BIOSYNTHETIC PATHWAYS OF ISOQUINOLINE ALKALOIDS

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PLANTS elaborate a large variety of alkaloids in which isoquinoline ring system is present as such or in a modified form. The simplest examples of isoquinoline alkaloids are found in certain cactii such as *Lophophora* species. Introduction of a substituted benzyl moiety at position 1 in the isoquinoline system gives rise to *l*-benzylisoquinoline alkaloids. Coclaurine and norlaudanosoline, the simplest members of this group of compounds then elaborate in nature, proaporphines, aporphines, oxoaporphines, cularines phthalideisoquinolines, protopines, benzophenanthridines, pavines, isopavines, hydrophenanthrenes, protoberberines, rhoeadines, spirobenzylisoquinolines, *bis*-benzylisoquinolines, proaporphine-benzylisoquinoline dimers, tapsine, protostephanine, *N*-benzyltetrahydroisoquinolines and normal and abnormal *Erythrina* alkaloids[1]. A number of biogenetic theories[1-5] have been put forward to explain the formation of these alkaloids in nature. With the use of recent tracer experiments in biosynthetic studies some of the earlier hypotheses have been rejected, while others have been modified and in some cases new ideas have been put forward. The current biosynthetic status of isoquinolines and derived alkaloids is as follows:

Extensive feeding experiments with several hydroxy- and methoxy-, derivatives of phenethylamine have traced a reasonable biosynthetic sequence to the isoquinoline alkaloids found in Cactus *Lophophora williamsii*. Pellotine which differs from anhalonidine in having an only *N*-methyl group is not close biosynthetically to the latter alkaloid. The high incorporations of compounds, thought to be on the direct route to these alkaloids, are quite dramatic. It is also clear that several minor or 'aberrant' pathways can take place in this species. Thus the observed incorporation of a particular hydroxylated phenethylamine has little significance unless it is compared with other potential precursors. For example, the observed incorporation (0.12%) of 3-hydroxy-4,5-dimethoxyphenethylamine into pellotine is quite respectable, however, this becomes insignificant compared with the incorporation (15.9%) of *N*-methyl-3-hydroxy-4,5-dimethoxyphenethylamine into the same alkaloid. It is reasonable to assume that 3-hydroxy-4,5-dimethoxyphenethylamine can be converted into its *N*-methyl derivative, presumably by non-specific methylating enzymes[6]. Paul[7] has isolated from *L. williamsii* an *o*-methyl transferase and has examined its ability to catalyse the methylation of various hydroxy- and methoxy-, phenethylamines with S-adenosyl-L-methionine as the methyl donor. Dopamine was methylated to its *o*-methyl ether. The results obtained by use of a cell free system are consistent with the biosynthetic relationships which was deduced from labelled precursor feedings with intact plants.

Several 1,2,3,4-tetrahydroisoquinoline acids have been isolated from natural sources. 1,2,3,4-Tetrahydro-6-hydroxy-*l*-methylisoquinoline-3-carboxylic acid is obtained from *Euphorbia myrsinitis*, 1,2,3,4,-tetrahydro-6,7-dihydroxy-isoquinoline-3-carboxylic acid is isolated from *Mucuna mutsiana* together with large quantities of 3',4'-dihydroxy phenylalanine[8]. 1,2,3,4-Tetrahydro-6,7, dihydroxy-*l*-methylisoquinoline-3-carboxylic acid is a constituent of velvet beans. 1,2,3,4-Tetrahydro-8-hydroxy-6,7-dimethoxyisoquinoline-*l*-carboxylic acid and its *l*-methyl derivative, both are constituents of peyote cactus. It has been shown that these isoquinolines are produced in the cactus by condensation of 3-hydroxy-4',5'-dimethoxyphenylethylamine with glyoxylic acid or pyruvic acid, with subsequent decarboxylation to give the alkaloids anhalamine and anhalomidine. Supposedly other structurally related amino acids are intermediates in similar alkaloid biosynthesis[9].

m-Tyrosine, present in the latex of *Euphorbia*

myrsinitis is known to be derived from shikimic acid, yet not *via* phenylalanine as an intermediate. If administered to shoots of *E. myrsinitis*, ^{14}C-labelled *m*-tyrosine is mostly excreted into the latex. A small part however, is transformed into 1,2,3,4-tetrahydro-6-hydroxy-*l*-methylisoquinoline-3-carboxylic acid. When *m*-tyrosine is introduced directly into either fresh or boiled latex, the same conversion into isoquinoline derivative takes place, presumably through a non-enzymatic Mannich condensation with formaldehyde or its equivalent[10]. Most probably a similar condensation between formaldehyde and 3′,4′- dihydroxyphenylalanine is responsible for the formation of 1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline-3-carboxylic acid

Lophocerine is unusual among isoquinoline alkaloids in having an isobutyl group at C-1. This group together with C-1 forms a five carbon unit which is specifically labelled by mevalonic acid and leucine[11,12]. The observation[11] that the former is a more efficient precursor of lophocerine than the latter has been confirmed[13]. One interpretation of these results is that leucine is incorporated into the alkaloid through conversion *in vivo* into mevalonic acid. This hypothesis was examined[13] by feeding 3-methylbutanoic acid which in the form of its coenzyme A ester is reported as an intermediate on the pathway from leucine to mevalonic acid. No activity was transferred to lophocerine from the [1-^{14}C]-3-methylbutanoic acid administered, thus suggesting that incorporation of leucine is not *via* mevalonic acid and supporting an alternate interpretation of the results above, namely a dual origin for C_5 unit of lophocerine. The steps which lie between mevalonic acid and lophocerine have been explored by feeding [1-^{14}C] -3-methyl-but-3-enylpyrophosphate, [1-^{14}C] 3-methyl-butan-*l*-ol and [1-^{14}C] -3-methyl butanol. All these labelled substances were assimilated into lophocerine. The aldehyde was the least efficient precursor but none the less was shown to be specifically incorporated. The apparent use of an aldehyde function to form the junction of the C_5 unit with phenethylamine fragment in lophocerine biosynthesis makes an interesting contrast with the biosynthesis of the related alkaloids anhalomine and anhalonidine, where the α-carboxylic acids, glyoxylic acid and pyruvic acid respectively are very evidently intermediates[9]. The analogous keto-acid for lophocerine can simply form from leucine by *trans*- amination. The possible intermediacy of this compound in lophocerine biosynthesis does not seem to have been examined yet. Since α-amino acid serve as a starting materials for the synthesis of protein and the elaboration of many plant alkaloids, there must be a sharing of an amino acid which is required for both these metabolic activities. The extent to which this happens has been the subject of a new study[14] in one particular plant, *L. williamsii* which produces isoquinoline and β-phenethylamine alkaloids. These bases are derived from α-amino acid, tyrosine and the results from feeding L-[U-^{14}C] tyrosine indicate that this amino acid is incorporated into the alkaloids approximately 3 times more efficiently than into protein. Only the L-isomer was examined.

The benzylisoquinoline alkaloids[15] are either of 1,2,3,4-tetrahydro type, such as coclaurine and nor-reticuline or of the completely aromatic type, as in case of papaverine, palaudine and esholamine. Ring A in the benzylisoquinolines may possess two or three oxygenated substituents, while ring C has only one or two substituents. The simple *l*-benzyltetrahydroisoquinolines, coclaurine, reticuline orientaline and norprotosinomenine are of considerable biosynthetic importance because they act as *in vivo* precursors to several naturally occurring isoquinolines. Tetra substituted *l*-benzylisoquinolines from which these alkaloids could derive, are themselves formed from norlaudanosoline precursor. Since 1910 it has been believed that dopa gives rise to both the 'halves' of norlaudanosoline. Recent feeding experiments have shown that dopa in fact contributes only to the formation of the phenethylamine part of reticuline in *Litsea glutinosa* and the benzylic portion is biosynthesised from 3,4-dihydroxy-phenylpyruvic acid, not derived from dopa. This is a most surprising result. Other aspects of the biosynthesis of reticuline have also been studied and it has

been demonstrated that there is no selectivity of *o*-methylation in the biosynthesis of reticuline. However, *N*-methylation of nor-reticuline is a specific process. Feeding experiments further suggest that *o*-methylation precedes *N*-methylation in the biosynthesis of reticuline[16]. Tracer experiments have shown that coclaurine an established precursor of proaporphine, aporphine and *bis*-benzylisoquinoline alkaloids, is biosynthesised from dopa and tyrosine *via* the intermediacy of norcoclaurine-*l*-carboxylic acid, 1,2-didehydro-norcoclaurine and norcoclaurine[17]. Papaverine, one of the major *l*-benzylisoquinoline alkaloids of *Papaver somniferum* and clinically used as an antispasmolytic agent has been shown to be biosynthesised from two units of tyrosine *via* norlaudanosoline[18] and reticuline[19]. The bioconversion of norlaudanosoline to papaverine requires methylation and dehydrogenation. Since biological reactions proceed in a definite sequence and generally show a high order of stereoselectivity, the biosynthesis of papaverine has been examined recently from these points of views. The tracer experiments carried out so far on the biosynthesis of papaverine in *P. somniferum* supports the following sequence: tyrosine → norlaudanosoline → (—) — norreticuline → norlaudanidine → norlaudanosoline → papaverine[20].

According to biogenetic theory[4] oxidative cyclisation of coclaurine derivatives which in turn can derive from dopa and tyrosine, can give rise to proaporphine bases. The dihydroproaporphines can form by selective reduction of one double bond of the dienone system. The normal aporphine bases could arise from proaporphines as intermediates by dienone-phenol rearrangement whereas abnormal aporphines which lack oxygen function in ring C could be formed from proaporphines by dienone — benzene rearrangements. Tracer experiments have supported the biogenetic theory and it has been demonstrated that in *Croton sparsiflorus* the proaporphine alkaloid, *N*-methylcrotsparine and the dihydroproaporphine, *N*-methylcrotsparinine with opposite configuration at the asymmetric carbon atoms are stereospecifically formed from biosynthesised (S)-and (R)-, *N*-methylcoclaurines respectively[21]. The normal aporphine alkaloid, *N*-methylsparsiflorine[21] and the abnormal aporphine alkaloid, nornuciferine -*l*[22], both are biosynthesised from (S)-*N*-methylcoclaurine. In the former a dienone-phenol and in the latter dienone-benzene rearrangements are involved. Yet another proaporphine alkaloid, crotonosine has been shown to be formed in nature from coclaurine[23]. Further it has been shown that the plants also biosynthesise abnormal aporphines, roemerine and anonaine from coclaurine[24]. The data clearly support the dienone-benzene, a biogenetic step in the biosynthesis of abnormal aporphine alkaloids.

Although both 1,2,10,11–, and 1,2,9,10–tetrasubstituted aporphines could be formed in plants by direct oxidative coupling of reticuline, one could also envisage the formation of both these types of aporphine bases from protosinomenine and orientaline *via* neoproaporphine and orientalinone respectively, followed in each case by dienone-phenol rearrangements. The evidence in favour of direct oxidative coupling of reticuline has come from recent tracer experiments. When [*N*-methyl-^{14}C] reticuline was fed to *Corydalis cava* Schweig, radioactive bulbocapnine was isolated[25]. The same results were obtained when the experiment was repeated with doubly labelled reticuline. Biosynthetic studies on isoboldine has also supported direct oxidative coupling of reticuline[26]. [*N*-methyl-^{14}C] Reticuline was also efficiently incorporated into magnoflorine in *Aquilegia*[27], whereas magnoflorine isolated after administrating labelled norprotosinomenine, was practically radioinactive. These results thus further support direct *ortho-ortho*-oxidative coupling of reticuline in the biosynthesis of 1,2,10, 11-tetrasubstituted aporphines. An alternative pathway from norprotosinomenine *via* the neoproaporphine intermediate thus was not operative in this case. The biosyntheses of quaternary aporphines magnoflorine and laurifoline have been studied recently in details and it has been found that both the bases are stereospecifically biosynthesised in *Cocculus laurifolius* from (S)-reticuline[28].

The most likely biosynthetic route to corydine, glaucine and dicentrine is by direct oxidative coupling of reticuline. *Ortho-ortho* and *ortho-para* couplings of reticuline could give intermediates from which all three alkaloids could derive in principle by unexceptional steps. However, it has been reported that these alkaloids in *Dicentra exima* are formed from protosinomenine instead of reticuline[29]. In a recent report isocorydine, an isomer of corydine has been shown to be biosynthesised in *Annona squamosa* stereospecifically from (+)-nor-reticuline[30]. This result thus supports direct *ortho-ortho* coupling of reticuline. In view of this result the tracer experiments on glaucine and dicentrine in *Dicentra exima* need re-examination.

Boldine, a representative of 1,2,9,10-tetrasubstituted aporphines could be formed in nature from *l*-benzylisoquinoline precursors by alternate routes. Tracer experiments have formly supported the following sequence for the biosynthesis of boldine in *Litsea glutinosa*: 4'-*o*-methyl-norlaudanosoline → nor-reticuline → (+)- reticuline → (+)- isoboldine → (+)-boldine[31].

It has been suggested that oxidative coupling of orientaline could give orientalinone which by reduction followed by allylic elimination, could furnish isothebaine. The chemical synthesis of isothebaine from orientaline through this route supported this scheme. The evidence that the living plants also follow the same route in the elaboration of isothebaine has been obtained by tracer experiments[32]. It has been shown that isothebaine in *Papaver orientale* is stereospecifically biosynthesised from (+)-orientaline. Further orientalinol-I is well incorporated into isothebaine with the retention of ^{3}H from C_{-10}, while II-isomer is poorly utilized and the C_{-10} label is lost. Orientalinol-I, is thus shown to be a precursor of isothebaine. A redox conversion of the II-isomer into I-isomer accounts for the incorporation of II-isomer into isothebaine.

Protoberberine alkaloids exists in nature either as tetrahydroprotoberberines or as quaternary protoberberine salts. Some dihydroprotoberberines are also known. The relationship of *l*-benzyltetrahydroisoquinoline and protoberberine was recognised quite early[3]. That berberine-I has a modified *l*-benzyltetrahydroisoquinoline nucleus was shown when labelled norlaudanosoline was converted into berberine in *Berberis japonica*[33]. That C-8 of berberine and its relatives known as the 'berberine bridge' is formed in nature by oxidative modification of an *N*-methyl group was demonstrated when [*N*-methyl-^{14}C] reticuline was administered to *Hydrastis canadensis*[34]. The derived berberine was degraded and essentially all the radioactivity was resided at C-8. This was confirmed by feeding doubly labelled reticuline. Tracer experiments also confirmed that the methylenedioxy group in berberine is formed by oxidative cyclisation of an *o*-methoxyphenol. When both the labelled enantiomers of reticuline were fed separately to *H. canadensis*[34], (+)-reticuline was converted into berberine fifteen times more efficiently than (-)- reticuline. (-)- Canadine was also incorporated efficiently into berberine. The biosynthetic pathways of tetrahydropalmatine and palmatine in *Cocculus laurifolius* as verified by tracer experments, is as follows: norlaudanosoline → (+)- reticuline →tetrahydropalmatine → palmatine[35]. High incorporation of (+)- reticuline into coreximine in opium poppies showed that 10,11-substituted tetrahydroberberines are also derived from reticuline[36]. (+)- Reticuline was very efficiently incorporated into (-)- scoulerine which acted as an efficient precursor of stylopine in *Chelidonium majus*[37]. Efficient incorporation of berberine into jatrorrhizine in *Berberis aggregata* has been demonstrated[38]. By feeding singly and doubly labelled precursors it has been shows that the methylene - dioxy group of berberine is opened in the formation of jatrorrhizine[39]. Experiments with living plants have shown that the tetrahydroprotoberberines, stepholidine, corydalmine, capaurine and corynoxidine was stereospecifically biosynthesised from (S)- reticuline[40]. Further it has been demonstrated that protoberberinium salts in nature are formed by dehydrogenation of tetrahydroprotoberberine alkaloids, the rate of their conversion, however, is very different. In some plants both tetrahydroprotoberberine and

their corresponding quaternary protoberberine alkaloids co-exist while in others only quaternary salts are found.

The postulate that the phthalideisoquinoline alkaloids are formed in nature by oxidative modification of tetrahydroprotoberberines has been confirmed by recent tracer experiments. Hydrastine and narcotine have been shown to be specifically derived in nature from (+)- reticuline[41]. (S)- Scoulerine[41], isocorypalmine[42] and canadine[42] are also shown to be the precursors of narcotine. Further the conversion of scoulerine into narcotine involves removal of 13-pro-S-hydrogen atom[43]. Phthalideisoquinoline, corlumine has been shown to be stereospecifically biosynthesised from (R)-(–)- reticuline[44]. It has been proved firmly that 13-methyltetrahydroprotoberberine such as corydaline and spirobenzylisoquinoline alkaloids, ochotensine and benzophenanthridine alkaloid sanguinarine are all structural variant of *l*-benzyltetrahydroisoquinoline skeleton[45] and reticuline is the precursor of corydaline alkaloids. Further (S)-reticuline is shown to be specifically incorporated into sanguinarine. Yenhusomine has been shown to be stereospecifically derived from (R)-(-)-reticuline[44]. Tracer experiments define biosynthetic pathways to narcotine as: tyrosine →norlaudanosoline → (+)-reticuline → (–)-scoulerine →narcotine[41]. Two routes were postulated for the biosynthesis of benzophenanthridine alkaloid, chelidonine and related compounds. Tracer experiments have supported the biosynthetic pathways to chelidonine as: norlaudanosoline → (+)- reticuline → (—)- scoulerine → chelidonine[37]. Feeding experiments have defined the biosynthetic pathways of benzo (c) phenanthridines as: (–)-7,8,13, 13a-tetrahydrocoptisine → (–)- *cis*-*N*-methyl-7,8,13,13a-tetrahydrocoptisinium salt →protopine → sanguinarine → chelirubine → macorpine[46].

Morphine, thebaine and codeine are important drugs. That the carbon skeleton of these morphine and related alkaloids could be formed in nature from norlaudanosoline was recognised[47] as early as in 1925. However, the mechanistic details of this transformation were discussed much later[4]. Extensive tracer experiments have been conducted to delineate the biosynthetic pathways of morphine alkaloids in *Papaver somniferum* and the results strongly suggest the sequence as: norlaudanosoline → reticuline → salutaridine → salutaridinol-I → thebaine → neopinone → codeinone → codeine → morphine. It has been reported recently that the biosynthesis of thebaine in *P. bracteatum* proceeds by the same pathways as in the opium poppy. The limiting step in the sequence is the demethylation of the end ether group of thebaine to neopinone[48]. Oripavine, a morphine alkaloid has been shown to be derived in *P. orientale* from reticuline. The enzymatic recemization of reticuline, so essential to the biosynthesis of opium alkaloids, is very substrate specific and is completely blocked by minor structural modifications[50]. Tracer experiments have confirmed that sinomenine is derived in *Sinomenium acutum* from reticuline *via* sinoacutine[51]. The validity of biogenetic proposal has been thus confirmed. However, further steps in the biosynthesis of sinomenine need experimental verification. Morphinandienone alkaloid, flavinantine has been shown to be specifically biosynthesised in *Croton flavens* from reticuline[52]. The biosynthetic pathways of yet another morphinandienone alkaloid, sebiferine in *Cocculus* laurifolius have been delineated as: nor-recticuline → (+)-reticuline → didehydroreticuline → (–)- reticuline → sebiferine[53].

There has been many suggestions for the biogenesis of *Erythrina* alkaloids. Tracer experiments have confirmed that *Erythrina* alkaloids are stereospecifically biosynthesised in *Erythrina crista galli* from (+)-nor-protosinomenine *via* dibenzazonine and erysodienone as intermediates[54,55]. Several abnormal *Erythrina* alkaloids have been isolated recently from *Cocculus laurifolius*[56]. Tracer experiments have shown that these alkaloids are also stereospecifically biosynthesised in *C. laurifolius* from (+)-norprotosinomenine[57]. Dienone benzene rearrangement, however, is an additional step in the biosynthesis of these alkaloids. The later stages of biosynthesis of both normal and abnormal *Erythrina* alkaloids[58] have also been studied.

Feeding experiments have shown that the dibenz [d,f] azonine alkaloid laurifinine in *C. laurifolius* is stereospecifically biosynthesised from (+)-norprotosinomenine[59].

Several *bis*-benzylisoquinoline alkaloids are known. These bases are considered to be formed in nature by oxidative dimerization or by intermolecular oxidative coupling of simple *l*-benzyltetrahydroisoquinoline precursors such as coclaurine and *N*-methylcoclaurine. Recent experiments have strongly supported the hypotheses. Epistephanine[60], cocsulin[61], cocsulinin[62], oxyacanthine[63], isotetrandrine[64], tetrandrine[65], tiliacorine[66] tiliacorinine[66], nortiliacorinine—A[67] and tiliegeine[68] all have been shown to be specifically derived in nature from coclaurine and *N*-methylcoclaurine. Details of biosynthesis of these alkaloids have been also studied and pathways have been defined[61-68]. Thalicarpine, an aporphine-*l*-benzylisoquinoline alkaloid, has been shown to be biosynthesised stereospecifically from (S)- reticuline[69].

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ANNOUNCEMENT

RUBBER EXHIBITION 1984

The International Rubber Exhibition of 1984 will be held during 12–16 March 1984, at the National Exhibition Centre, Birmingham, England. Innovation is the theme for Rubberex 84 conference.

Rubberex 84 will host an important working conference to examine developments in the application and use of rubber materials and technology. The plastic and rubber institute will organise the conference in conjunction with Maclaren Exhibitions, at which much new work will be presented for the first time in the UK.

Forty six papers will be presented by speakers from the USA, the Continent and United Kingdom, covering a variety of subjects including temperature effects on polymers; hose and seal developments for the automotive industry; cover moulding, extrusion and developments in materials processing which includes the use of microprocessors. Details can be had from: Bill Mason, The National Exhibition Centre, Birmingham, England.