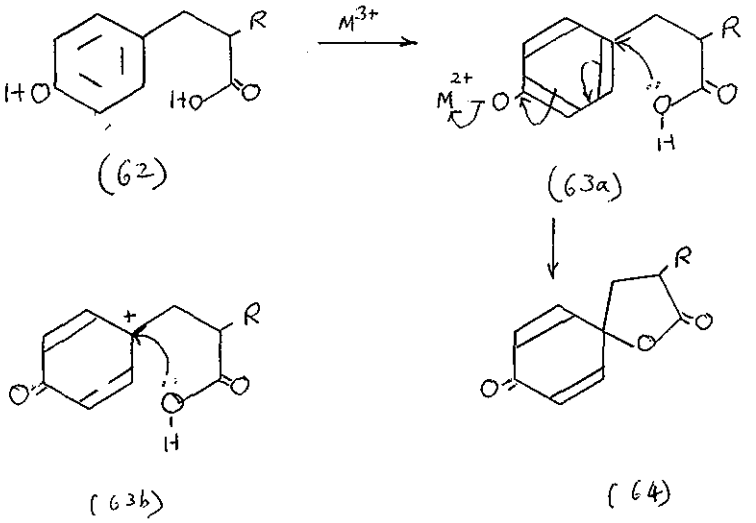
$$ArOH \rightarrow ArO^{-} \xrightarrow{-e} ArO^{\cdot} \qquad \text{..... eq 6}$$

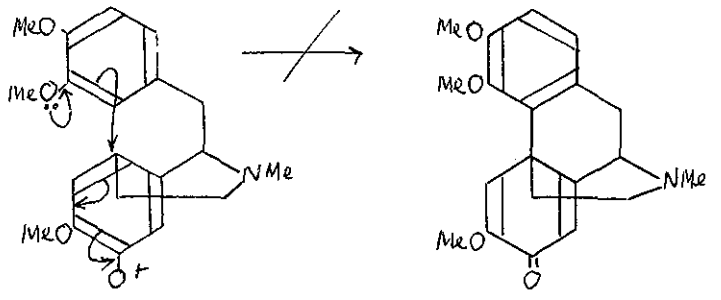
$$\text{then } 2 \times ArO^{\cdot} \rightarrow \left.\begin{matrix} C-O-C \\ C-C \end{matrix}\right) \text{ dimers}$$

chemistry, Barton[60] has briefly reviewed several other mechanisms that have been proposed from time to time, and in a chapter in that book McDonald and Hamilton[61] have examined very carefully the mechanism of phenolic oxidation reactions. In vitro oxidative coupling reactions are usually carried out using one-electron transfer agents (potassium ferricyanide is very commonly used); the evidence in favour of a radical mechanism for many of these reactions is overwhelming[62], but Thyagarajan[63] in his review of ferricyanide oxidations states "although the formation of products ..... is well understood as resulting from the radical substitution or radical pairing of the mesomeric aryloxy radicals, kinetic studies of the oxidation of phenols by ferricyanide show that the dimers could well be represented as arising from condensations between phenol molecules and mesomeric aryloxy cations[64]". Aryloxonium ions have been investigated in the past[65-67], and electrochemical studies have shown[68,69] that two electrons can be removed from a phenol.

Waters[70] points out that aryloxy cations should exist largely as the mesomeric carbonium ion and should be a powerful agent in carbon-carbon bond formation by electrophilic substitution, whereas the neutral radical species, ArO, should exist largely with the odd electron on oxygen and should give rise preferentially to carbon-oxygen coupling.

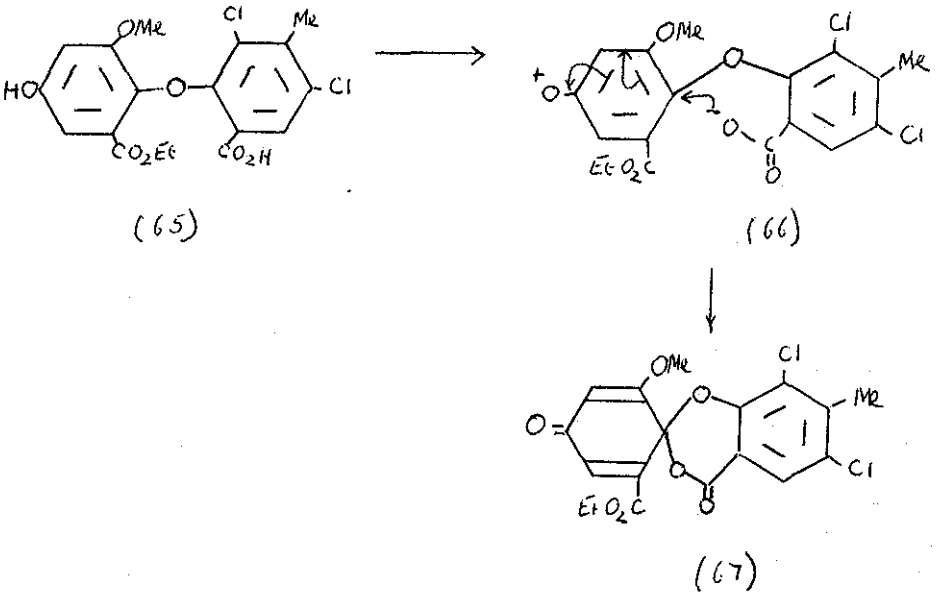
There are some oxidative coupling reactions that are best written as involving the aryoxy cation, or an equivalent species containing a metal to oxygen bond. Thus, oxidation of phloretic acid (62, R=H)[71] and N-carbomethoxytyrosine (62, R=NHCOMe)[72] to (64, R=H) and (64, R=NHCOMe), respectively can be regarded as proceeding through an intermediate (63a) rather than (63b).





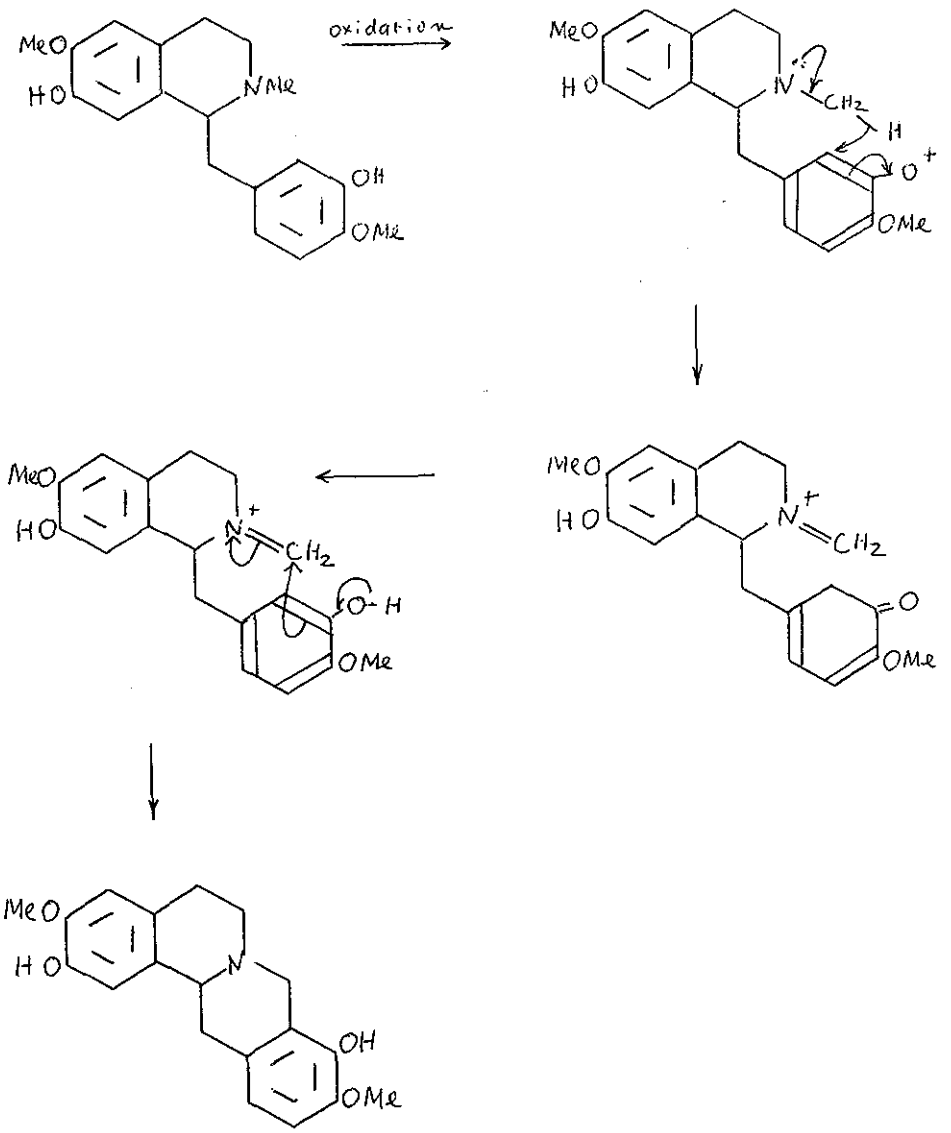
eq. 7

The oxidation[66] of (65) to (67) is best written as proceeding via the cation (66). An aryloxy cation was postulated[42] in the biosynthesis



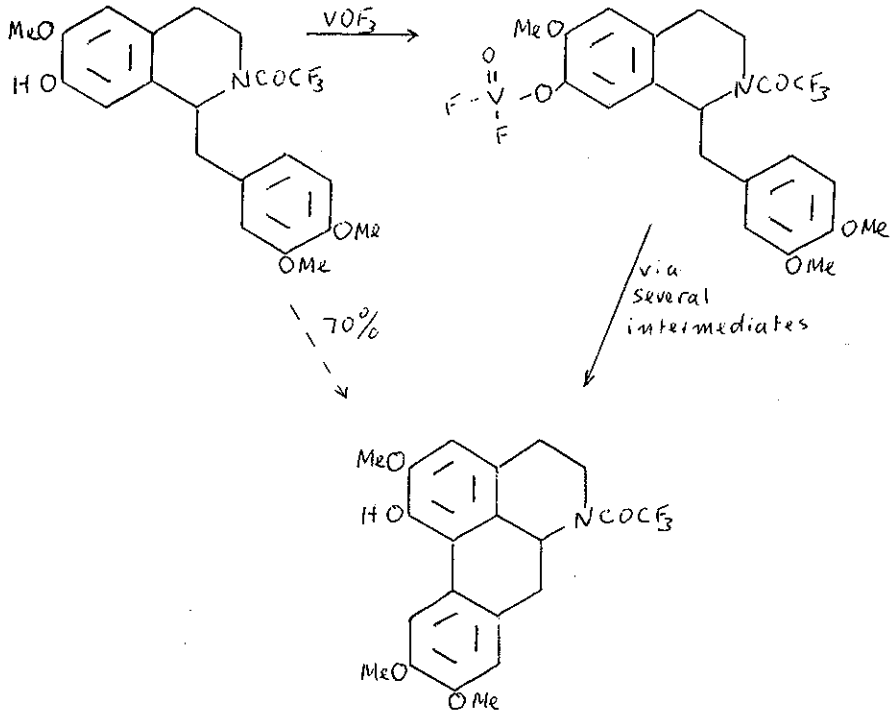
of tetrahydroprotoberberines from reticuline (Scheme VIII). It has been argued, however, that since codamine is not incorporated into thebaine in P.somniferum a cation cannot be involved (equation 7), but it is possible that activation by methoxyl is not sufficient; phenolic hydroxyl or even a phenolate anion may be needed.

SCHEME VIII

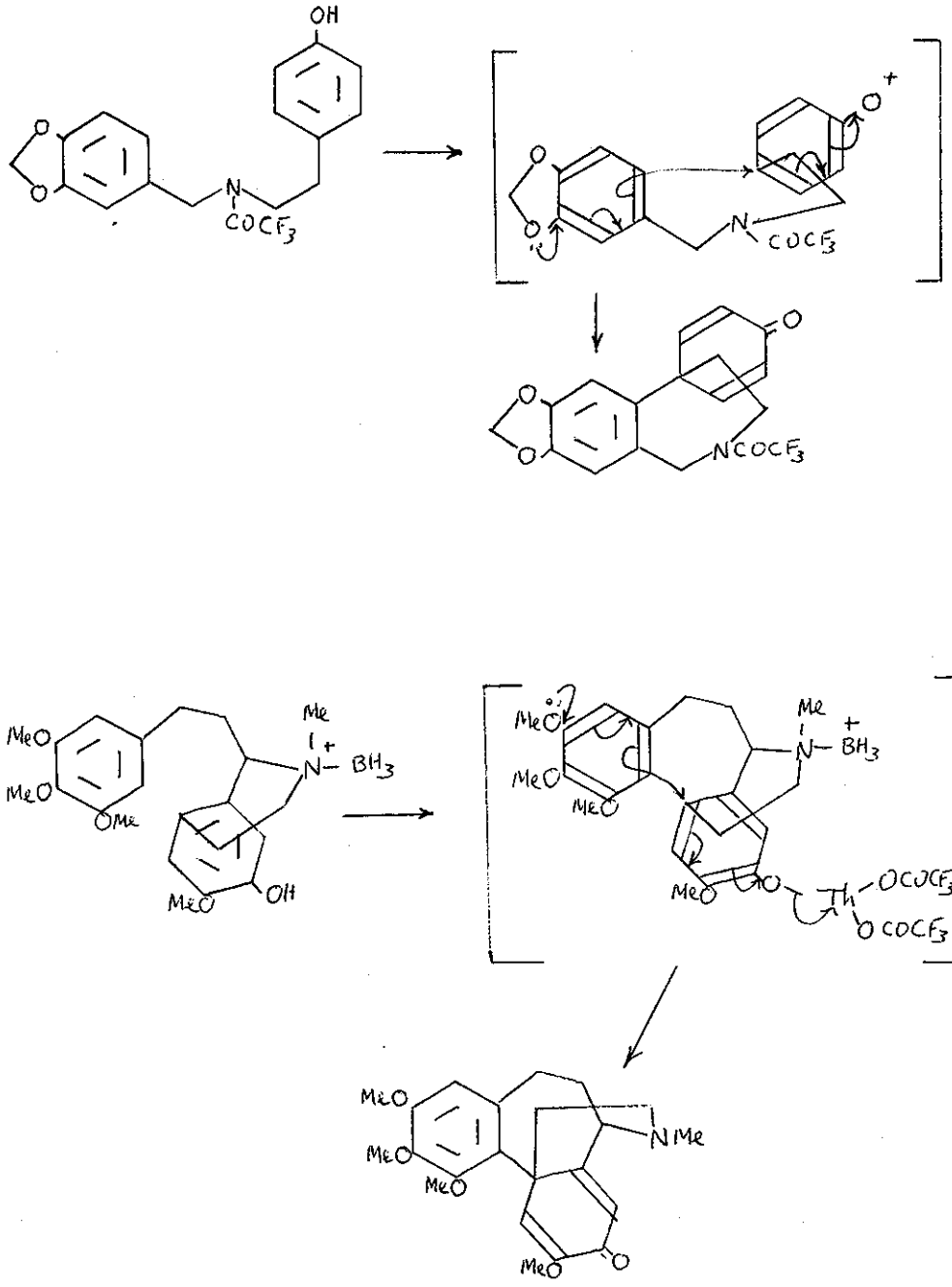

MeO
HO
NMe
oxidation
OH
OMe
MeO
HO
N
CH2
H
O+
OMe
MeO
HO
N+
CH2
O
OMe
MeO
HO
N+
CH2
O-H
OMe
MeO
HO
N
OH
OMe

Oxidative coupling of monophenolic compounds using thallic trifluoracetate[73] and vanadium oxyhalides[74] has recently attracted considerable attention. The reactions (Scheme IX) can be written as involving an aryloxy cation or the equivalent metal complex - a two-electrons process is involved. Yields of coupled products have been very high - in marked contrast to those reactions involving one-electron transfer agents such as ferricyanide[14].

SCHEME IX

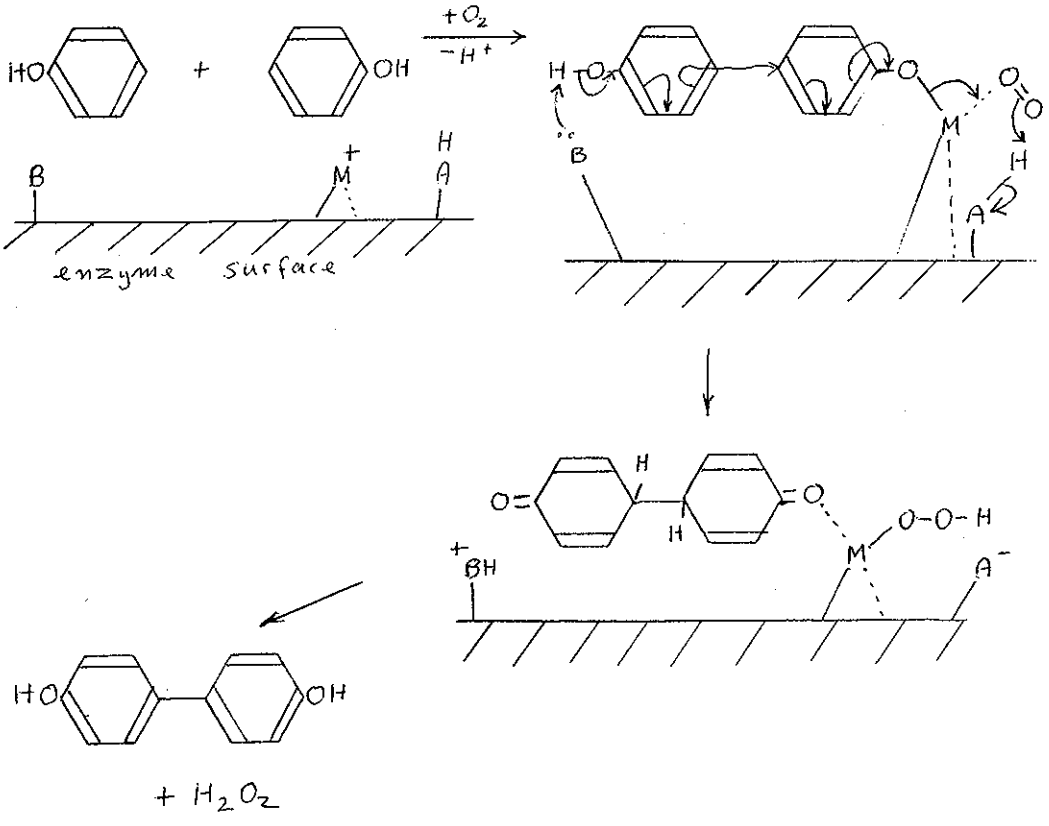


Scheme IX continued



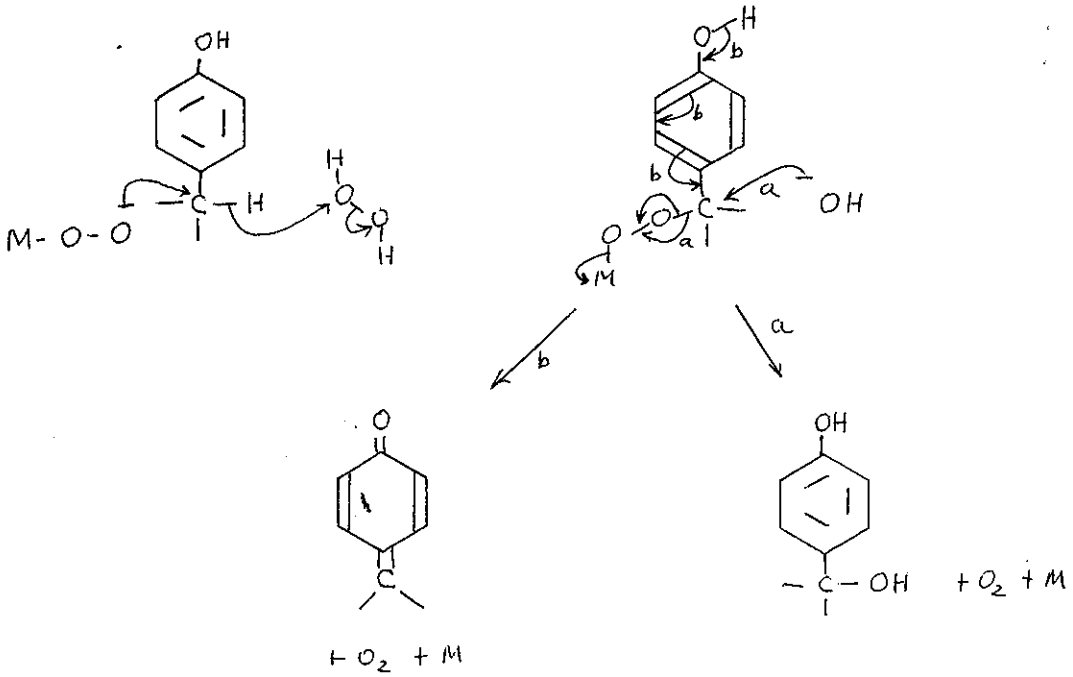
The argument in favour of radical mechanisms for oxidative coupling in vivo has always been that crude extracts of the "oxidase" enzymes, which can bring about phenolic coupling, seemed to be radical in character. The essential reaction has been thought to involve the $Fe^{3+} \rightleftharpoons Fe^{2+} + \epsilon$ couple. However cytochrome P-450, which is probably involved in alkaloid biosynthesis[75] is more complex in character[76,77]. Multi-electron oxidations are involved, where successive one-electron oxidations may be "stored", probably by an oxygen molecule so that the effective oxidant may be O_2^{--}, rather than Fe^{3+}. The mechanism of the coupling reaction can then be depicted[78] as in Scheme X.

SCHEME X



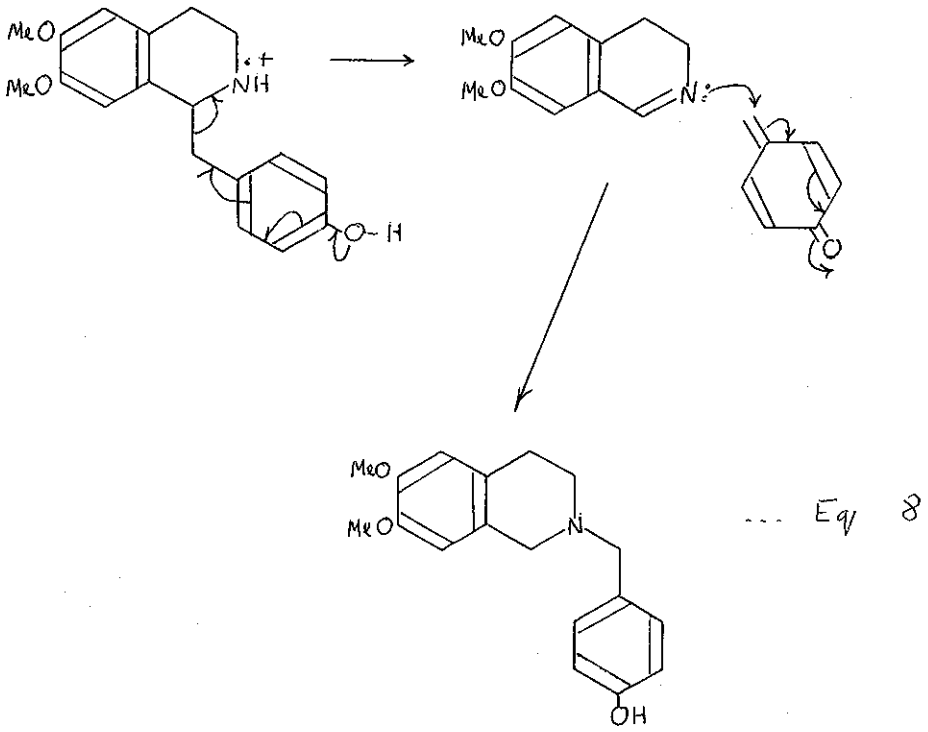
When a benzylic carbon-hydrogen bond is available an alternative site of attack can lead to the benzylic alcohol or the quinone methide (Scheme XI).

SCHEME XI



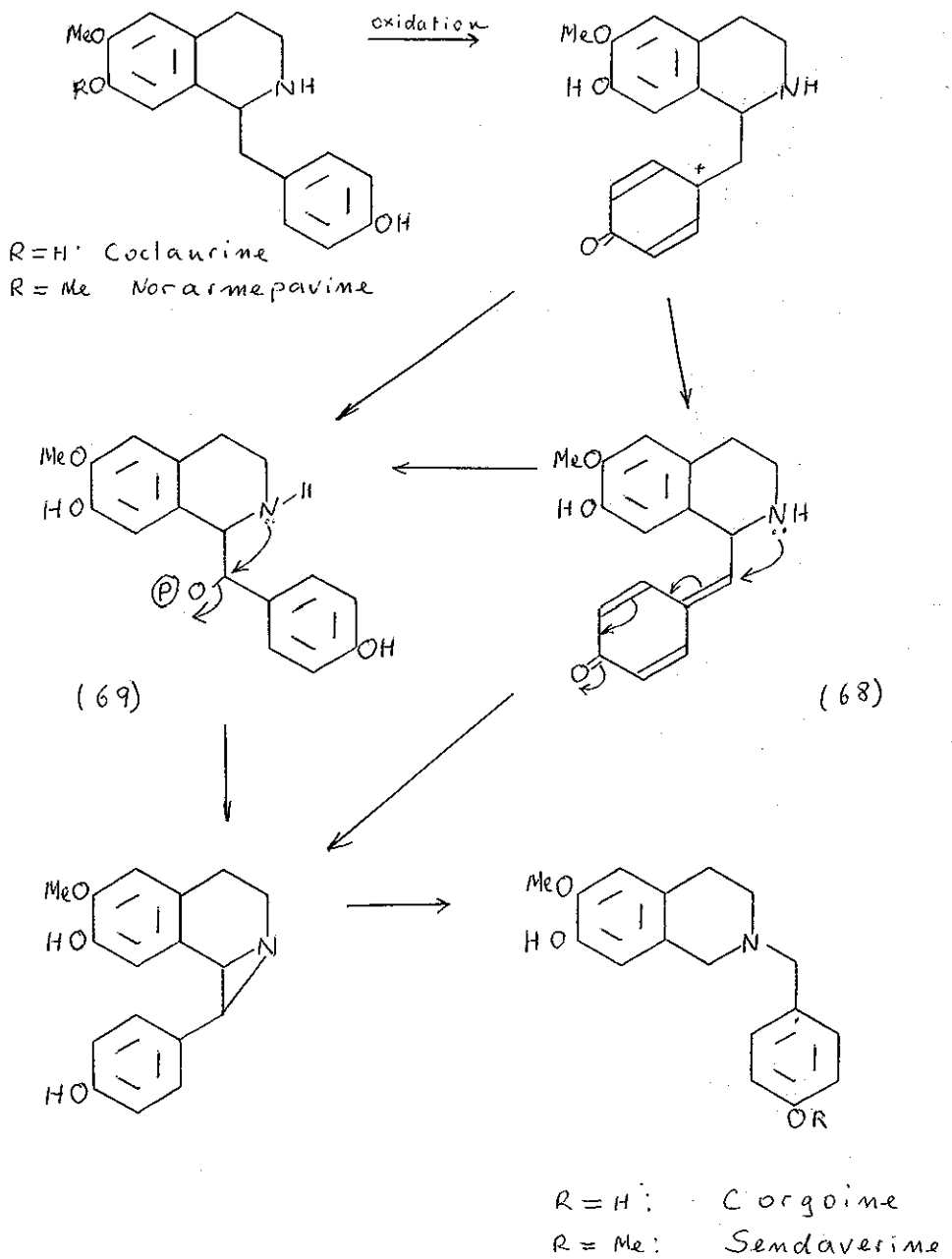
If the intermediacy of aryloxy cations is accepted it is possible to rationalise some otherwise puzzling biosynthetic sequences in the

isoquinoline alkaloids. Thus the 2-benzylisoquinolines sendaverine[79,80] and corgoine[81] might arise from the 1-benzyl isomers, for example coclaurine, either from a quinone methide (68) or the equivalent benzyl alcohol (69)(Scheme XII). When norarmepavine was oxidised with peroxidase and H_2O_2[82] one of the products was O-methylsendaverine. A diradical intermediate was postulated to account for this reaction (equation 8).

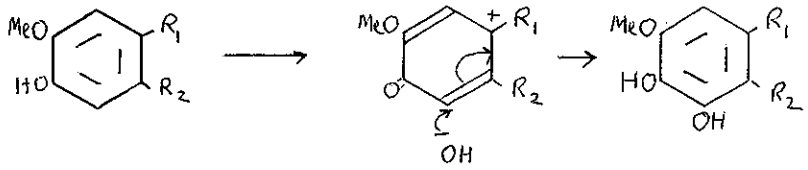


... Eq 8

SCHEME XII

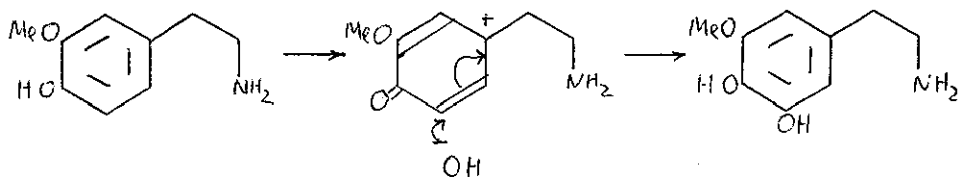

MeO
RO
NH
OH
oxidation
MeO
HO
NH
R=H : Coclaurine
R = Me Norarmepavine
MeO
HO
N
H
O
OH
(69)
MeO
HO
NH
O
(68)
MeO
HO
N
HO
MeO
HO
N
OR
R = H : Corgoine
R = Me : Sendaverine

If a mono ether of a 4,5-dialkylcatechol is oxidised and hydroxylated in an ionic process, the product obtained can be rationalised as shown in equation 9 .



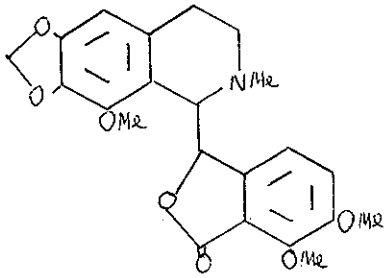
eq 9

The trioxyphenethylamines that are known[83-85] to be on the pathway to the "simple" tetrahydroisoquinolines can be generated as shown in equation 10.

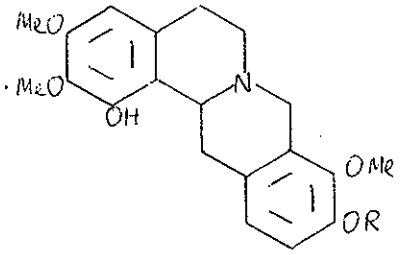


... eq 10

The derivation of narcotine (70), and some tetrahydroprotoberberines, such as capaurine (71) and capaurimine (72) are easily rationalised in the same way, with hydroxylation occurring probably at the 1-benzyltetrahydroisoquinoline stage (equation 11). If the alternative quinone methide can be



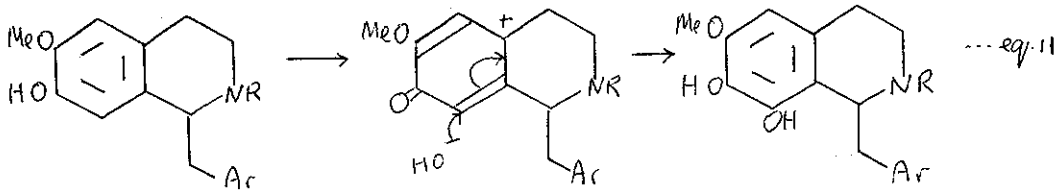
(70)



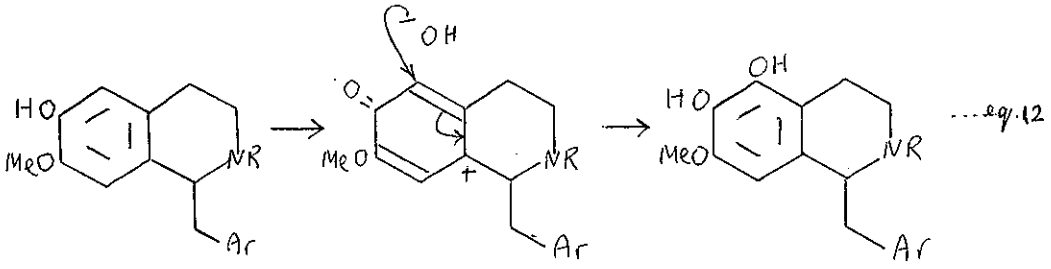
(71), R = Me

(72), R = H

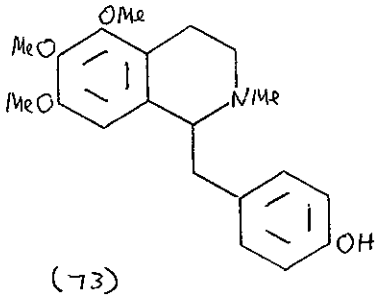
formed (equation 12), the oxygenation patterns of thalifendlerine (73) and takatonine (74) are also explained. The occurrence of 3-oxyaporphines



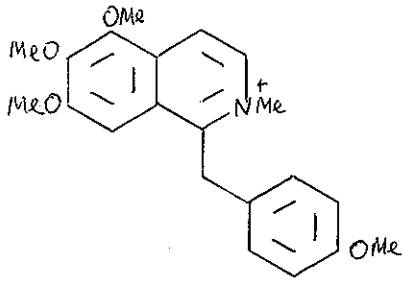
...eq.11



...eq.12

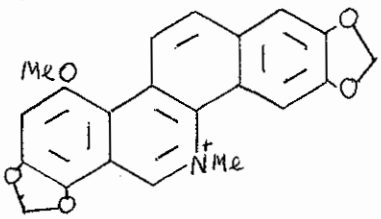


(73)



(74)

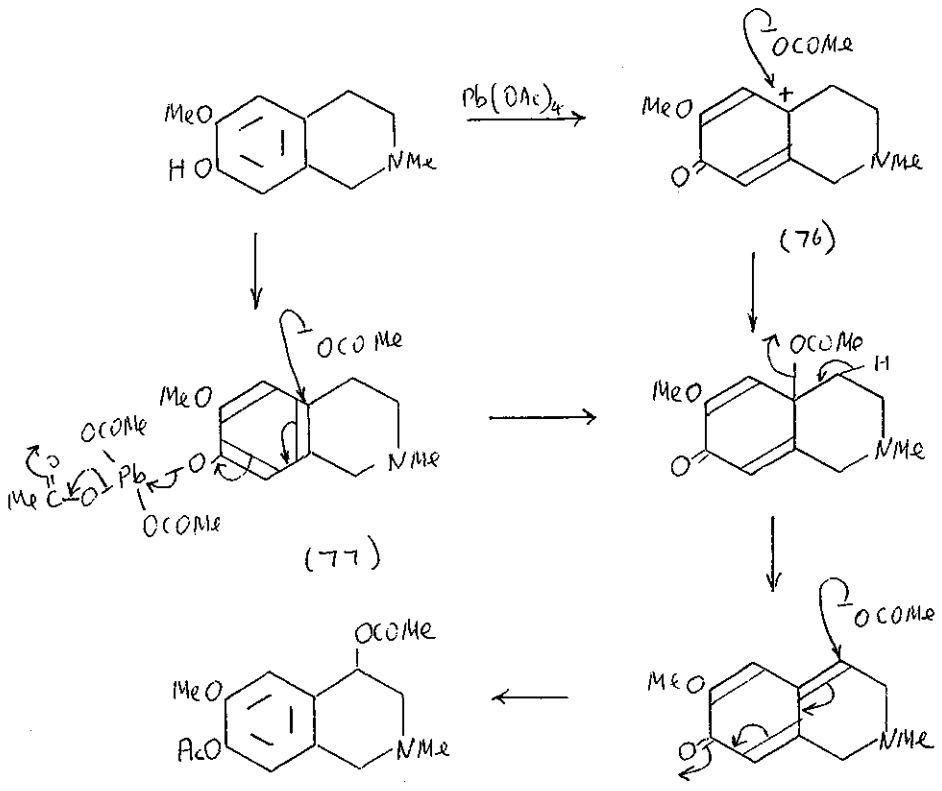
may also be rationalised in a similar way. It has recently been realised[86] that some of the penta-oxybenzo[c]phenanthridine alkaloids such as chelirubine are more properly represented with the fifth oxygen function at C_{10}, for example (75) rather than at C_{11} as hitherto. The biosynthetic origin of these compounds is not yet known.



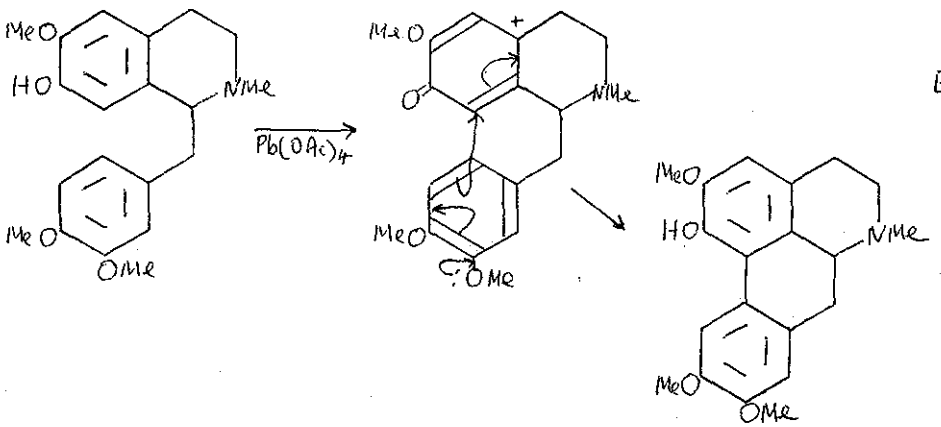
(75)

When 7-hydroxytetrahydroisoquinolines are treated with lead tetraacetate, the 4-acetoxy derivative is produced[53] and this reaction can be written as involving the cation (76), although the processes summarised in (77) may be preferred (Scheme XIII).

SCHEME XIII


MeO
HO
NMe
Pb(OAc)4
OCOMe
MeO
O
NMe
(76)
OCOMe
MeO
OCOMe
Me C
O
Pb
O
OCOMe
NMe
(77)
OCOMe
MeO
H
NMe
O
OCOMe
MeO
O
NMe
OCOMe
MeO
AcO
NMe

The reaction has been applied to the synthesis of aporphines[87] (equation 13).



Eq. 13

It might be worthwhile considering the biosynthesis of aporphines to involve aryloxy cations instead of the diradical processes usually aasumed. The latter concept requires two separate one-electron oxidations at different sites in the molecule. It is difficult to envisage such oxidations occurring from two different haem units in one enzyme; the alternative, two separate oxidations from one haem unit by movement of the 1-benzylisoquinoline radical to bring the second site into position, is hard to visualise. Annelations could be more simply effected by a two-electrons oxidation at the same site on the substrate molecule.

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