# CHEMICAL AND BIOCHEMICAL ASPECTS OF ISOQUINOLINE ALKALOIDS

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Abstract —— Some chemical and biochemical aspects of isoquinoline alkaloids are reviewed.

## INTRODUCTION

Since the isolation of morphine by Sertürner in 1805, a tremendous amount of chemical study in the field of isoquinoline alkaloids has been carried out. Other aspects of isoquinoline alkaloids have evolved from research on their biosynthesis, metabolism and biotransformation. Discovery of tetrahydroisoquinoline derivatives in mammalian tissue (Mammalian TIQ Alkaloids) gave rise to speculation that their in vivo formation causes alcoholic addiction and mental disorders in Parkinsonism[1-6]. Therefore we would like to account for the mammalian alkaloids, the biosynthesis of isoquinoline alkaloids and related chemistry as follows.

(1) Mammalian Isoquinoline Alkaloids
(2) Biosynthesis and Biotransformation of Isoquinoline Alkaloids
  (a) Cactus Alkaloids
  (b) Benzylisoquinoline Alkaloids
  (c) Berberine Alkaloids and Related Alkaloids
  (d) Morphine Alkaloids
  (e) Aporphine Alkaloids
  (f) Enzymic Phenol Oxidation
  (g) Biotransformation with Mammalian Enzymes
(3) Mimic Chemical Reactions
  (a) Phenolic Cyclisation
  (b) Phenol Oxidation
  (c) Redox Reaction Involving N-Oxides

## (1) Mammalian Isoquinoline Alkaloids

The resemblance of the symptoms occurring upon withdrawal of either alcohol or the opium alkaloids would indicate the possibility that addiction to these chemicals is very similar.[7] The metabolite of alcohol, acetaldehyde, competitively inhibits the action of the enzyme aldehyde dehydrogenase which oxidises the aldehydes derived from catecholamines to the corresponding carboxylic acids.[8,9] With excessive concentrations of aromatic aldehydes in the brain, Pictet-Spengler condensation with dopamine could form 1-benzyltetrahydroisoquinolines, such as tetrahydropapaveroline (4), which can then undergo further transformation to morphine (5) or other complicated isoquinoline alkaloids.

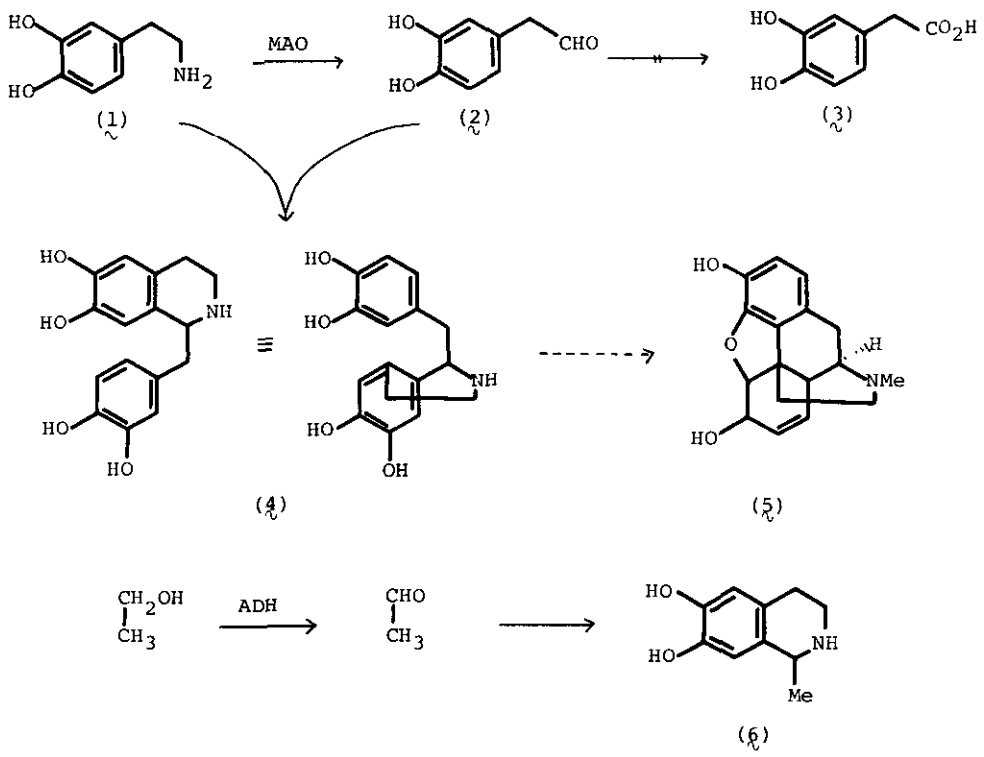
In a test of this hypothesis, Davis and Walsh carried out incubation studies with brain stem homogenates.[7] It was demonstrated that $^{14}$C-dopamine (1) was converted to $^{14}$C-tetrahydropapaveroline (4) in 47 % yield and further, that the transformation increased to 58, 64 and 65 % on addition of acetaldehyde, 0.5, 1.0 and 2.0 mM, respectively. This result indicated that acetaldehyde causes accumulation of 3,4-dihydroxyphenylacetaldehyde (2) which led to the formation of tetrahydropapaveroline (4). In this experiment $^{14}$C-salsolinol (6) was also formed by direct condensation of dopamine and acetaldehyde.[7] A small amount of salsolinol (6) was also formed when the acetaldehyde was replaced by ethanol, a result of which indicated that an alcohol dehydrogenase (ADH) is present in the homogenate.[10]

Scheme 1

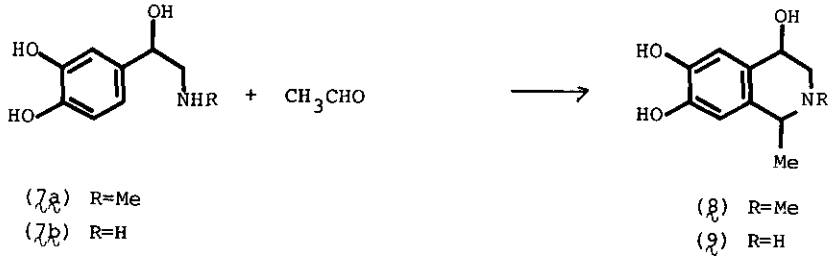
Furthermore, cow adrenal gland, which is known to be rich in adrenalin (7a) and noradrenalin (7b), was perfused with a dilute solution of acetaldehyde to produce the tetrahydroisoquinoline alkaloids (8 and 9) whose formation was determined by tlc analysis. These alkaloids are known to exhibit phamacological actions such as excitation, narcosis, blood pressure changes, and convulsions.[11]

Scheme 2

The above interesting hypothesis, regarding the physical dependence of alcohol due to formation of isoquinoline derivatives, is questioned by Haluskka[12], Seevers[13] and Goldstein[14]. The main problem was that the physical effects of alcohol ingestion are substantially different from those resulting from morphine uptake and that no




Scheme 1




Scheme 2

specific mutual cross dependence or cross tolerance exists between morphine-like drugs and ethanol.

Furthermore, since phenolic phenethylamines readily react with carbonyl compounds as described in Chapter (3), it is possible that the cyclisation in the above *in vitro* experiment occurred non-enzymatically.

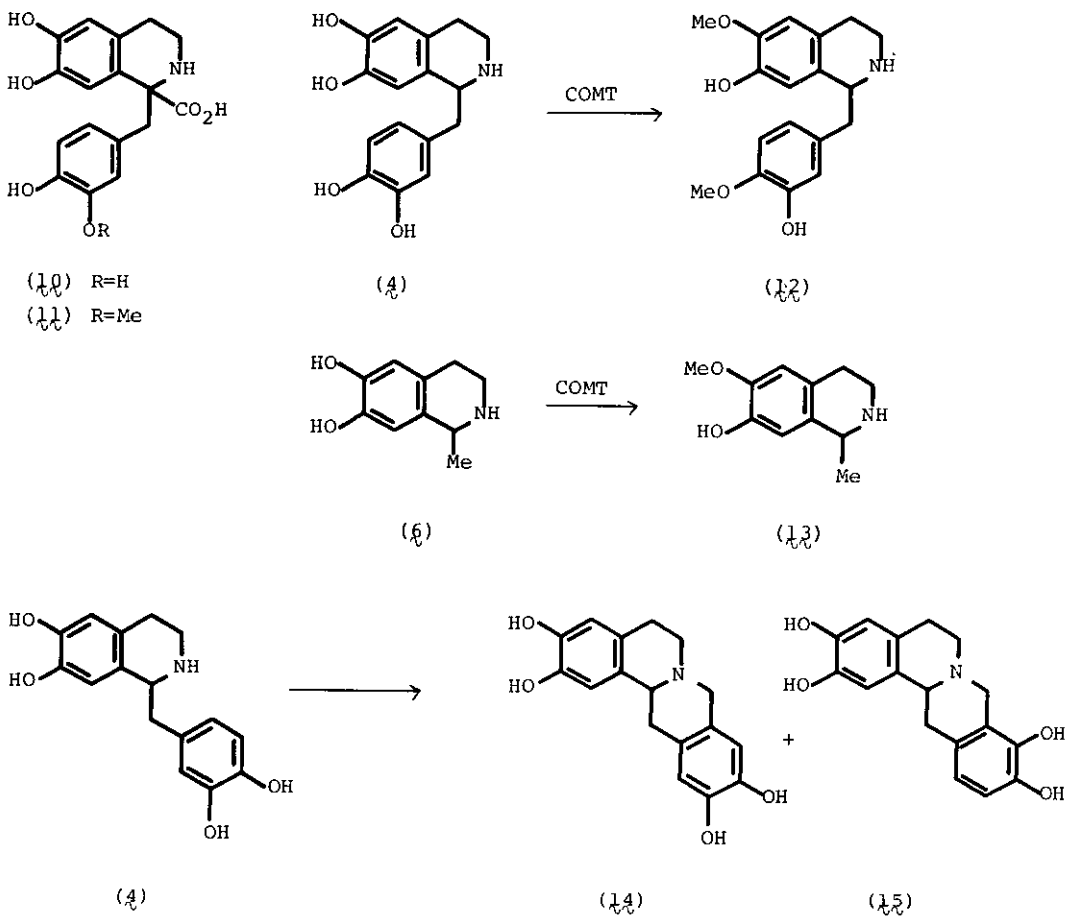
Sourkes attributed the mental disorders of Parkinson's disease after the medicinal use of L-dopa to the formation of aporphine derivatives.[15] Salsolinol (6) and tetrahydropapaveroline (4) were found in significant concentration in the urine of patients with Parkinson's disease during oral L-dopa treatment. The formation of the alkaloids was detected by gas chromatography of their pentafluoropropionyl derivatives.[16] Tetrahydropapaveroline (4) was also found in the central nervous system of animals injected with L-dopa or dopamine in addition to ethanol.[17] Tetrahydroisoquinoline-1-carboxylic acids (10 and 11) were also detected in the urine of Parkinsonian patients under L-dopa therapy.[18] The formation of these amino acids was proved by mass fragmentographical techniques after esterification with pentafluoropropanol and acylation of the phenolic and amino groups with heptafluorobutyric anhydride. The existence of these amino acids in brain of rats after treatment with L-dopa was confirmed by a tracer experiment.[18] Tetrahydropapaveroline (4) and salsolinol (6) were converted by catechol O-methyl-transferases (COMT) to norreticuline (12) and isosalsoline (13).[19] It was further demostrated that tetrahydropapaveroline (4) was transformed *in vivo* by rats, and by rat-liver and brain preparations in the presence of S-adenosyl-L-methionine (SMA), to protoberberine alkaloids (14 and 15). The latter alkaloids were also identified in the urine of Parkinsonian patients receiving L-dopa therapy by gas chromatographical analysis after silylation.[20]

Scheme 3

## (2) Biosynthesis and Biotransformation of Isoquinoline Alkaloids

### (a) Cactus Alkaloids

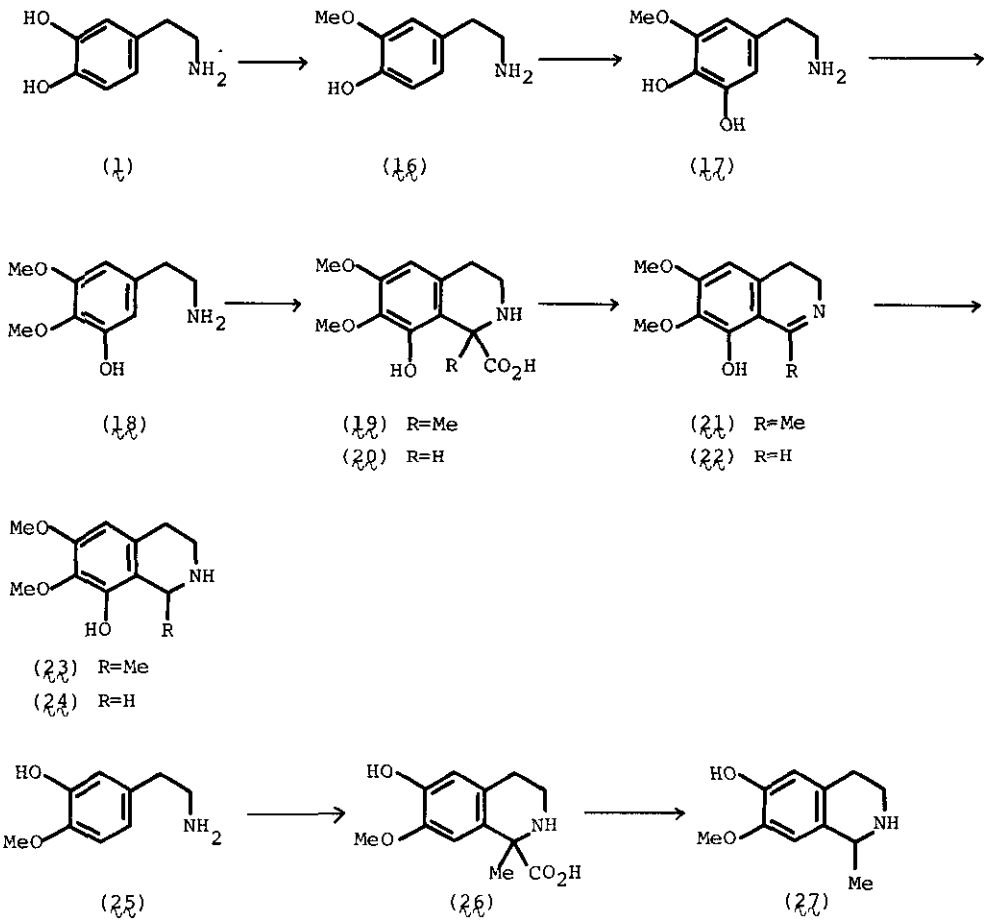
The nitrogen of anhalonidine (23) and anhalamine (24) is derived from dopamine (1). O-Methylation of dopamine to produce 16 is followed by hydroxylation, and methylation of the resulting diphenol (17) gives 3,4-dihydroxy-5-methoxyphenethylamine (18).[21-23] There are two possibilities for the conversion of 18 to the alkaloids (23 and 24); (A) the direct condensation of the amine (18) with the corresponding




Scheme 3

aldehydes; (B) the reaction of 18 with keto acids followed by decarboxylation. Kapadia showed the latter to be the case in the biosynthesis of cactus alkaloids.[24] Decarboxylation of the amino acids, peyoruvic acid (19) and peyoxylic acid (20), occurs in an oxidative manner to form the corresponding imines (21 and 22). Salsoline (27) is also biosynthesised, from 25 , via the carboxylic acid (26).[25]

Scheme 4




(1) (16) (17)

(18) (19) R=Me (20) R=H (21) R=Me (22) R=H

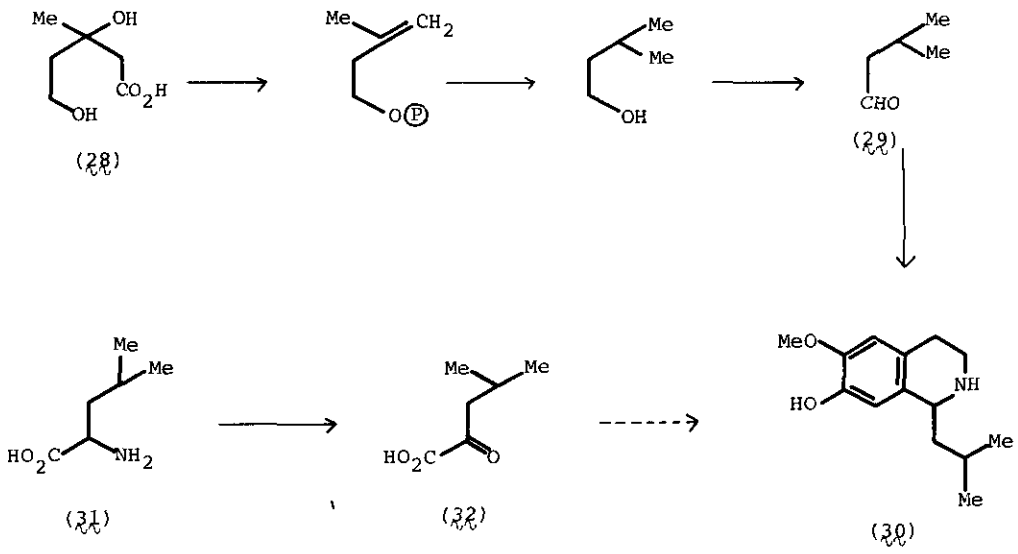
(23) R=Me (24) R=H

(25) (26) (27)

Scheme 4

On the other hand, lophocerine (30) is formed by condensation of the phenethylamine and the aldehyde (29) derived from mevalonic acid (28). It is not likely that the keto acid (32) from leucine (31) is the precursor.[26]

Scheme 5



Scheme 5

(b) Benzylisoquinoline Alkaloids

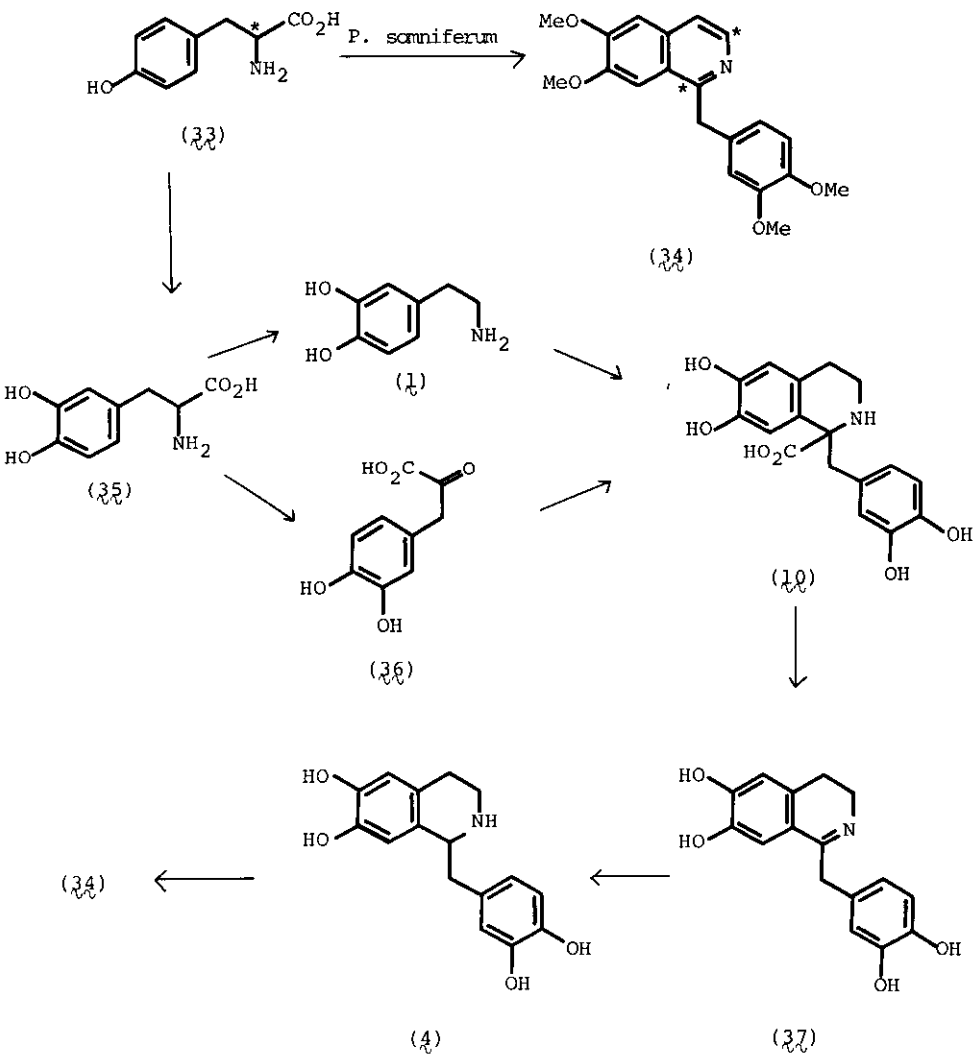
The benzylisoquinoline alkaloids in opium are biosynthesised from two molecules of tyrosine (33). *Thus tyrosine (33) labeled with carbon-14 at the* $C_2$ position was incorporated, in Papaver somniferum, into papaverine (34) labeled at the $C_1$ and $C_3$-positions.[27]

*Dopa (35), derived from tyrosine (33),* is converted to dopamine (1) and to the phenylpyruvic acid (36). Condensation of these two compounds (1 and 36) affords the amino acid (10), which is transformed to tetrahydropapaveroline (4) by oxidative decarboxylation followed by reduction of the resulting imine (37). The formation of the amino acid (10) from dopa and dopamine was demostrated in P. orientale,[28] while the transformation of 10 into 4, and into morphine (5), was proved in P. somniferum.[29] Therefore the direct formation of 4 by condensation of 1 with the corresponding aldehyde is not considered to be a main pathway in plants.

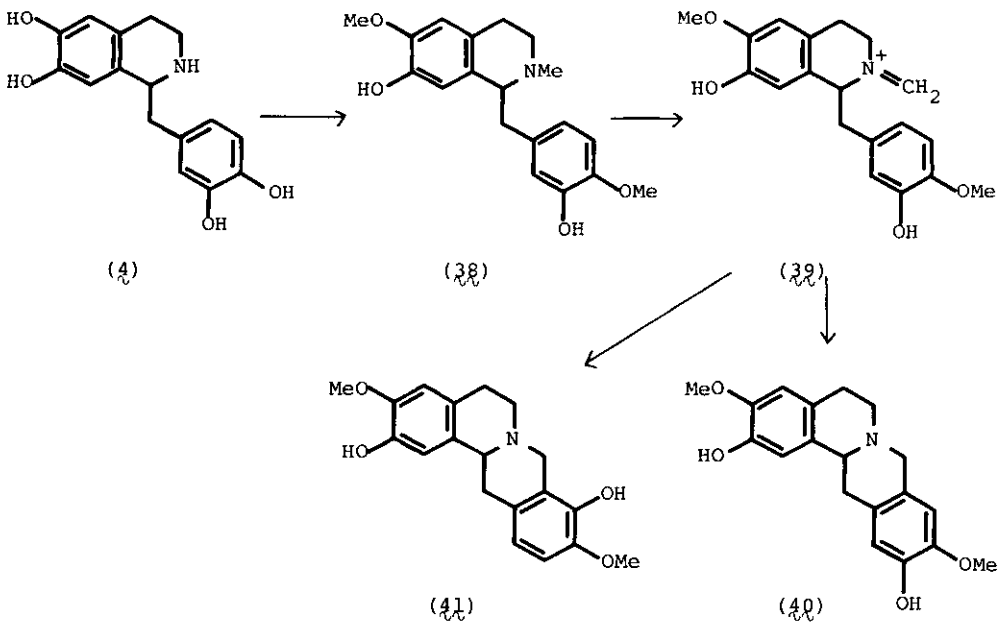
Scheme 6

(c) Berberine Alkaloids and Related Alkaloids

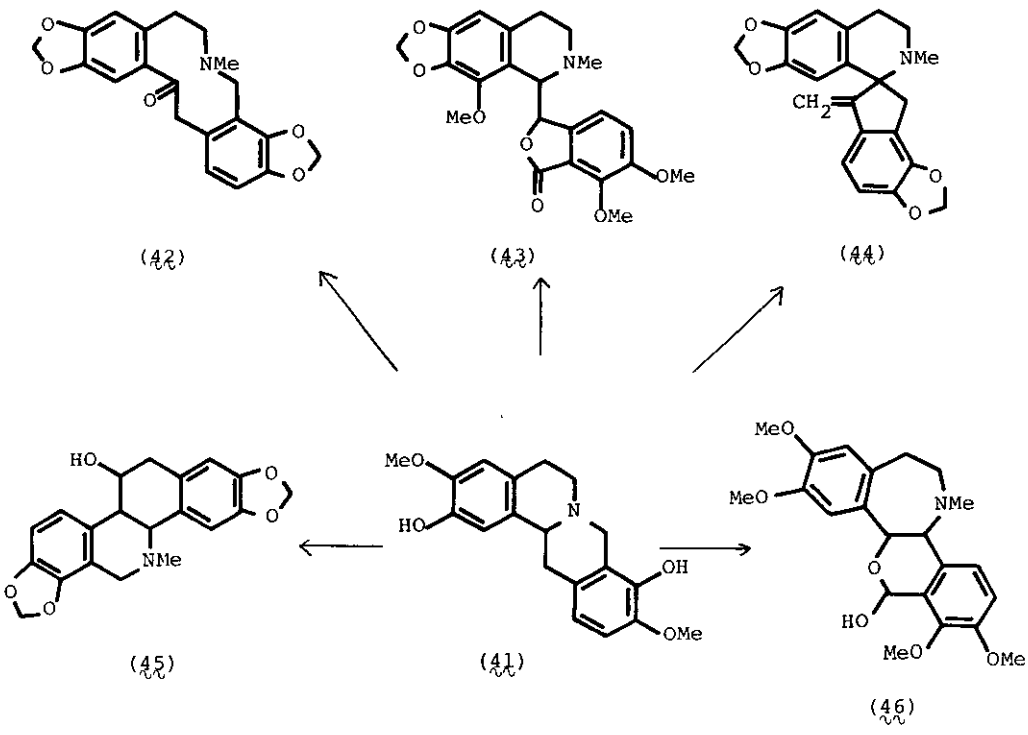
Methylation of tetrahydropapaveroline (4) forms reticuline (38) which was shown to be a precursor of berberine alkaloids.[30] Thus the N-methyl group of reticuline is oxidised to produce imine (39)[31,32] which cyclises to coreximine (40)[33] and




Scheme 6




Scheme 7




Scheme 8

scoulerine (41).[34]

Scheme 7

Furthermore, scoulerine (41) is known to be a precursor of several types of alkaloid, namely protopine (42)[35], phthalideisoquinoline (43)[35], spirobenzylisoquinoline (44)[36], benzophenanthridine (45)[36] and rheadan alkaloids (46)[37].

Scheme 8

(d) Morphine Alkaloids

The two enantiomers of reticuline (38) were efficiently incorporated into morphine (5)[38]. Its dehydro derivative (47) was also shown to be a precursor of morphine alkaloids.[39] Para-ortho coupling of reticuline forms salutaridine (48) which is converted to morphine (5) through salutaridinol (49), thebaine (50), codeinone (51) and codeine (52)[40,41]. It was shown that certain enzyme systems in P. somniferum are not substrate specific by virtue of the in vivo conversion of unnatural codeine derivative to corresponding morphine analogues.[42] Para-para coupling of reticuline yields pallidine (53)[43], which is transformed to flavinantine (54) by rearrangement of the O-methyl group.[44]

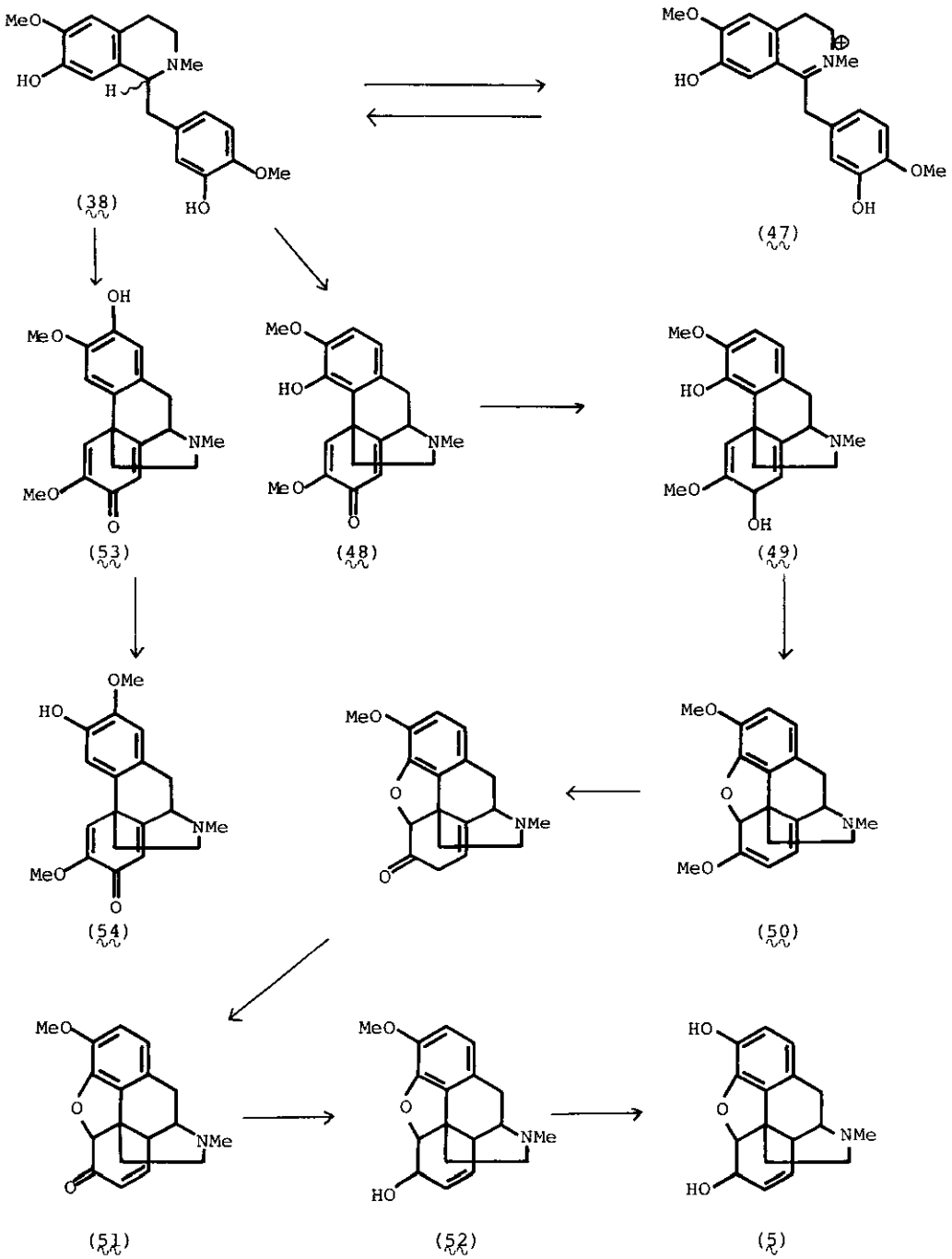
Scheme 9

(e) Aporphine Alkaloids

There are two possible routes for the biosynthesis of aporphine alkaloids; (A) the direct formation of aporphine alkaloids by phenol oxidative coupling; (B) their formation through the dienone derivatives (proaporphines). Ortho-papa coupling of reticuline forms isoboldine (55)[45] which leads to boldine (56).[46] Magnoflorine (58)[47] and bulbocapnine (59)[48] are derived by ortho-ortho coupling of reticuline and the intermediate must be corytuberine (57).

*Scheme 10*

Isothebaine (61)[49], corydine (64)[50], glaucine (66)[50] and dicentrine (67)[50] are biosynthesised according to the latter route, which involves the dienol-benzene or


MeO
HO
NMe
H
OMe
HO
(38)
MeO
HO
NMe
OMe
OH
(47)
OH
MeO
NMe
MeO
O
(53)
MeO
HO
NMe
MeO
O
(48)
MeO
HO
NMe
MeO
OH
(49)
OMe
HO
NMe
MeO
O
(54)
MeO
O
NMe
O
MeO
O
NMe
MeO
(50)
MeO
O
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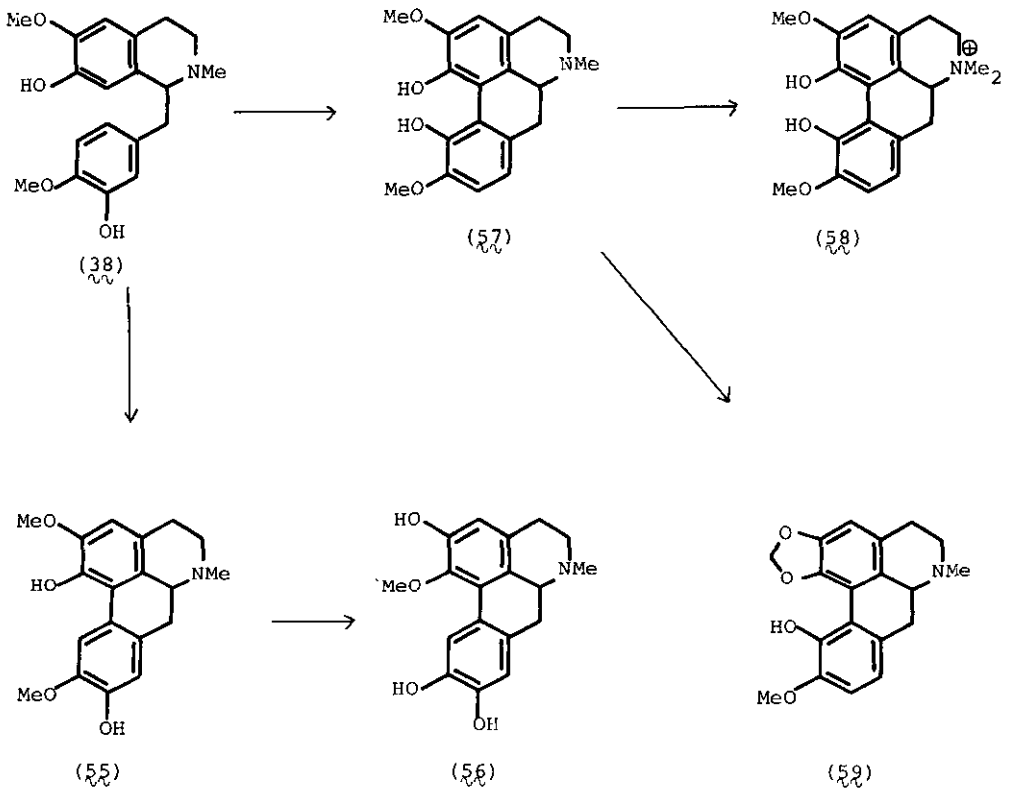
O
MeO
O
NMe
HO
HO
O
NMe
HO
(51)
(52)
(5)

Scheme 9



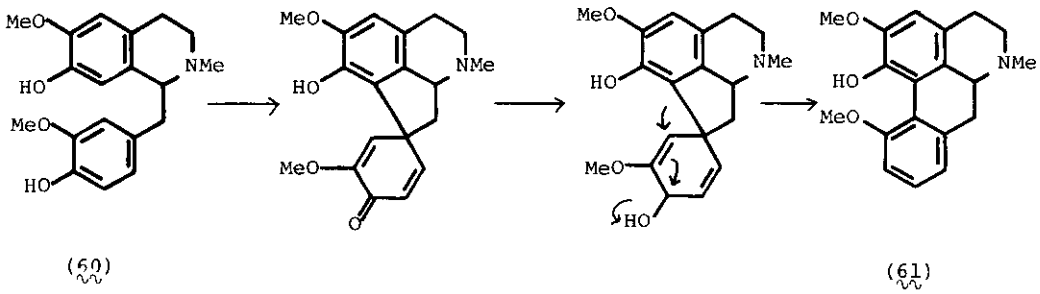

Scheme 10

dienone-phenol rearrangement as shown in Scheme 11.

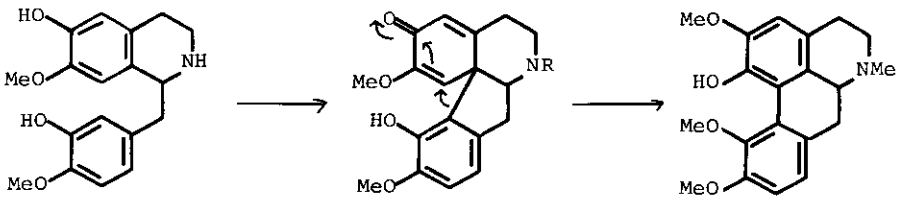
Scheme 11

## (f) Enzymic Phenol Oxidation

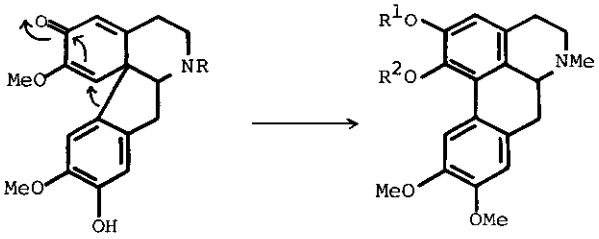
Enzymic phenol oxidation in plants is mainly conducted by tyrosinases, laccases and peroxidases. The former two enzymes contain copper ion. From epr studies it was shown that the state of the copper ion in tyrosinases is monovalent throughout the reaction and that activated molecular oxygen is the actual oxidising species. On the other hand, the oxidation state changes during the reaction of laccases; the phenol is oxidised by divalent copper to the phenoxy radical.




(60) (61)




(62) (63) (64)




(65)

(66) $R^1=R^2=Me$
(67) $R^1+R^2=CH_2$

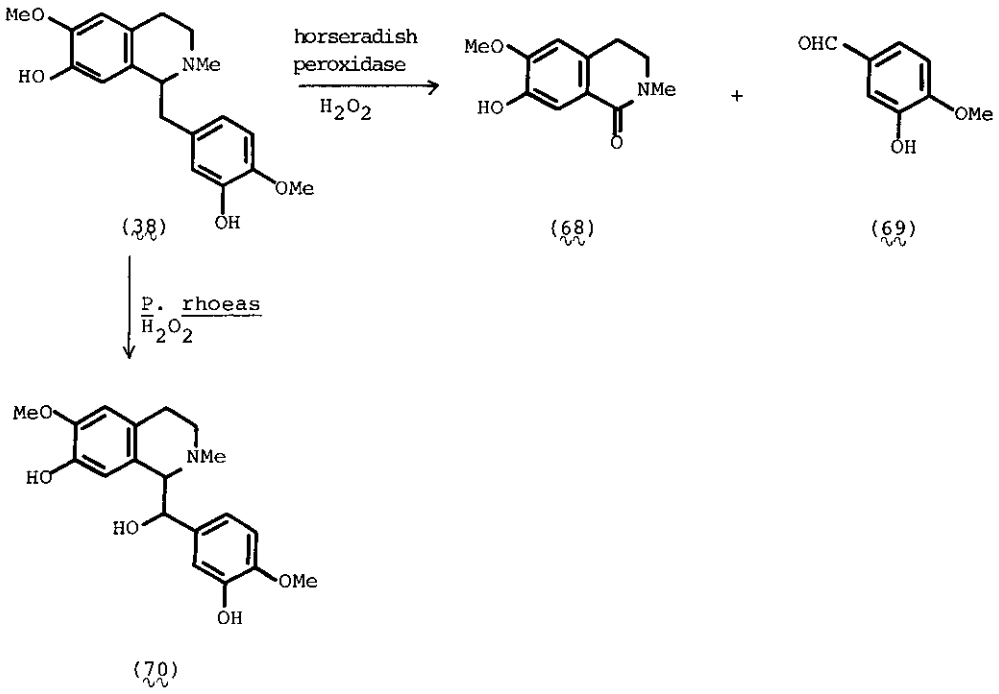
Scheme 11

Peroxidases involve iron porphyrin and require hydrogen peroxide. In vitro phenol oxidation of isoquinoline alkaloids has been mainly carried out using the peroxidases. On treatment with horseradish peroxidase in the presence of hydrogen peroxide at pH 7.5 and 20°C, reticuline (38) afforded thalifoline (68) along with the aldehyde (69).[51] β-Hydroxyreticuline (70) was obtained by reaction with the homogenate of P. rhoeas.[52]

Scheme 12

N-Methylcoclaurine (71) gave the dimer (72) and the trimer (73) by reaction with the homogenate of potato peelings in the presence of hydrogen peroxide at pH 4.8.[53] Oxidation of 71 with horseradish peroxidase and hydrogen peroxide followed by reduction with sodium borohydride yielded the dimer (74), coupled head to head, together with corypalline (75) and the rearranged product (76).[54]

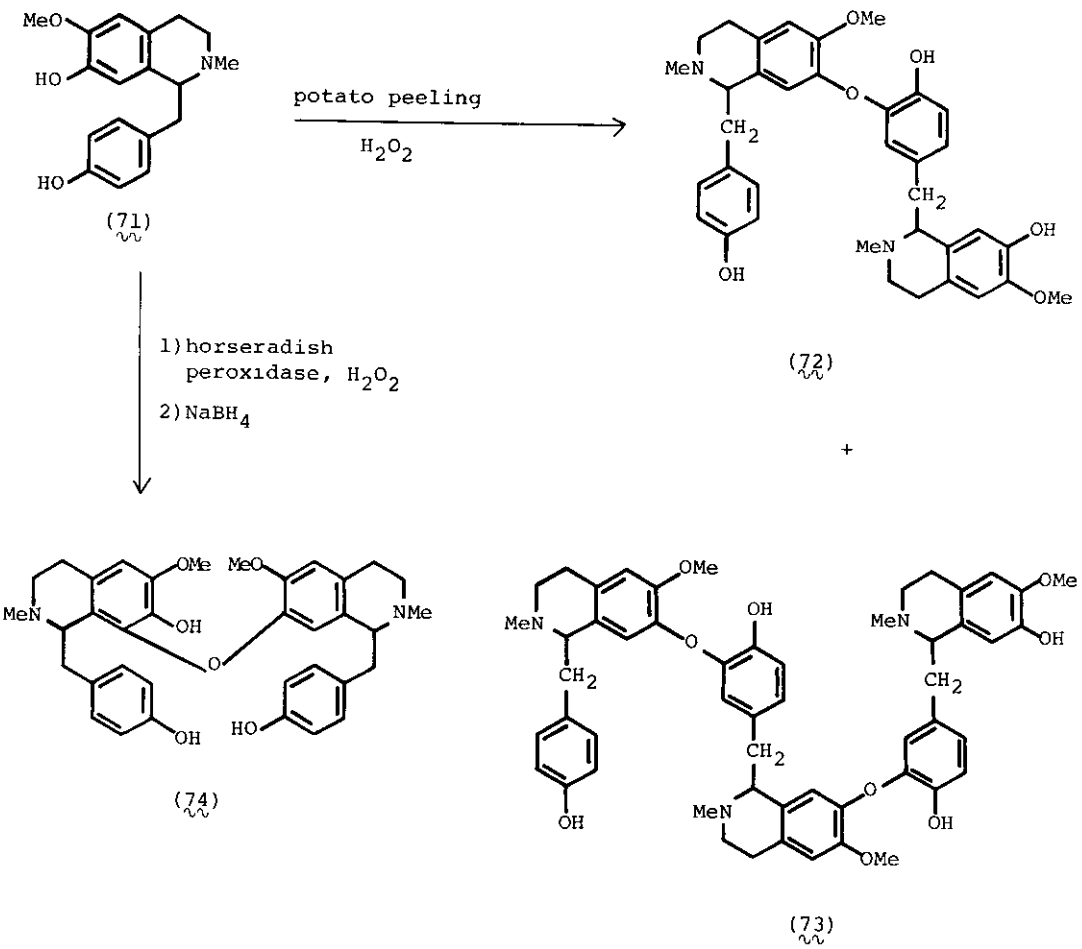
Scheme 13




(38) (68) (69)

(70)

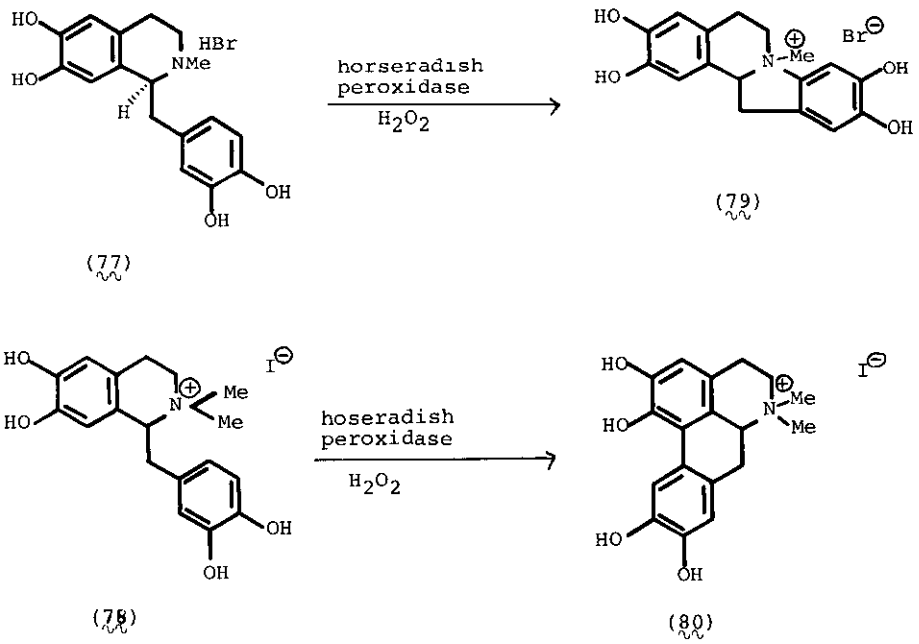
Scheme 12


potato peeling
$H_2O_2$
1) horseradish peroxidase, $H_2O_2$
2) $NaBH_4$
(71)
(72)
(73)
(74)
(75)
(76)

Scheme 13

Intramolecular coupling was observed in the oxidation of tetrahydropapaveroline derivatives using pure horseradish peroxidase and hydrogen peroxide.[55] Thus (+)-laudanosoline hydrobromide (77) and (-)-laudanosoline methiodide (78) gave the dibenzopyrrocoline (79) in 81 % yield and the aporphine (80) in 50 % yield, respectively.

Scheme 14



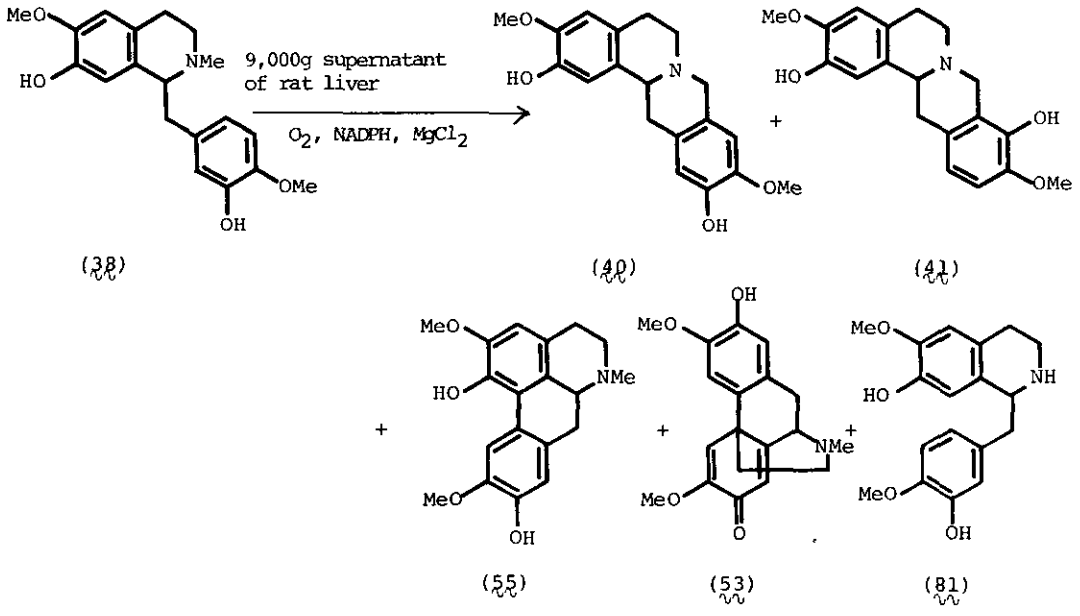

Scheme 14

(g) Biotransformation with Mammalian Enzymes

Initially we observed the presence of coreximine (40) in the urine of rats injected with (+)-reticuline (38).[56] The alkaloid was identified by gas chromatography and mass spectrometry. Using the supernatant of rat liver homogenate, the formation of coreximine (40) and scoulerine (41) was then confirmed by tracer experiments. The coreximine formed was a racemate, a result of which was confirmed by application of the reverse dilution method.[57] Transformation of reticuline to protoberberine alkaloids proceeded effectively on addition of NADPH and magnesium chloride. Using a practical amount of reticuline, the phenol oxidative products, isoboldine (55) and pallidine (53), were obtained in addition to coreximine (40) (22.24 %) and scoulerine (41) (7.41 %).[58]

Oxygen was required in the above enzymatic reactions. Production of the N-nor-compound (81) was also observed and yields increased on the addition of NADPH.[57]

Scheme 15




(38) (40) (41)

(55) (53) (81)

Scheme 15

Laudanosine (82) was converted less effectively to xylopinine (83) and tetrahydropalmatine (84) along with norlaudanosine (85).[57] Deuterium labelling experiments confirmed that the N-methyl group was incorporated into the berberine bridge at the $C_8$-position.[58] The berberines and the N-nor-products could be formed through the imine intermediate (86).

Scheme 16

(3) Mimic Chemical Reactions

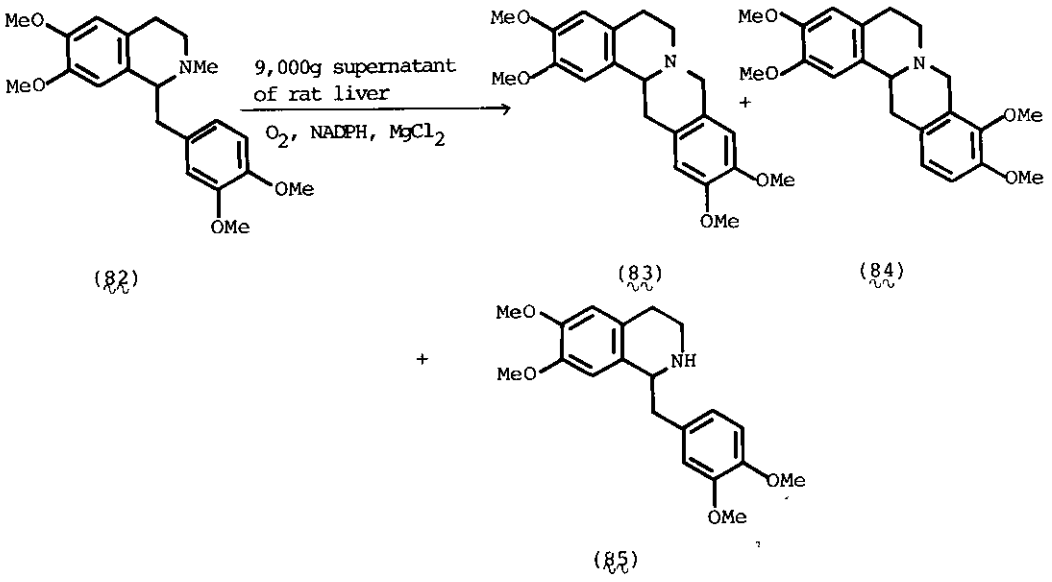
(a) Phenolic Cyclisation

Ordinary Pictet-Spengler reaction is carried out under acidic conditions and is frequently used for the synthesis of isoquinoline and protoberberine derivatives.[59] If the position of cyclisation is to be para or ortho to a phenolic hydroxy-group, no acid catalyst is required for phenolic cyclisation.[60] Thus 2-amino-1-(3-hydroxyphenyl)ethanol (87) reacted with acetone to give the isoquinoline (88) in 79 % yield. Heating norreticuline (81) with formalin in ethanol yielded coreximine (40).[60] The position of cyclisation depends on pH and temperature. Reaction of norreticuline with formalin at pH 6.3 and room temperature formed a mixture of coreximine (40) and scoulerine (41) in a 1 : 2 ratio.[61]

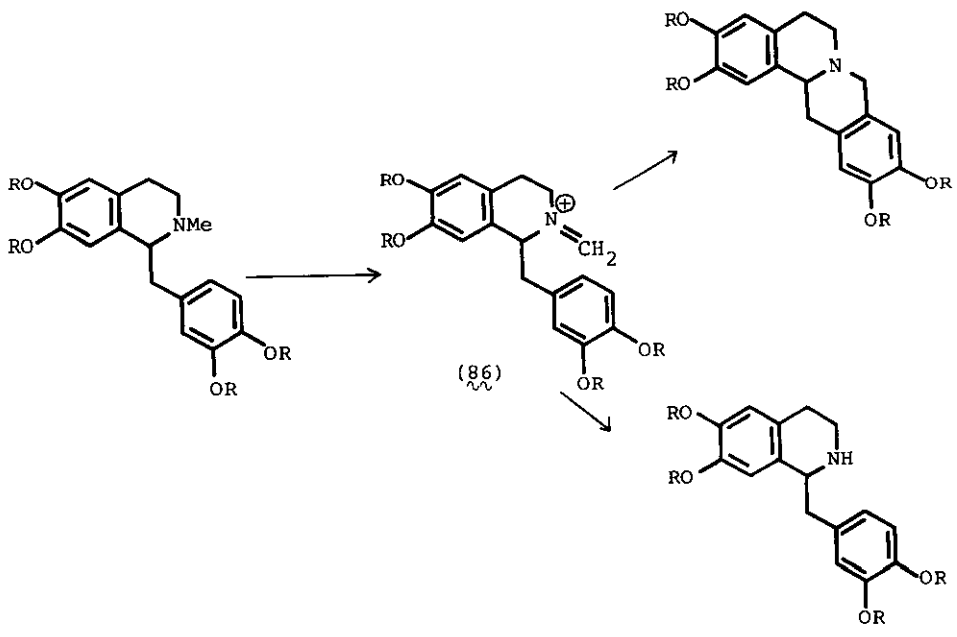
Scheme 17

Reaction of the phenolic base (89, R=H) with formalin at pH 6.4 and room temperature produced the two positional isomers (90 and 91, R=H) in a ratio of 1 : 4. The latter (91) was converted into the alkaloid (±)-kikemanine (92).[62] Capaurimine (93) was also synthesised from the phenol (89, R=$OCH_2Ph$) using a similar procedure.[63] The mono phenolic base (94) reacted with acetaldehyde in hot acetic acid to form (±)-corytenchirine (95) and its positional isomer (97) in a 3 : 1 ratio, together with trace amounts of their stereoisomers.[64] Condensation of 94 with propionaldehyde yielded 96 and 98 in a ratio of 1 : 2.[65]

Scheme 18

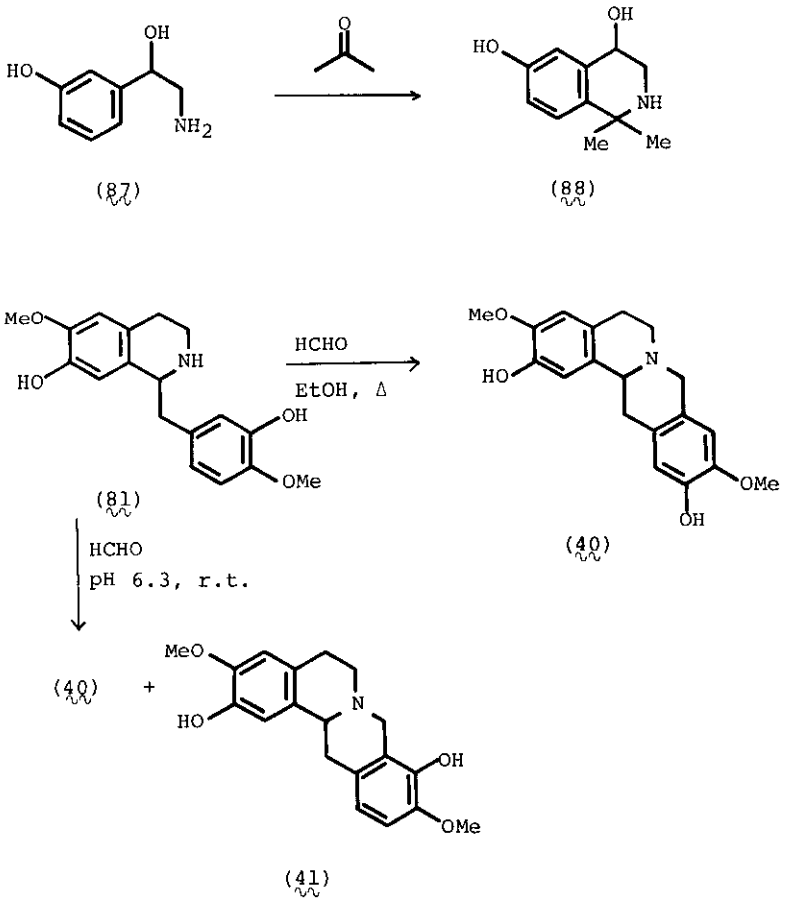



(82) (83) (84) (85)

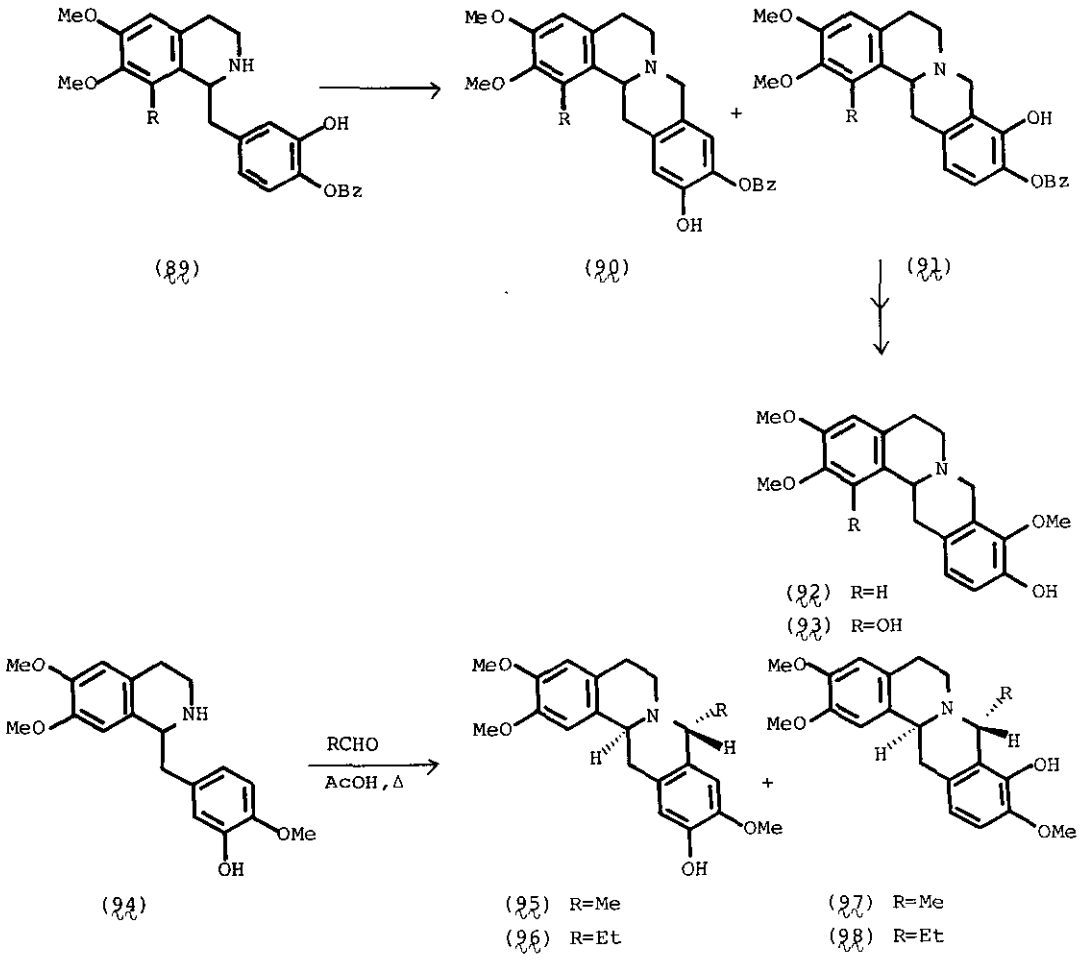



(86)

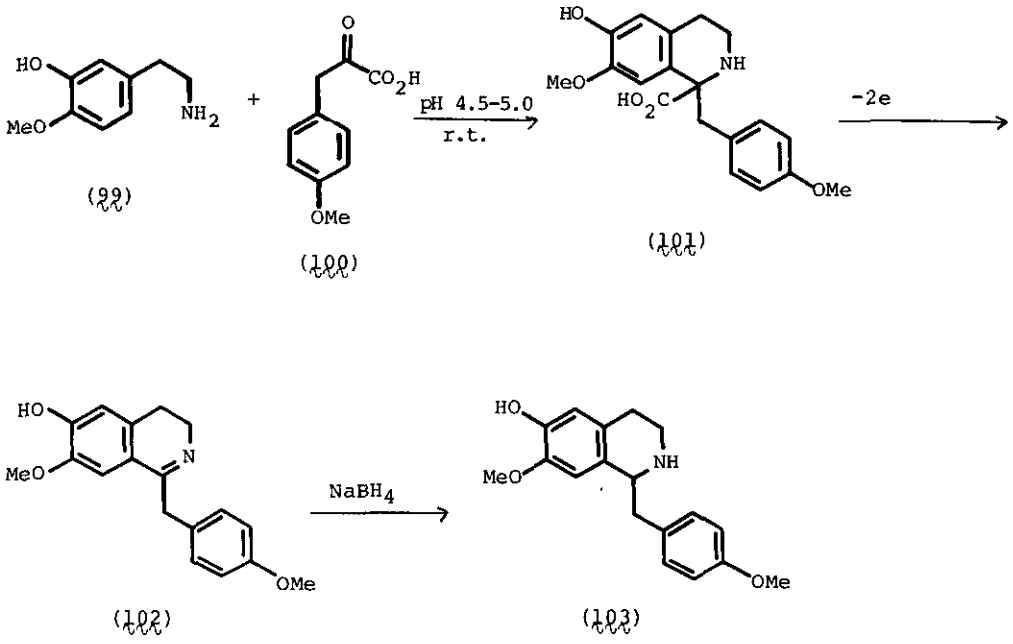
Scheme 16


HO
OH
NH2
O
HO
OH
NH
Me
Me
(87)
(88)
MeO
HO
NH
OH
OMe
HCHO
EtOH, Δ
MeO
HO
N
OMe
OH
(81)
(40)
HCHO
pH 6.3, r.t.
(40)
+
MeO
HO
N
OH
OMe
(41)

Scheme 17


MeO
MeO
R
NH
OH
OBz
(89)
N
OH
(90)
(91)
OMe
(92) R=H
(93) R=OH
RCHO
AcOH, Δ
H
(94)
(95) R=Me
(96) Et
(97) R=Me
(98) R=Et

Scheme 18




Scheme 19

The pyruvic acid (100) also reacted with the phenolic phenethylamine (99) under physiological conditions to produce the 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (101). Oxidative decarboxylation of 101 was performed by electrolysis. This reaction was promoted by the existence of a hydroxyl group at the $C_6$ or $C_8$-positions. Reduction of the imine (102) with sodium borohydride produced the tetrahydroisoquinoline (103) in good yield.[66] Oxidative decarboxylation was also observed when 101 was stirred in an alkaline medium in the presence of oxygen.[67] Thus benzyltetrahydroisoquinolines could be synthesised in a manner analogous to their biogenesis.

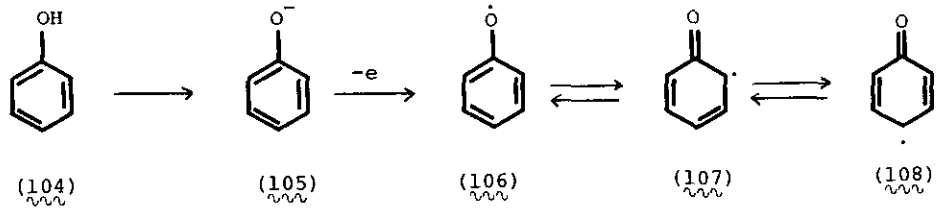
Scheme 19

(b) Phenol Oxidation

The phenoxy anion (105), derived from the phenol (104), is oxidised to the radicals (106, 107 and 108), which are easily coupled to form carbon-oxygen and carbon-carbon bonds. This is regarded as the mechanism of phenol oxidation although

mechanisms such as that involving a phenoxy cation can be considered. Ferric chloride, potassium ferricyanide or manganese dioxide have usually been used as the chemical oxidising agent.

Scheme 20




(104) (105) (106) (107) (108)

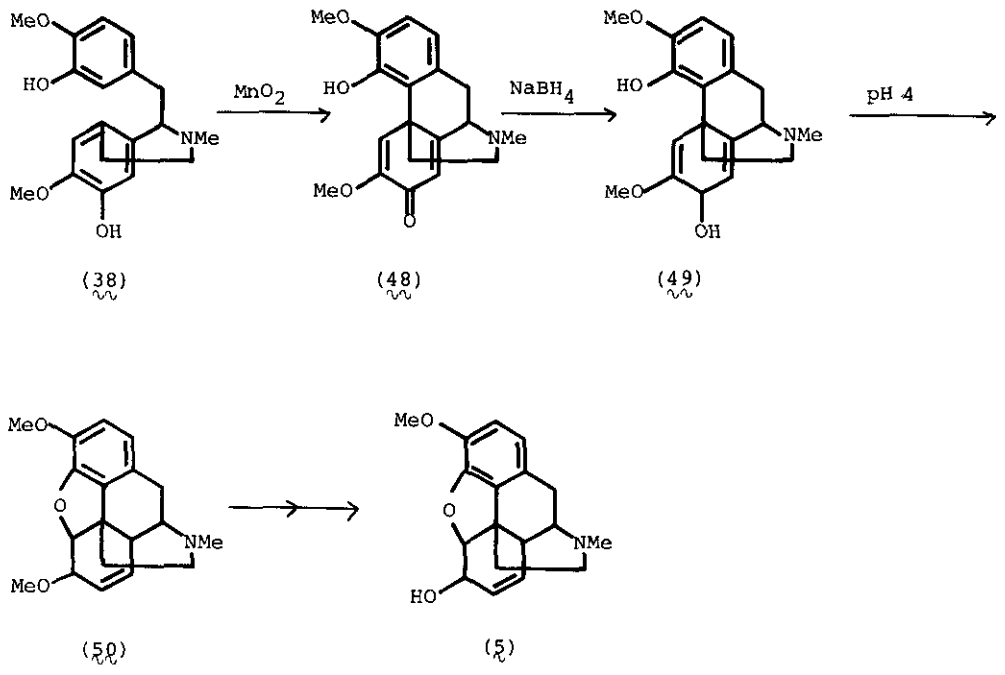
Scheme 20

Barton and co-workers accomplished the synthesis of morphine (5) according to a biogenetic route involving the phenol oxidation of reticuline (38) as the key step.[68] Reticuline was oxidised using *manganese dioxide to produce salutaridine* in 0.024 % yield. This salutaridine was converted to thebeine (50) which had already been correlated with morphine (5).

On oxidation of reticuline with potassium ferricyanide, isoboldine (55) and pallidine (53) were obtained in poor yields.[69] Using phenol oxidation, a number of alkaloids have been synthesised and many modifications have been investigated.[70-72]

Scheme 21

Because tyrosinases and laccases are copper-containing enzymes, we studied phenol oxidation by application of a copper-amine-oxygen stystem which had been used for polymerization of simple phenols.[73,74] A solution of cuprous chloride in pyridine quickly absorbs oxygen to form a dark green solution.[74,75] On treatment with this solution at room temperature, the perchlorate of (+)-reticuline (38) yielded (+)-corytuberine (57) (28 %), (+)-isoboldine (55) (8 %) and pallidine (53) (6 %). By the same reaction, (±)-orientaline (60) was transformed into (±)-orientalinone (110) (19.4 %) and (±)-isoorientalinone (112) (6.5 %), while the corresponding homoisoquinoline (109) formed (±)-kreysiginone (111) (11.4 %) and its stereoisomer (113) (26.6 %).[76]




(38) (48) (49)

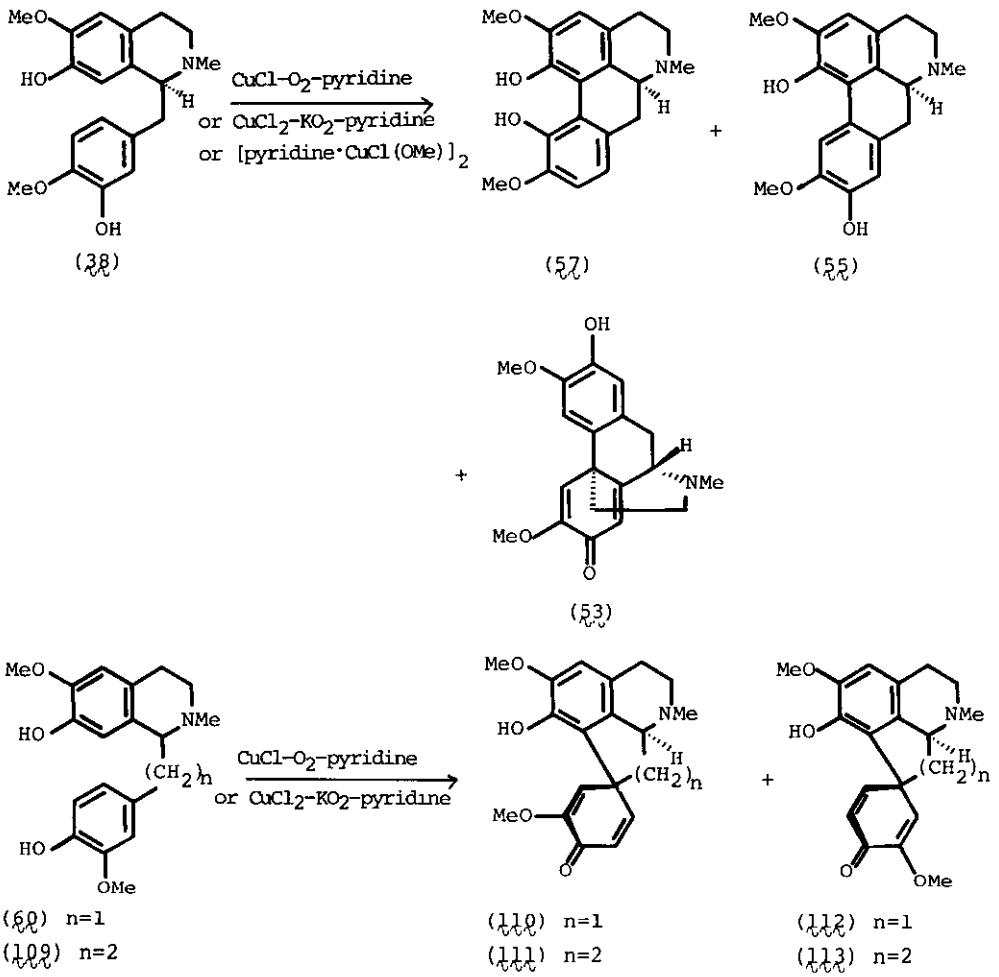
(50) (5)

Scheme 21

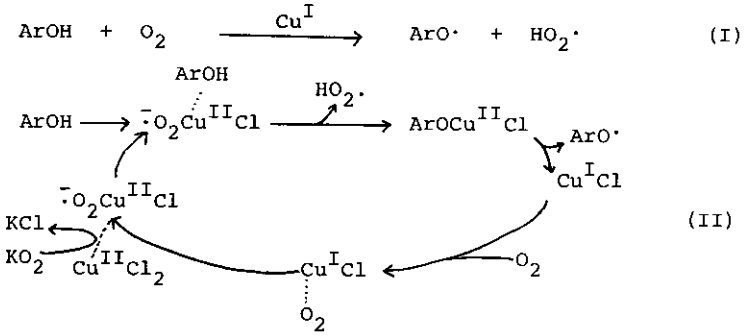
We found that a mixture of cupric chloride and potassium superoxide in pyridine also formed the dark green solution in the absence of oxygen. Using this solution, (±)-reticuline (38) and (±)-orientaline (60) produced the same mixtures of the above alkaloids in almost the same ratios.[76] Furthermore, corytuberine was obtained as the main product from the reaction of (+)-reticuline with a divalent copper complex, [pyridine. CuCl(OMe)]$_2$.[76]

Scheme 22

On the basis of the above observations, the mechanism of the reaction using cuprous chloride-oxygen-pyridine is not likely to model that of the tyrosinases as shown in formula I. Since the actual oxidising species seems to be divalent copper, the above




Scheme 22




Scheme 23

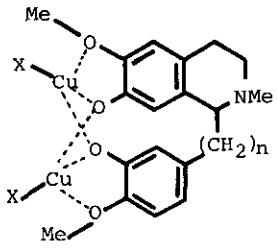
reaction could be regarded as a simulation of the laccases as shown in II.

Scheme 23

Oxidation of N-methylcoclaurine (71) by the above reaction systems gave no corresponding proaporphine and only a tarry product. It is thus probable that the ortho-methoxyphenol moiety is necessary for oxidative coupling.

The ortho-ortho oxidative coupling of reticuline to corytuberine with chemical reagents had not been reported before. It is assumed that two associated copper ions (114) hold the two hydroxyl groups together leading to the predominant formation of the ortho-ortho coupling products.[76]

Scheme 24




(114)

Scheme 24

(c) Redox Reaction Involving N-Oxides

Recent work has revealed that tertiary amine oxides mediate both in the metabolic dealkylation of tertiary amines[77] and in the foramtion of heterocyclic rings in the biogenesis of certain alkaloids.[78,79] Particularly in the field of indole alkaloids, the inherent reactivity of N-oxide was demonstrated in the biosynthesis and utilised in the synthesis of the clinically important indole dimer.[80-82]

From our investigations of biotransformation using the supernatant of rat liver homogenate described in the previous Chapter, we consider that N-oxides could also play an important role in the biogenesis of the isoquinoline alkaloids. The N-oxides of reticuline (38) and orientaline (60) were easily prepared in excellent yields by oxidation with m-chloroperbenzoic acid followed by purification using a

reverse phase liquid chromatography. Reticuline N-oxide (115) was treated with excess hydrated ferrous sulphate in methanol at ambient temperature to give coreximine (40) (42 %) and scoulerine (41) (23 %), together with a mixture of reticuline and norreticuline. On the other hand, none of the protoberberines was obtained from the reaction of orientaline N-oxide (116) with ferrous sulphate in methanol. Cyclisation to protoberberine (118) was however observed in the reaction carried out under acidic conditions. Thus 118 was obtained in 55 % yield by heating with the catalyst in acetic acid at 70 - 80°C.[83]
The above results indicate that the imine intermediates (39 and 117) are generated from the oxides on treatment with ferrous sulphate in a succesive redox manner.[84]
Cyclisation of this imine intermediate occurs at positions ortho and para to the phenolic hydroxyl group under neutral conditions, and this result is in accord with phenol cyclisation.

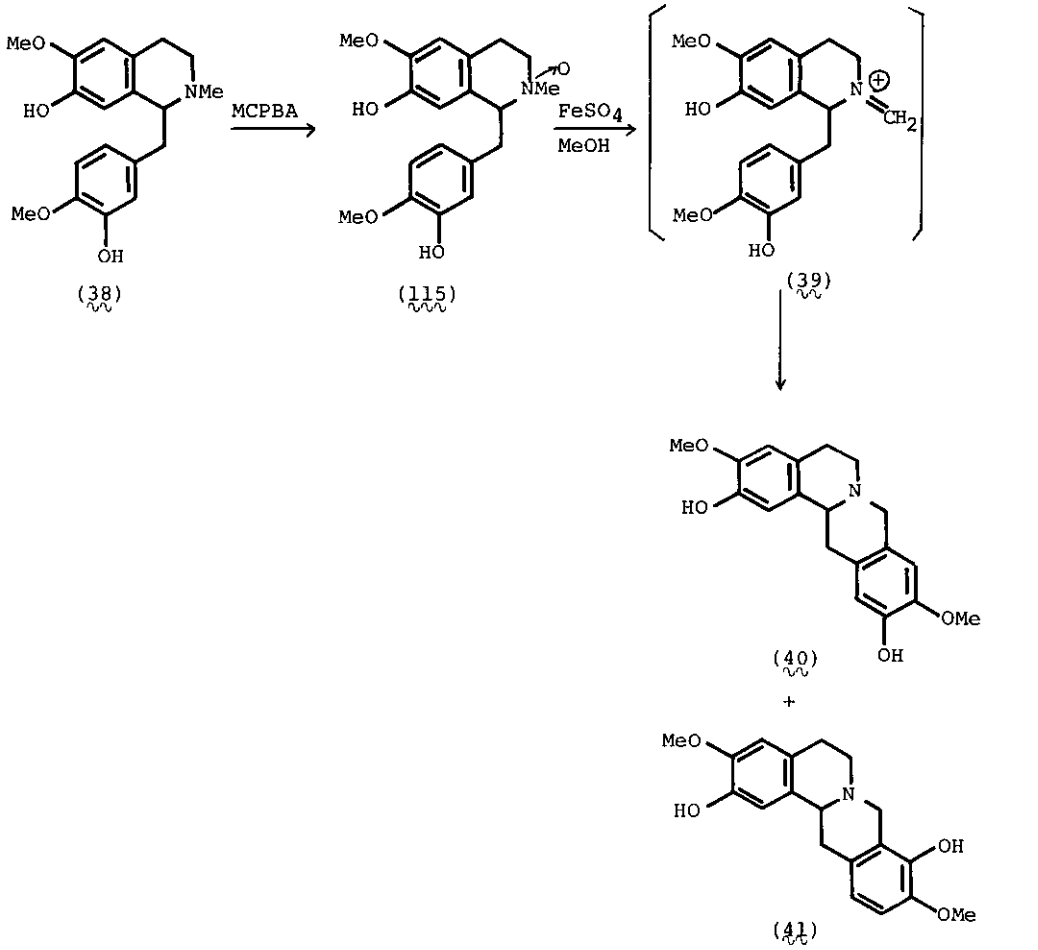
Scheme 25

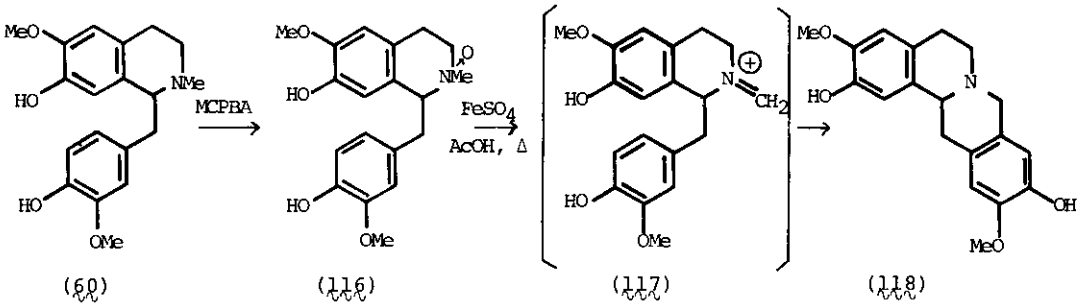
Interestingly, reaction of reticuline N-oxide (115) with cuprous chloride in methanol under nitrogen gave corytuberine (57) in 61 % yield after treatment of the reaction mixture with sodium hydrosulphite. On the other hand, reaction of orientaline N-oxide (116) with cuprous chloride in methanol formed a diastereoisomeric mixture of orientalinone (110 and 112). It was assumed that cuprous chloride is oxidised by the N-oxides to give an active cupric species which is very effective for ortho-ortho phenol oxidative coupling in methanol, in accord with the findings described in the previous section. The above reaction could thus be regarded as an intramolecular redox cyclisation.

Scheme 26

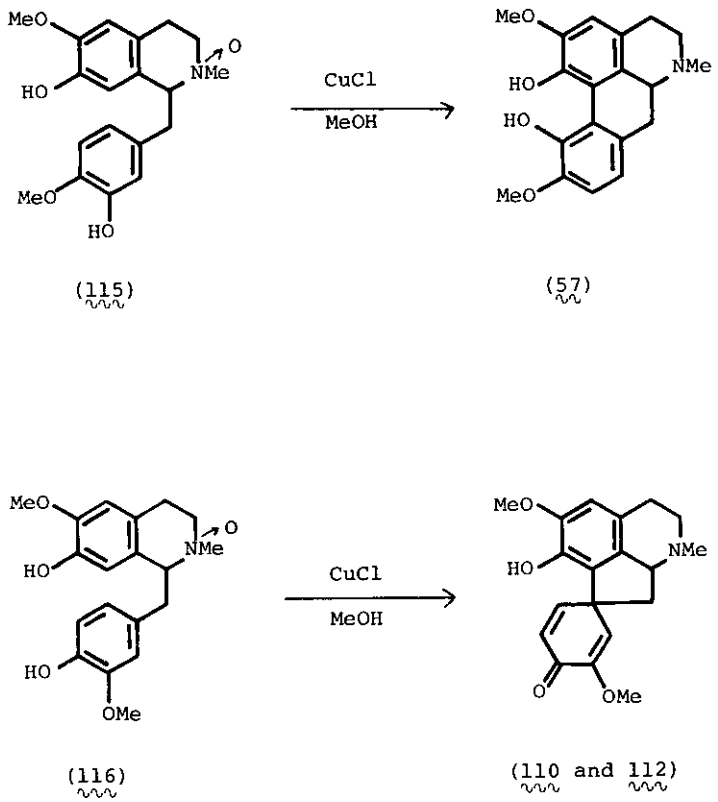
## CONCLUSION

As described in the Chapter on mimic chemical reactions, phenolic 1-benzylisoquinolines can readily be formed under physiological conditions and can be easily transformed into more complicated molecules. It is thus possible that some physiologically


MeO
HO
NMe
MeO
OH
MCPBA
MeO
HO
NMe
O
MeO
HO
FeSO4
MeOH
MeO
HO
N
CH2
MeO
HO
(38)
(115)
(39)
MeO
HO
N
OMe
OH
(40)
+
MeO
HO
N
OH
OMe
(41)


MeO
HO
NMe
HO
OMe
MCPBA
MeO
HO
NMe
O
HO
OMe
FeSO4
AcOH, Δ
MeO
HO
N
CH2
HO
OMe
MeO
HO
N
OH
MeO
(60)
(116)
(117)
(118)

Seheme 25




Scheme 26

active isoquinoline derivatives are formed enzymatically or non-enzymatically in animal bodies. Further studies on mammalian alkaloids are expected. Furthermore, such studies along the above lines could also be expected to lead to the development of novel synthetic methodology. Morphine is still one of the most effective analgesics, so the facile and efficient synthesis of such compounds remains an important area of investigation.

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