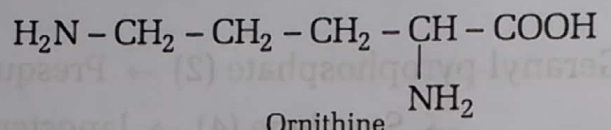
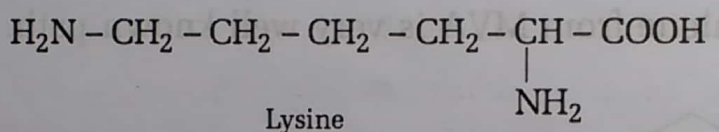
1.8. BIOSYNTHESIS OF ALKALOIDS

Precursors of alkaloids are amino-acids and amino-aldehydes or amines. Amino aldehydes and amines are derived from amino acids. There is great diversity in th structure of alkaloids. Because of this great diversity of structure, It is not possible t develop only one pathway for the biosynthesis of all alkaloids. Thus many pathways hav been proposed, each one accounting for the biosynthesis of a number of alkaloids o related structure.

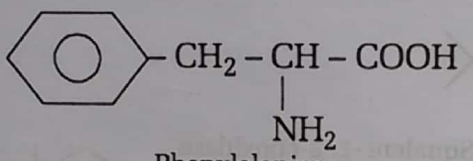
The most common amino acids that act as precursors in alkaloid biosynthesis are a follows :



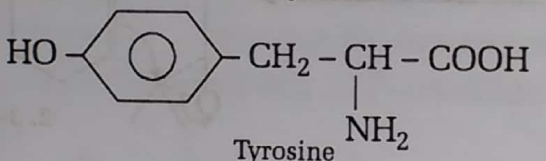
Ornithine



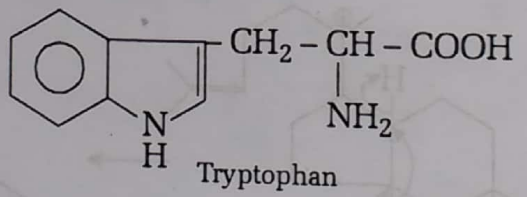
Lysine



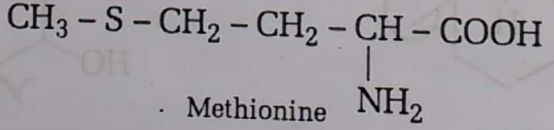
Phenylalanine



Tyrosine



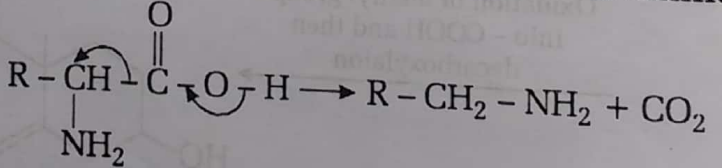
Tryptophan



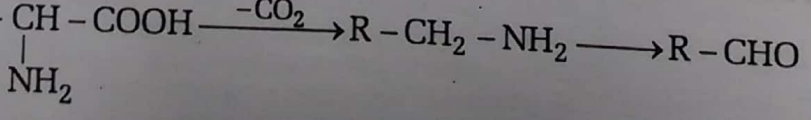
Methionine

Many type of reactions are involved for the biosynthesis of alkaloids. These reaction take place in the presence of specific enzymes. The reactions are :

(i) Decarboxylation : Decarboxylation reactions converts amino acid into amine.



(ii) Oxidative deaminaion : This reaction converts amino acid into aldehyde. This reaction can take place via two ways :

(a) 

(b) $R-\underset{\underset{NH_2}{|}}{CH}-COOH \longrightarrow R-\underset{\underset{O}{||}}{C}-COOH \xrightarrow{-CO_2} R-CHO$

(iii) Condensation between carboxyl compound and amine (Schiff's base formation). Aldehyde reacts with amine to give enamine.

$$R-CHO + R'-NH_2 \longrightarrow R-CH=N-R'$$

(iv) Mannich reaction : This reaction is very important in the biosynthesis of alkaloids. This leads the formation of C–C–N bond.

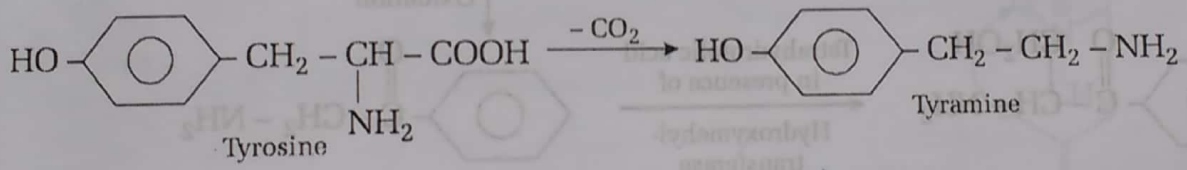
$$R-\overset{\overset{O}{||}}{C}-CH_3 + CH_2O + HN\begin{matrix}R'\\R'\end{matrix} \longrightarrow R-\overset{\overset{O}{||}}{C}-CH_2-CH_2-N\begin{matrix}R'\\R'\end{matrix}$$

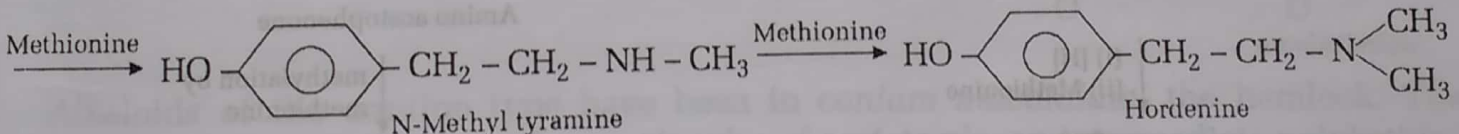
1.8.1. Formation of Alkaloids derived from phenylalanine

The main alkaloids of this group are ephedrine, nor-ψ-ephedrine, hordenine, dopamine, adrenaline and mescaline. The main precursor is the phenylalanine.

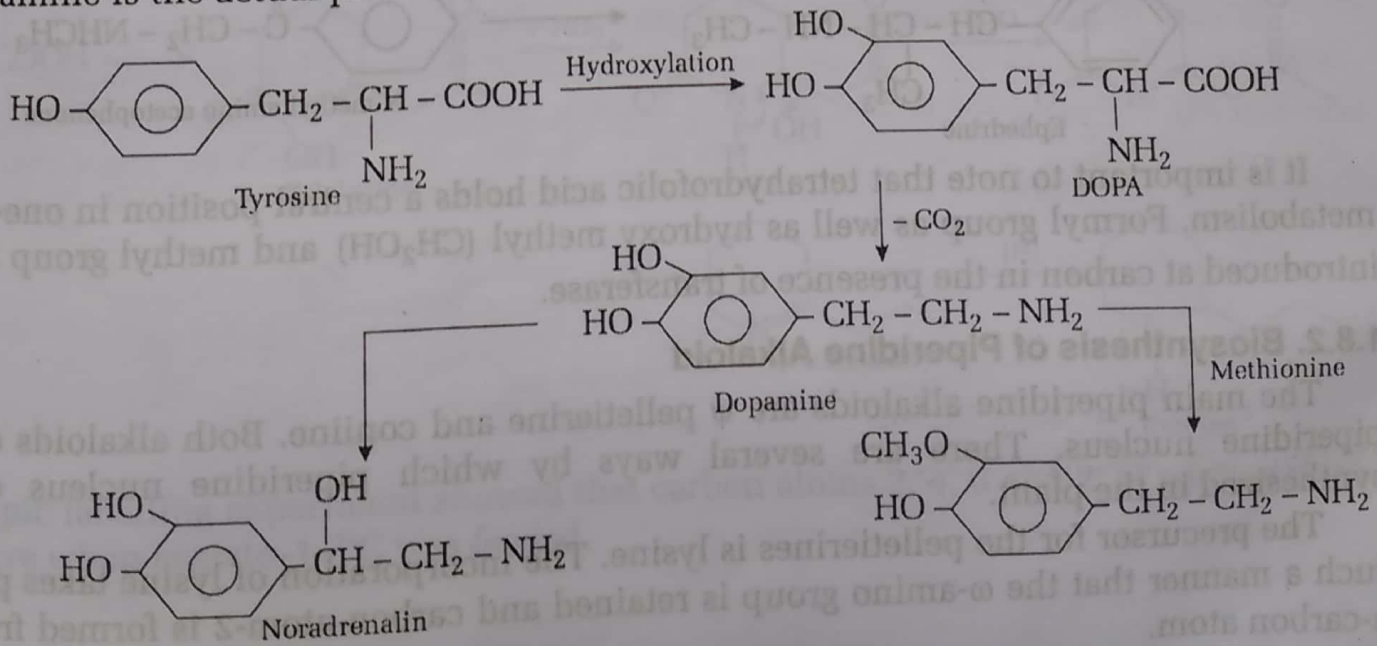
Hardenine, dopamine, adrenaline and mescaline are phenyl ethyl amines. They originate by decarboxylation of the amino acids thyrosine and DOPA. They have ethyl side chain and are frequently methylated by methionine. Tyrosine is the actual precursor of hardenine.

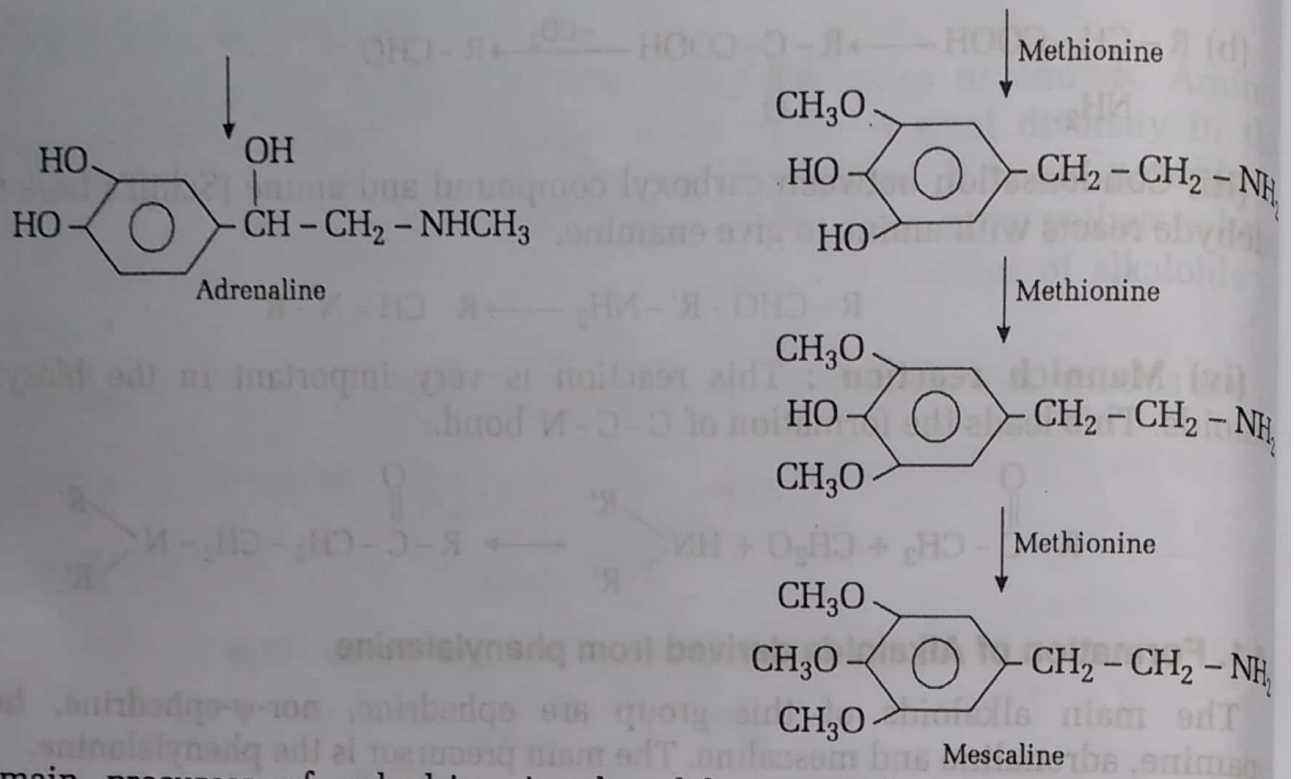
Tyrosine → Tyramine → N-methyl tyramine → Hordenine



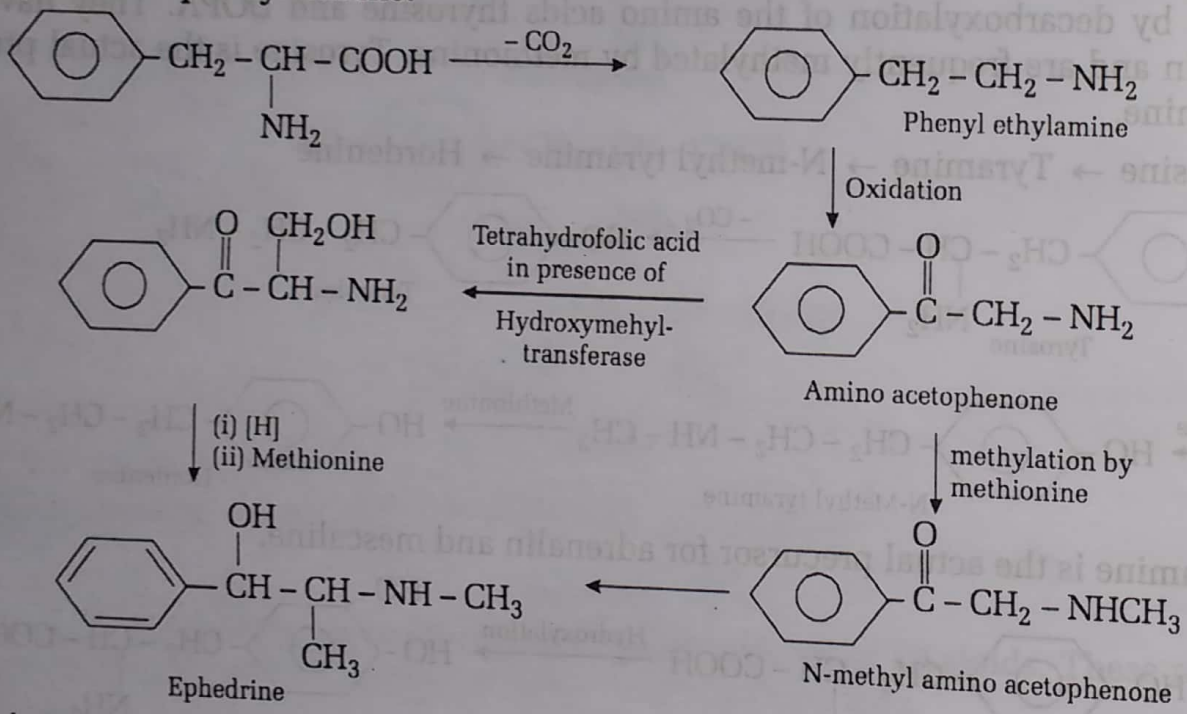


Dopamine is the actual precursor for adrenalin and mescaline.





The main precursor of ephedrine is phenylalanine. Ephedrine originate from decarboxylation of phenylalanine.

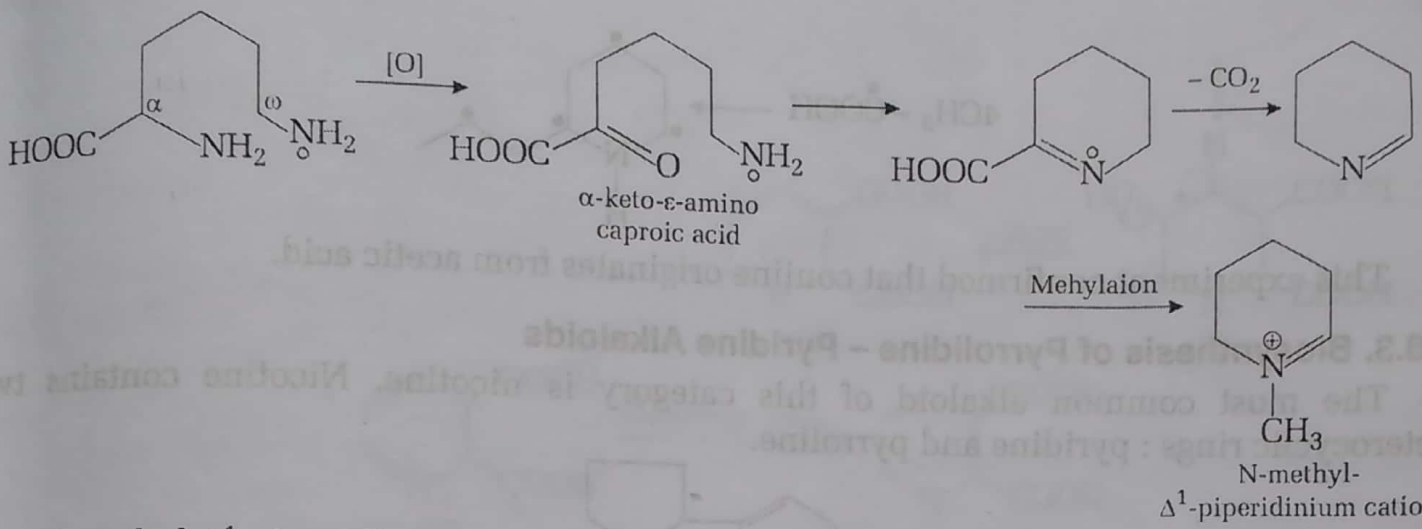


It is important to note that tetrahydrofolic acid holds a central position in one-carbon metabolism. Formyl group as well as hydroxy methyl (CH_2OH) and methyl group may be introduced at carbon in the presence of transferase.

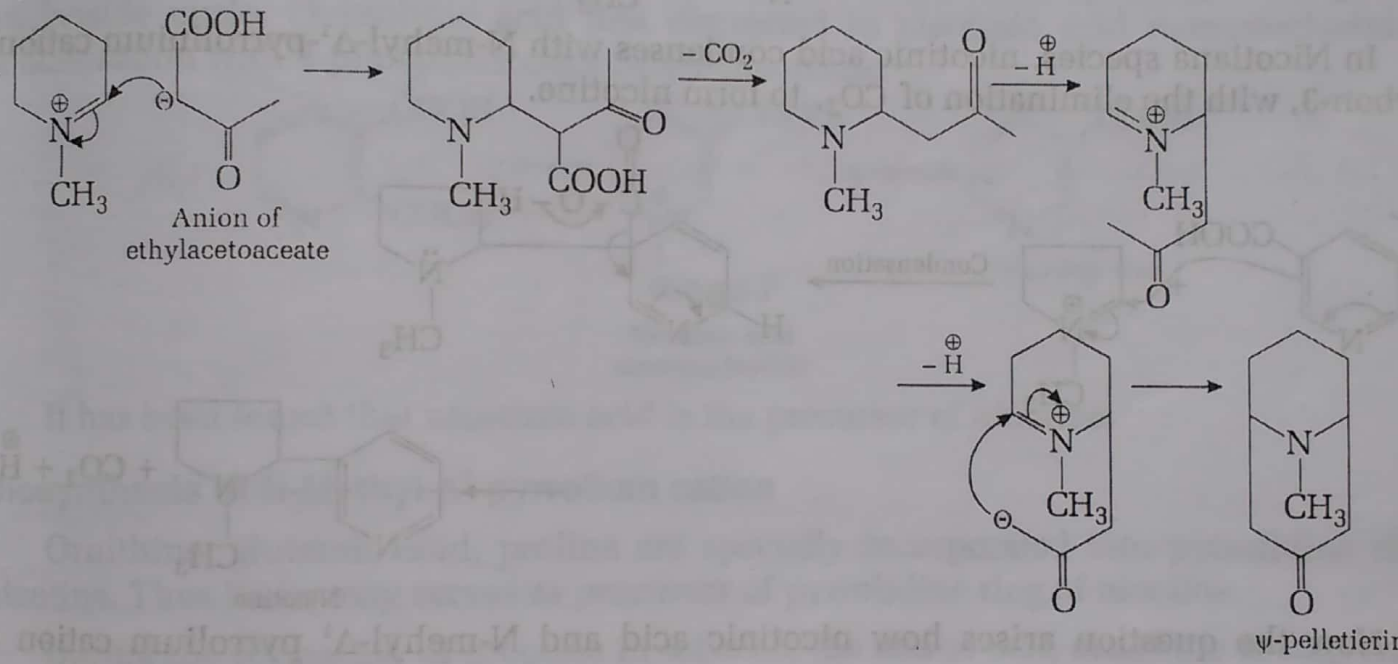
1.8.2. Biosynthesis of Piperidine Alkaloid

The main piperidine alkaloids are ψ pelletierine and coniine. Both alkaloids contain piperidine nucleus. There are several ways by which piperidine nucleus can be synthesized in the plant.

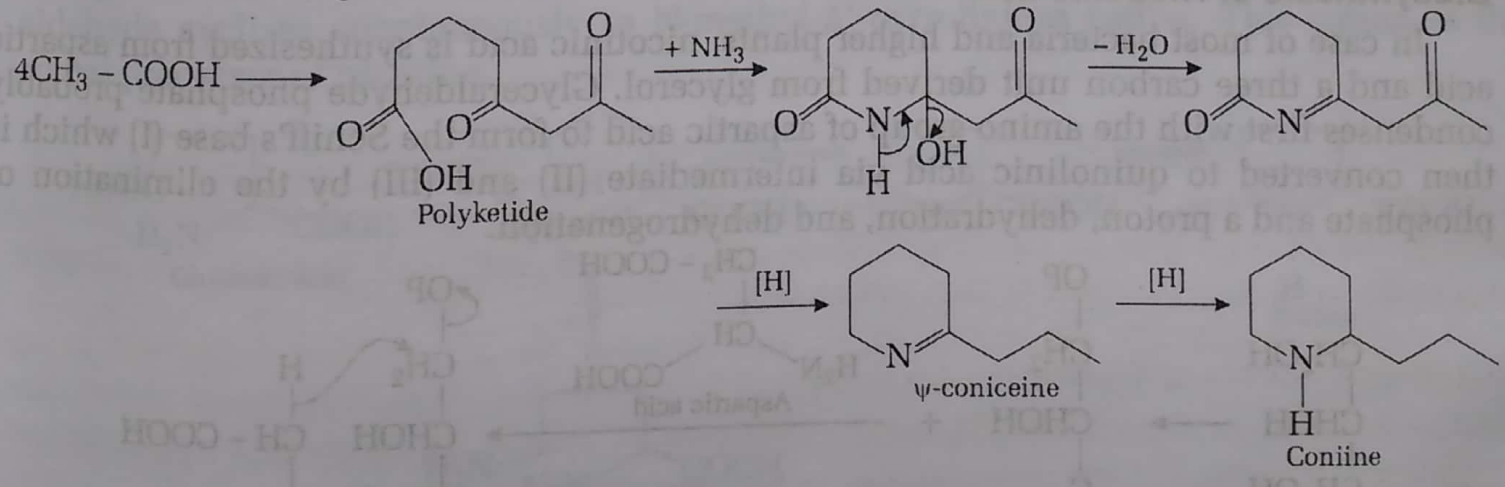
The precursor for the pelletierines is lysine. The incorporation of lysine takes place in such a manner that the ω-amino group is retained and carbon atom-2 is formed from the α-carbon atom.



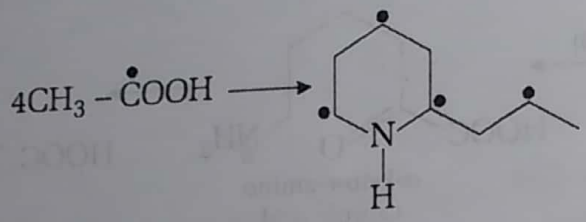
N-methyl-Δ^1-piperidinium cation then undergoes a Mannich type reaction with ethylacetoacetae.



Alkaloids of the coniine type have been in *conium maculalum,* the hemlock. The conium alkaloids originate from four molecules of acetate *via*, an intermediate polyketide.



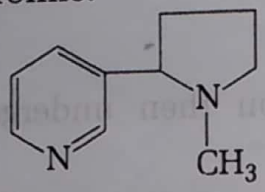
Isotopic labelling experiment showed that carbon atoms 2, 4, 6 and 2′ of coniine were radioactive when acetate–1–^{14}C was feeded.



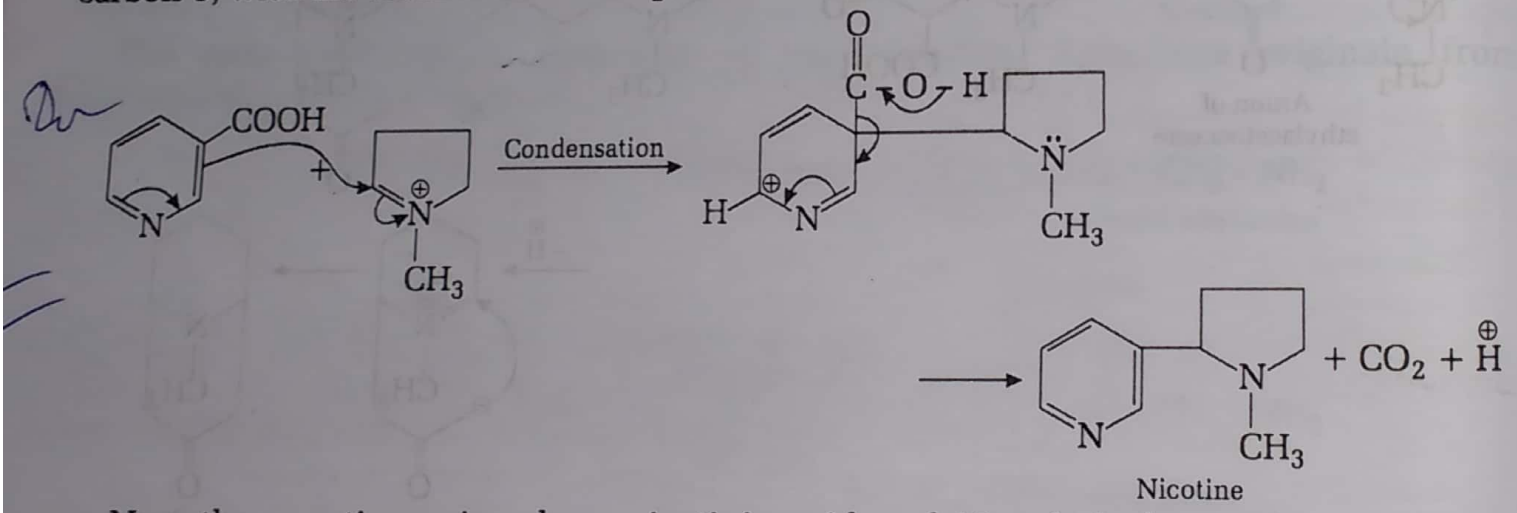
This experiment confirmed that coniine originates from acetic acid.

1.8.3. Biosynthesis of Pyrrolidine – Pyridine Alkaloids

The most common alkaloid of this category is nicotine. Nicotine contains two heterocyclic rings : pyridine and pyrroline.



In Nicotiana species, nicotinic acid condenses with N-mehyl-Δ^1-pyrrolinium cation at carbon-3, with the elimination of CO_2, to form nicotine.

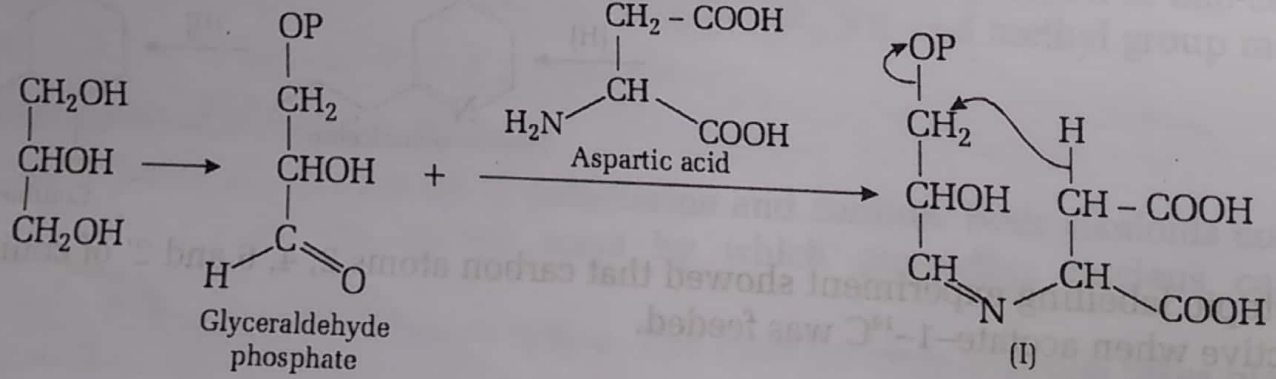


Nicotine

Now the question arises how nicotinic acid and N-mehyl-Δ^1 pyrrolium cation are biosynthesised?

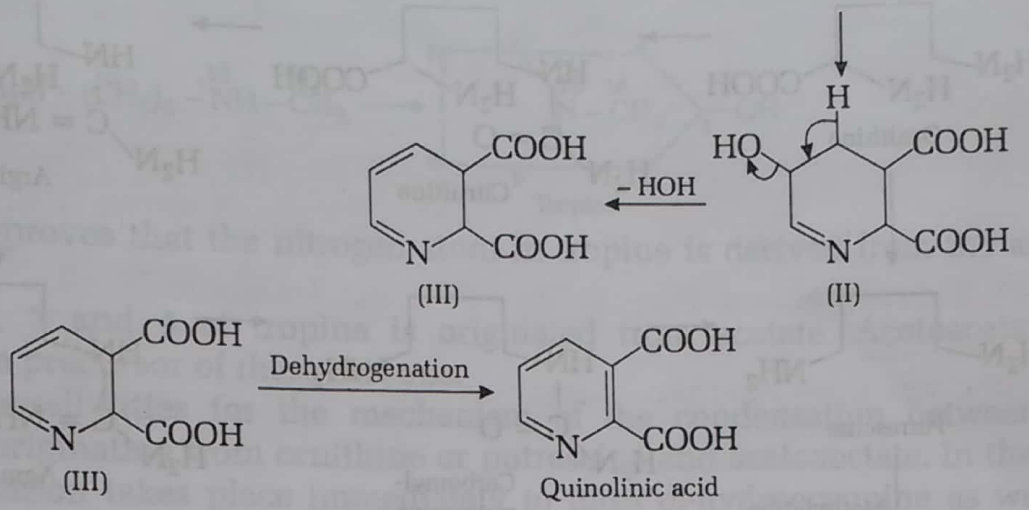
Biosynthesis of Nicotinic acid

In case of most bacteria and higher plants, nicotinic acid is synthesized from aspartic acid and a three carbon unit derived from glycerol. Glyceraldehyde phosphate probably condenses first with the amino group of aspartic acid to form the Schiff's base (I) which is then converted to quinolinic acid via intermediate (II) and (III) by the elimination of phosphate and a proton, dehydration, and dehydrogenation.

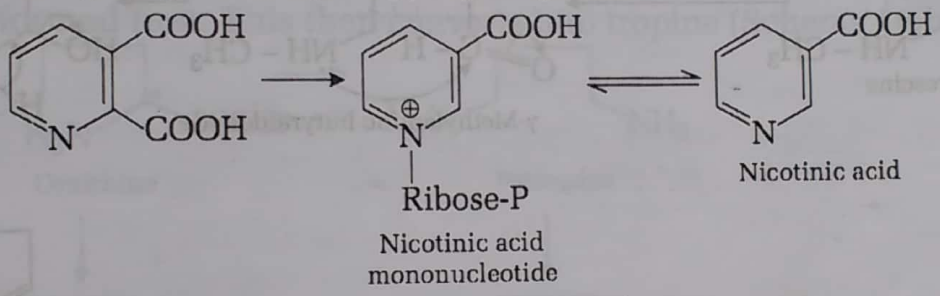


Glyceraldehyde phosphate

(I)



Nicotinic acid does not originate from quinolinic acid. It is synthesized by pyridine nucleoside cycle. Quinolinic acid first converted to nicotinic acid mononucleotide by condensation with 5-phosphoribosyl-1-pyrophosphate.

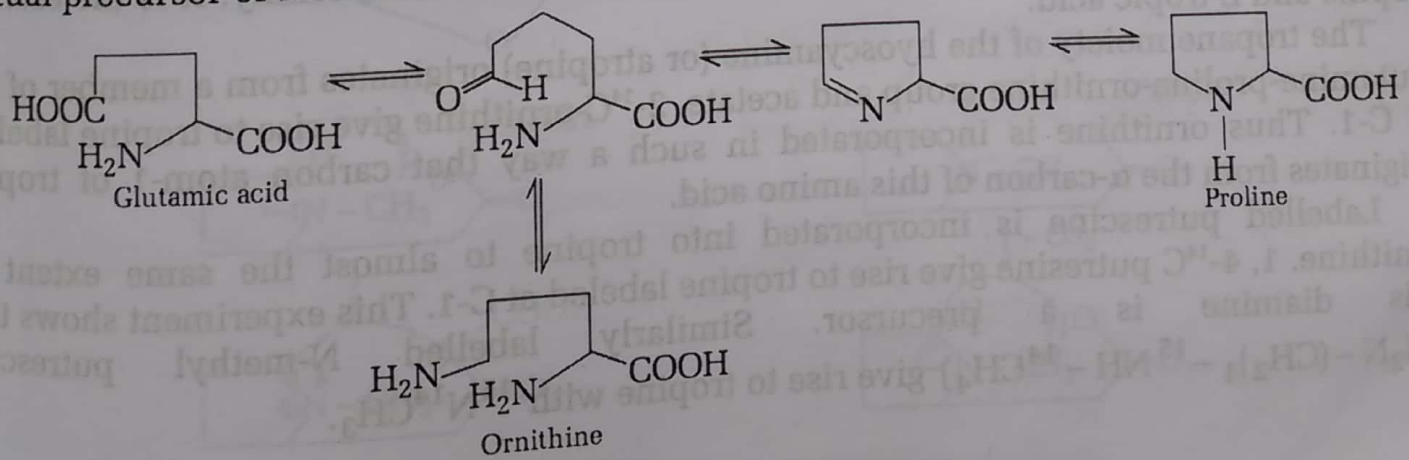


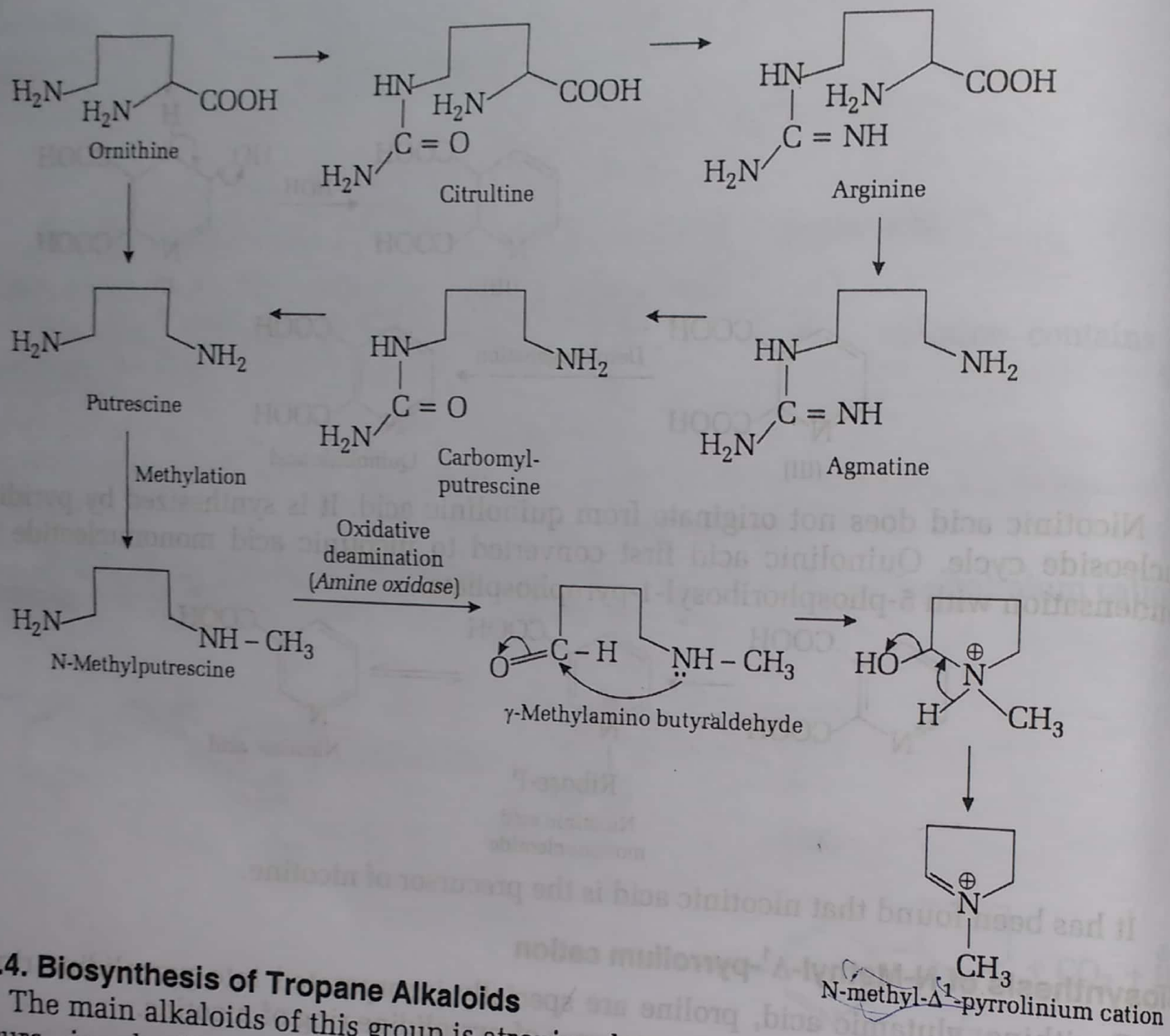
It has been found that nicotinic acid is the precursor of nicotine.

Biosynthesis of N-Methyl-Δ^1-pyrrolium cation

Ornithine, glutamic acid, proline are specially incorporated into pyrrolidine ring of nicotine. Thus these may serves as precursor of pyrrolidine ring of nicotine.

During the formation of nicotine in tobacco, the amino acid ornithine is converted to putrescine *via* citrulline, arginine, agmatine and carbamylputrescine. Putrescine is then methylated and oxidised to γ-methyl aminobutyraldehyde by an *amine oxidase*. The aldehyde cyclises spontaneously to N-methyl-Δ^1-pyrrolinium cation. This cation is the actual precursor of nicotine.





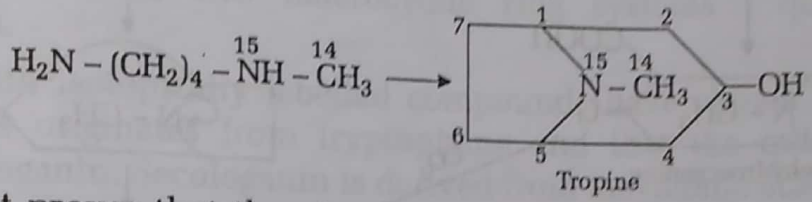
1.8.4. Biosynthesis of Tropane Alkaloids

The main alkaloids of this group is atropine, hyoscyamine and scopolamine, Atropine occurs in deadly right shade (*Atropa belladonna*) together with hyoscyamine. Hyoscyamine is optically active (leavorotatory) but readily racemises into (±) hyoscyamine when warmed with ethanolic KOH. This (±) mixture of hyoscyamine is commonly known as **atropine**.

The alkaloid hyoscyamine is wide spread in the solanacaeae family. It is the ester of tropine and L-tropic acid.

The tropane moiety of the hyoscyamine (or atropine) originates from a member of the glutamine-proline-ornithine group and acetate. 2-^{14}C-ornithine give rise to tropine labelled at C-1. Thus ornithine is incorporated in such a way that carbon atom-1 of tropine originates from the α-carbon of this amino acid.

Labelled putrescine is incorporated into tropine to almost the same extent as ornithine. 1, 4-^{14}C putresine give rise to tropine labeled at C-1. This experiment shows that this diamine is a precursor. Similarly labelled N-methyl putrescine ($H_2N-(CH_2)_4-{}^{15}NH-{}^{14}CH_4$) give rise to tropine with $^{15}N^{14}CH_3$.



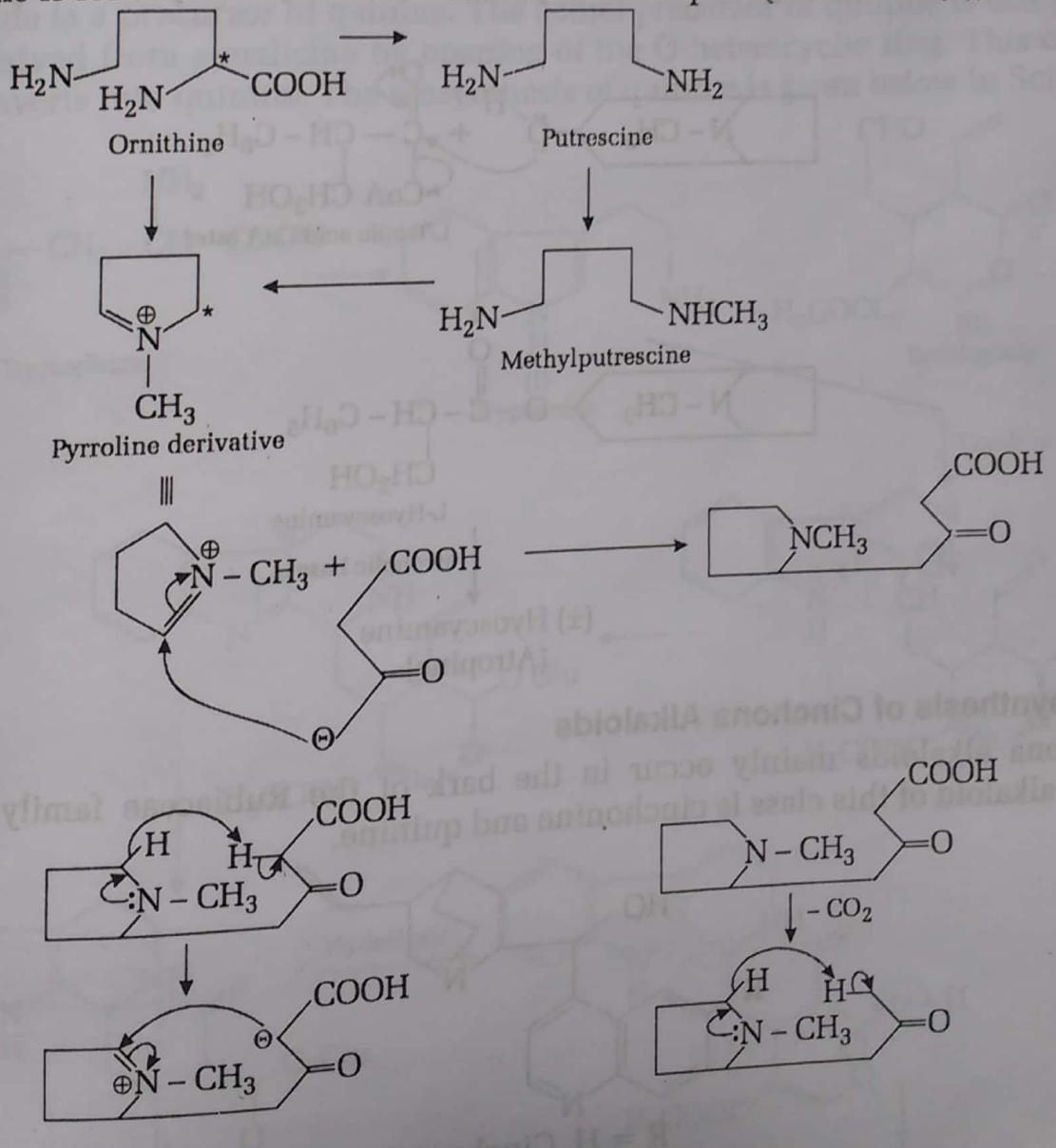
Tropine

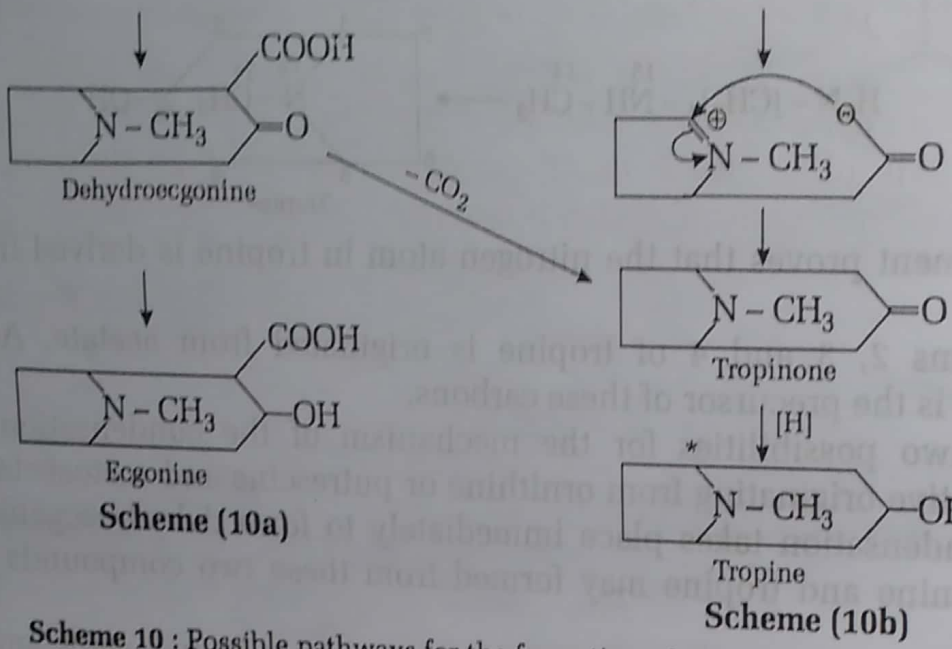
This experiment proves that the nitrogen atom in tropine is derived from the amino acid precursor.

Carbon atoms 2, 3 and 4 of tropine is originated from acetate. Acetoacetate or acetoacetyl CoA is the precursor of these carbons.

There are two possibilities for the mechanism of the condensation between the pyrroline derivative originating from ornithine or putrescine and acetoacetate. In the first case double condensation takes place immediately to form dehydroecgonine as well as tropinone. Ecgonine and tropine may formed from these two compounds by reduction (Scheme 10(a)).

In the second case, the linkage of acetoacetate occurs in two steps and monocyclic base hygrine is formed first. This then converts into tropine (Scheme 10(b)).

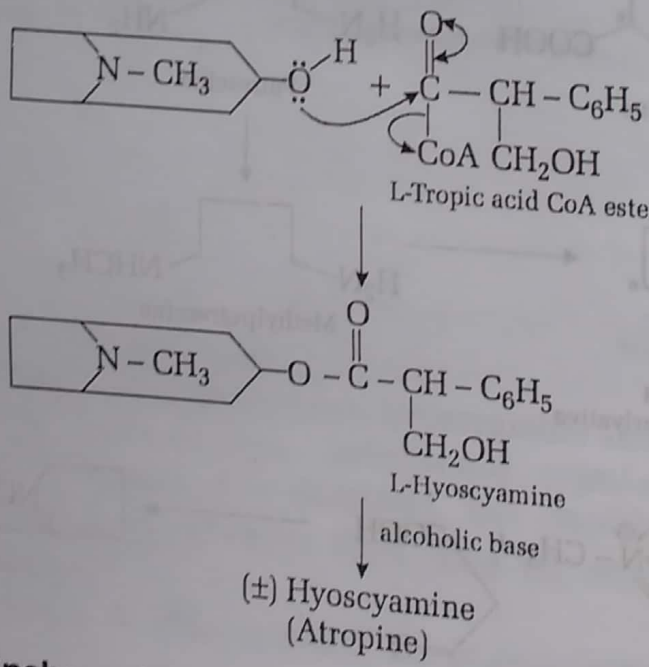




Scheme (10a) **Scheme (10b)**

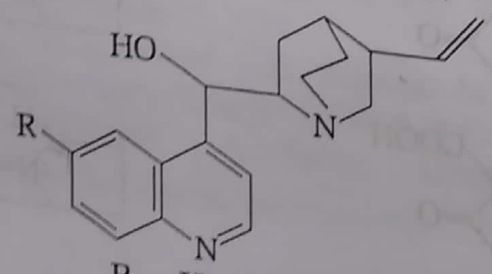
Scheme 10 : Possible pathways for the formation of ecgonine and tropine

The esterification of tropine with L-tropic acid is catalysed by the enzyme *tropine esterase*.



1.8.5. Biosynthesis of Cinchona Alkaloids

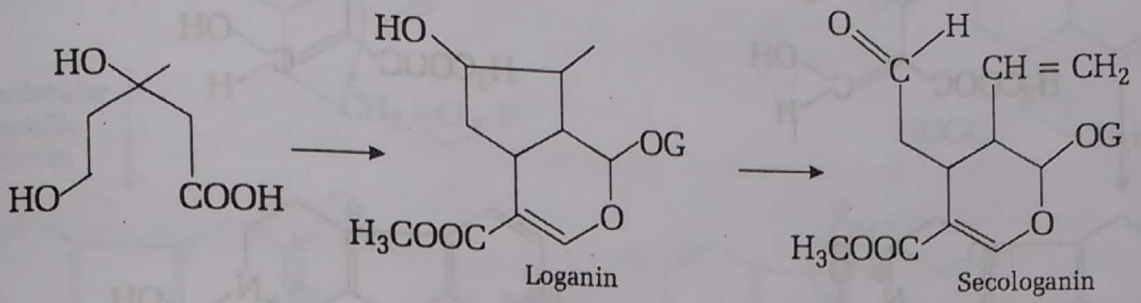
Cinchona alkaloids mainly occur in the bark of the Rubiaceae family. The most important alkaloid of this class is cinchonine and quinine.



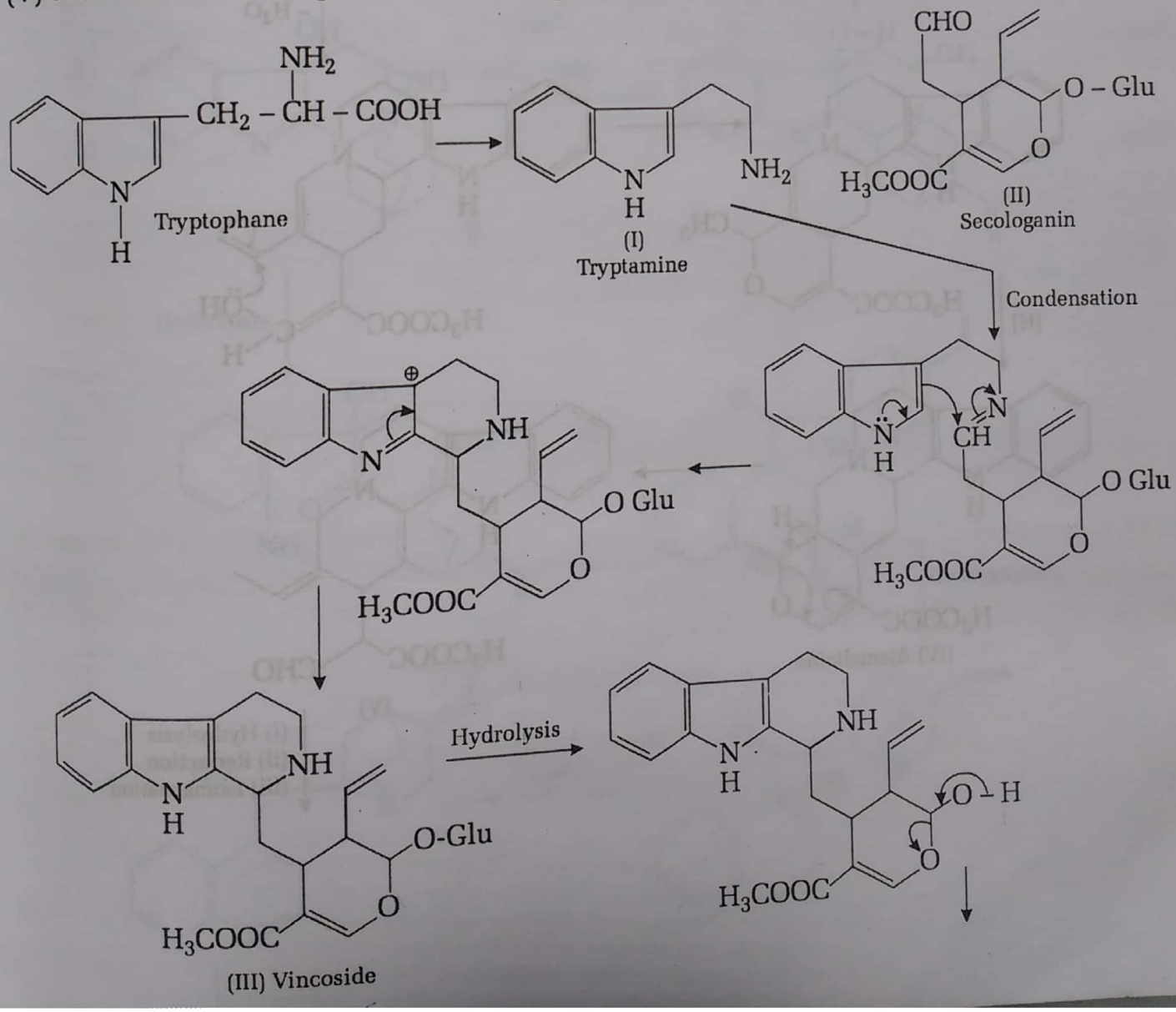
R = H, Cinchonine
R = OCH_3; Quinine

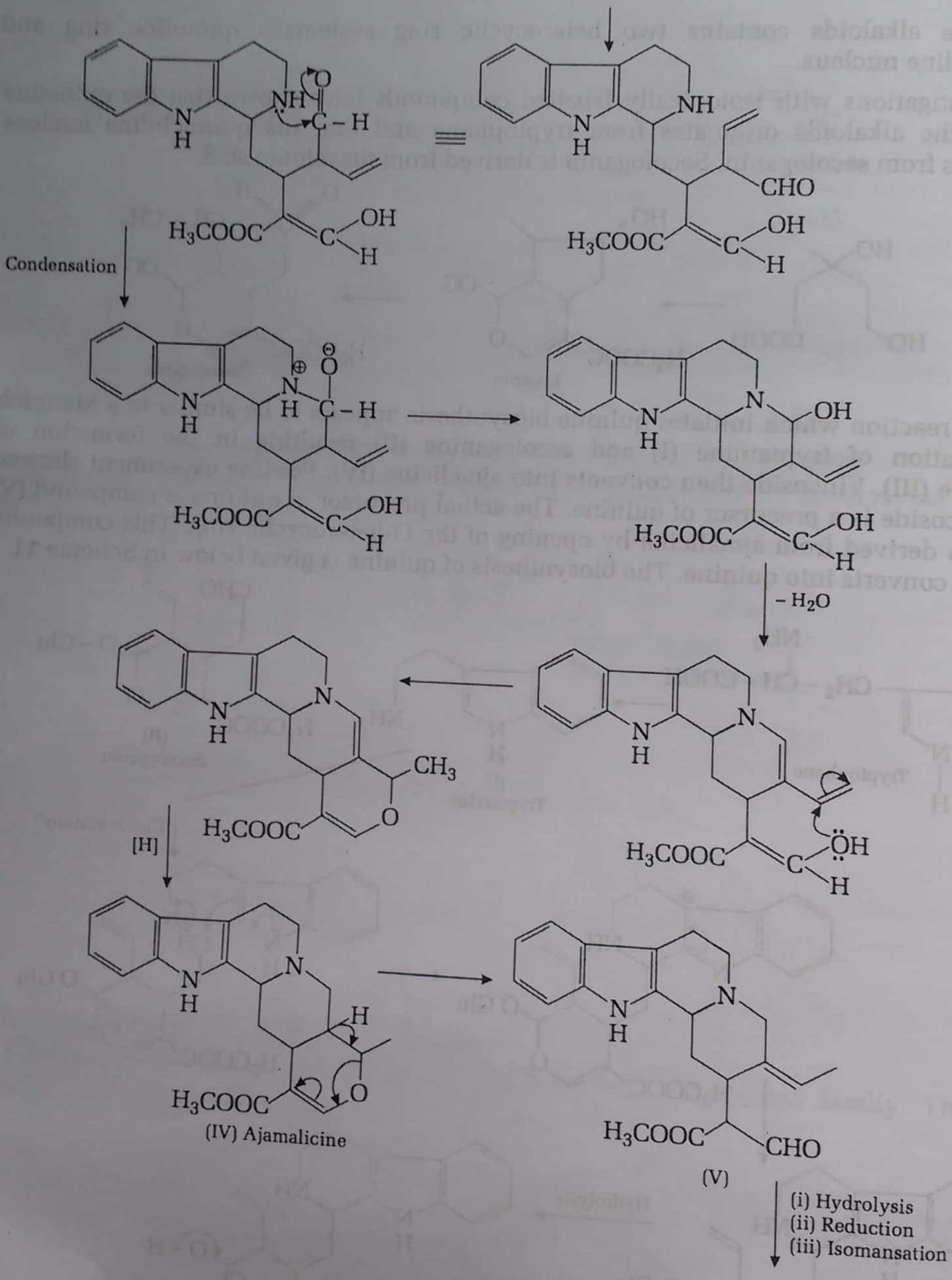
These alkaloids contains two heterocyclic ring systems : quinoline ring and quinuclidine nucleus.

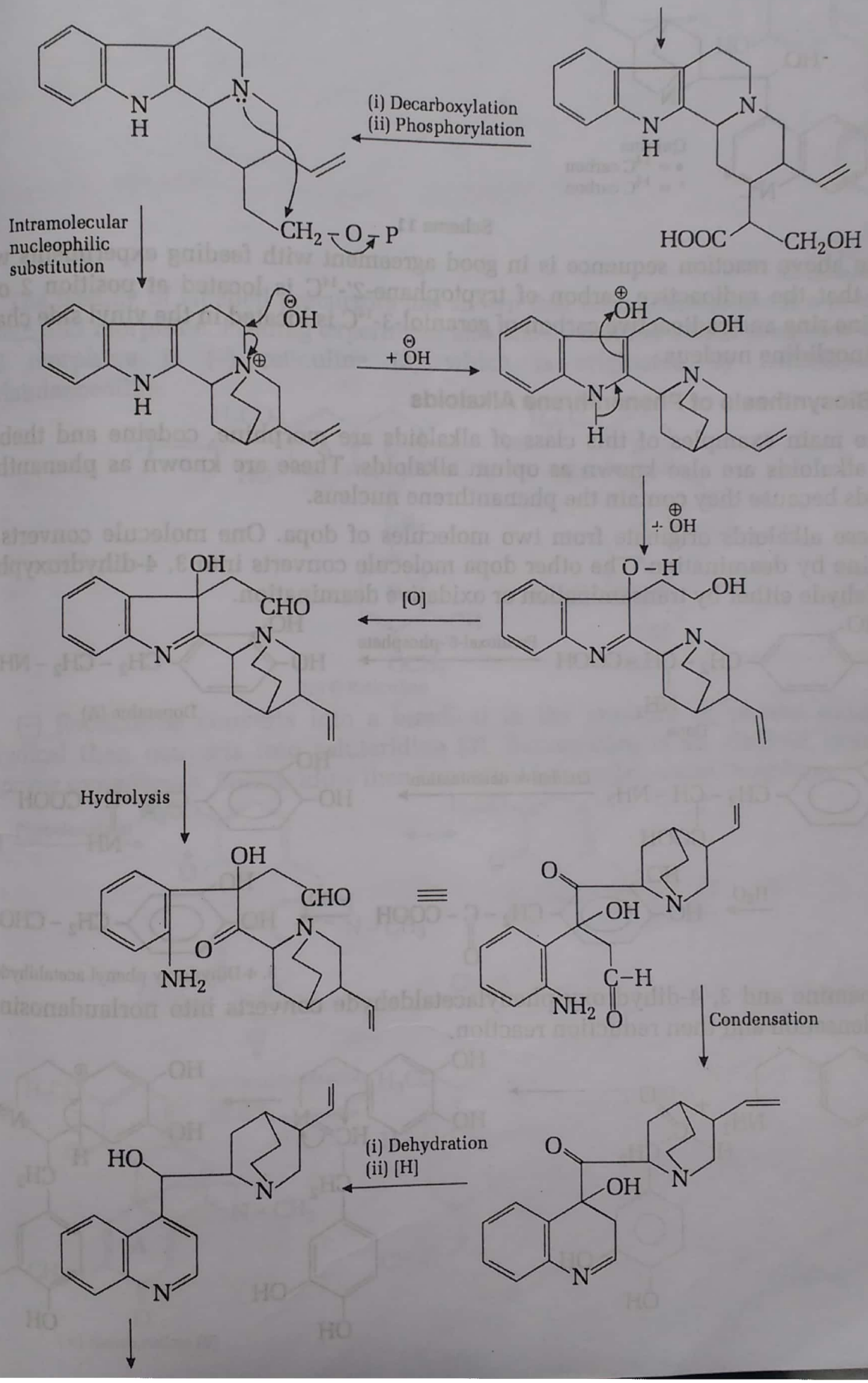
Investigations with isotopically labelled compounds have shown that the quinoline ring of the alkaloids originates from tryptophane and that the quinuclidine nucleus originates from secologanin. Secologanin is derived from mevalonic acid.

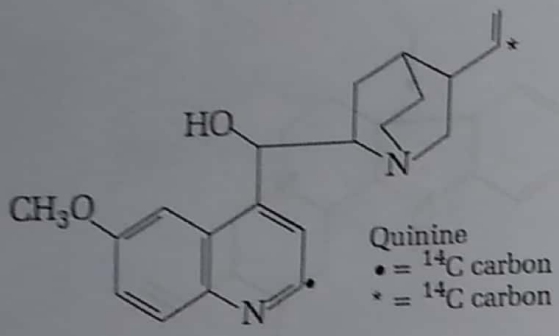


The reaction which initiates quinine biosynthesis appears to be similar to a Mannich condensation of tryptamine (I) and secologanine (II) resulting in the formation of vincoside (III). Vincoside then convents into ajmalicine (IV). Feeding experiment showed that vincoside is a precursor of quinine. The actual precursor of quinine is compound (V) which is derived from ajmalicine by opening of the O-heterocyclic ring. This compound (V) then converts into quinine. The biosynthesis of quinine is given below in Scheme 11.









Quinine
• = ^{14}C carbon
* = ^{14}C carbon

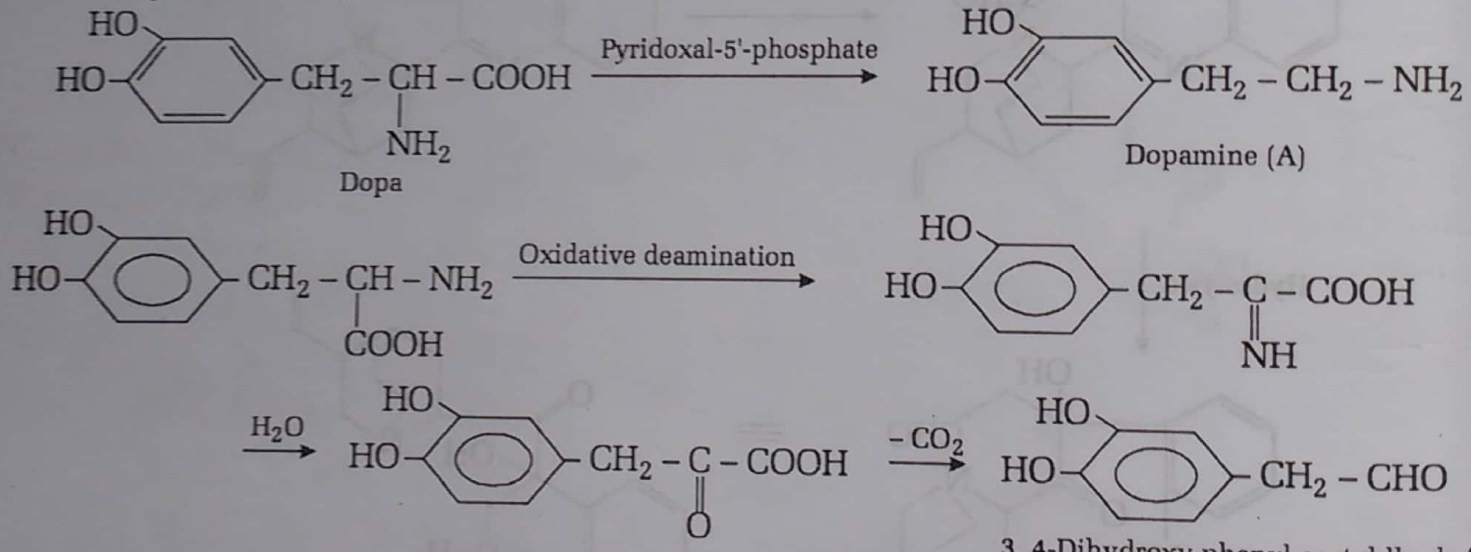
Scheme 11

The above reaction sequence is in good agreement with feeding experiments which shows that the radioactive carbon of tryptophane-2'-^{14}C is located at position 2 of the quinoline ring and radioactive carbon of geraniol-3-^{14}C is located in the vinyl side chain of the quinoclidine nucleus.

1.8.6. Biosynthesis of Phenanthrene Alkaloids

The main examples of this class of alkaloids are morphine, codeine and thebaine. These alkaloids are also known as opium alkaloids. These are known as phenanthrene alkaloids because they contain the phenanthrene nucleus.

These alkaloids originate from two molecules of dopa. One molecule converts into dopamine by deamination. The other dopa molecule converts into 3, 4-dihydroxyphenyl acetaldehyde either by transamination or oxidative deamination.

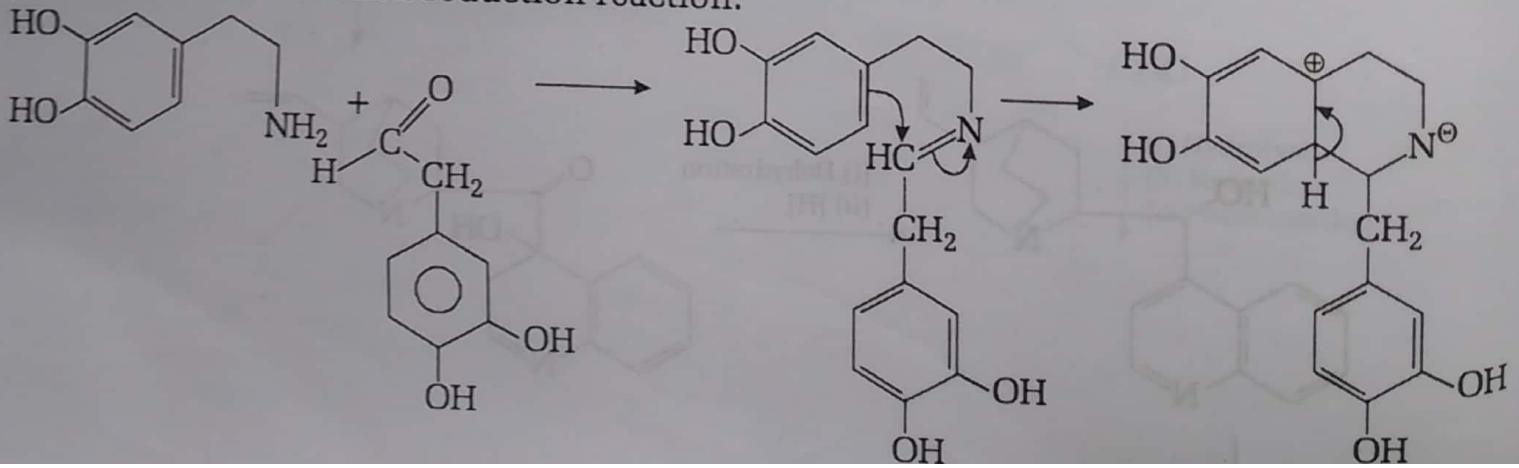


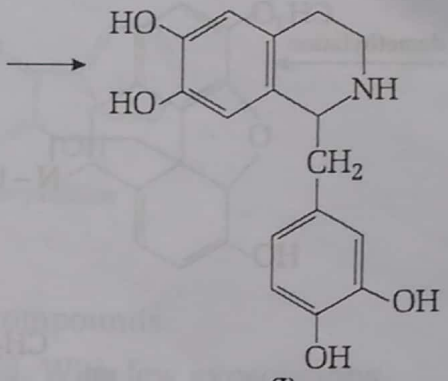
Dopa

Dopamine (A)

3, 4-Dihydroxy phenyl acetaldhyde (B)

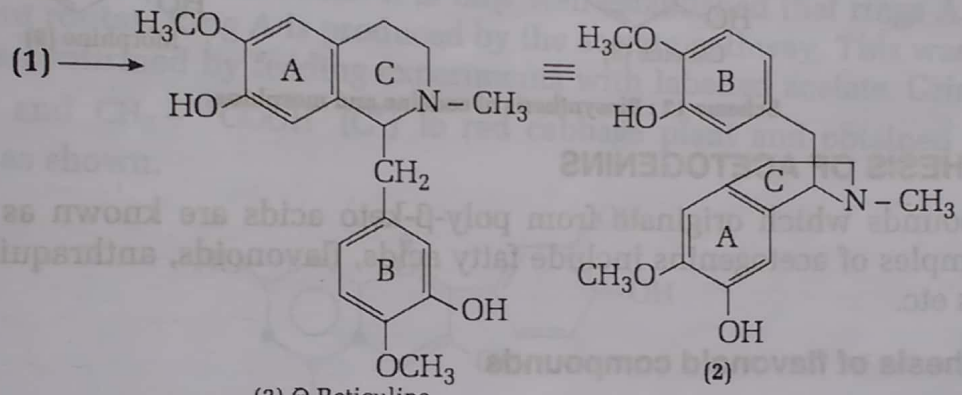
Dopamine and 3, 4-dihydroxy phenylacetaldehyde converts into norlaudanosine (1) by condensation and then reduction reaction.





(I)
Norlaudanosoline

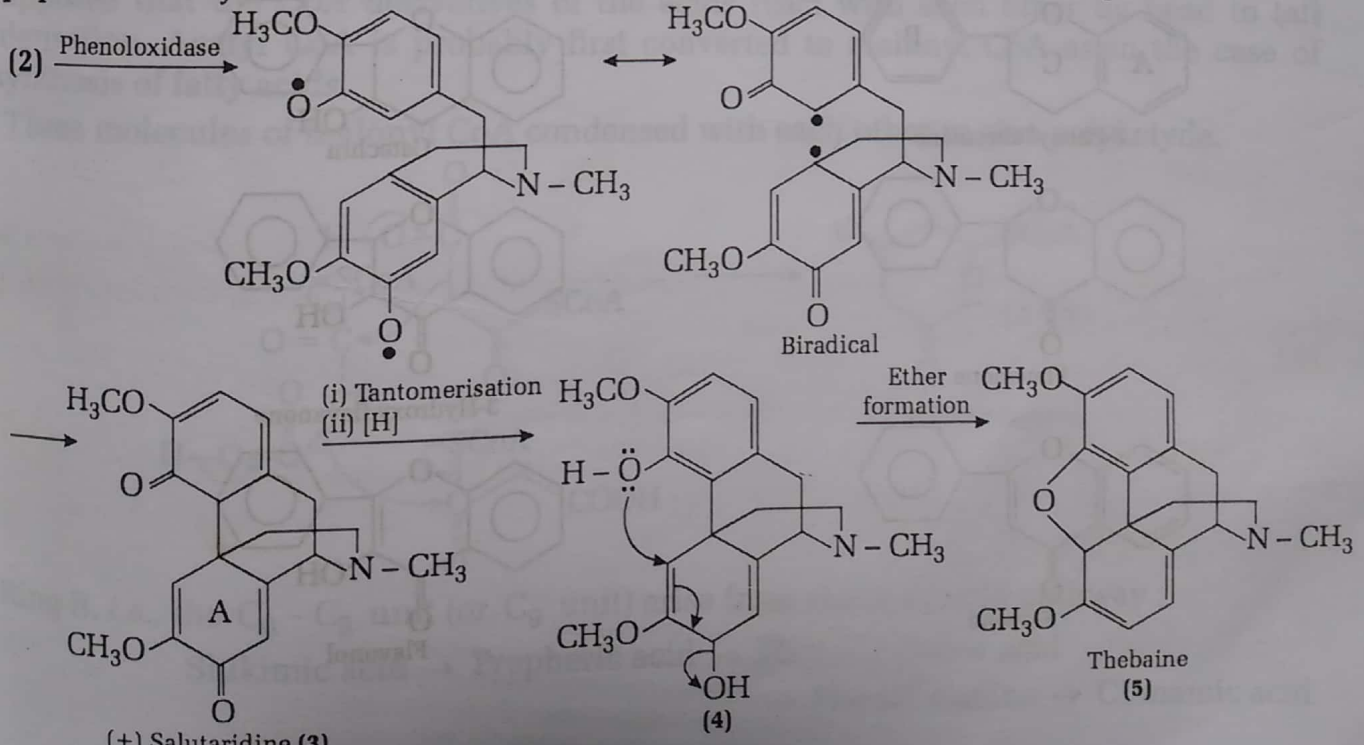
The feeding of labelled precursors has shown that norlaudanosoline is a precursor of codein and morphine. Feeding experiment also shows that the actual precursor of codein and morphine is (–) reticuline (2) which is originated by trimethylation of norlaudanosoline.



(2) ⊖ Reticuline

(2)

(–) Recticuline converts into a biradical in the presence of phenol oxidase. This diradical then converts into salutaridine **(3)**. Salutaridine is an alkaloid isolated from *papaver somniferum*. Solutaridine then converted into codeine and morphine.

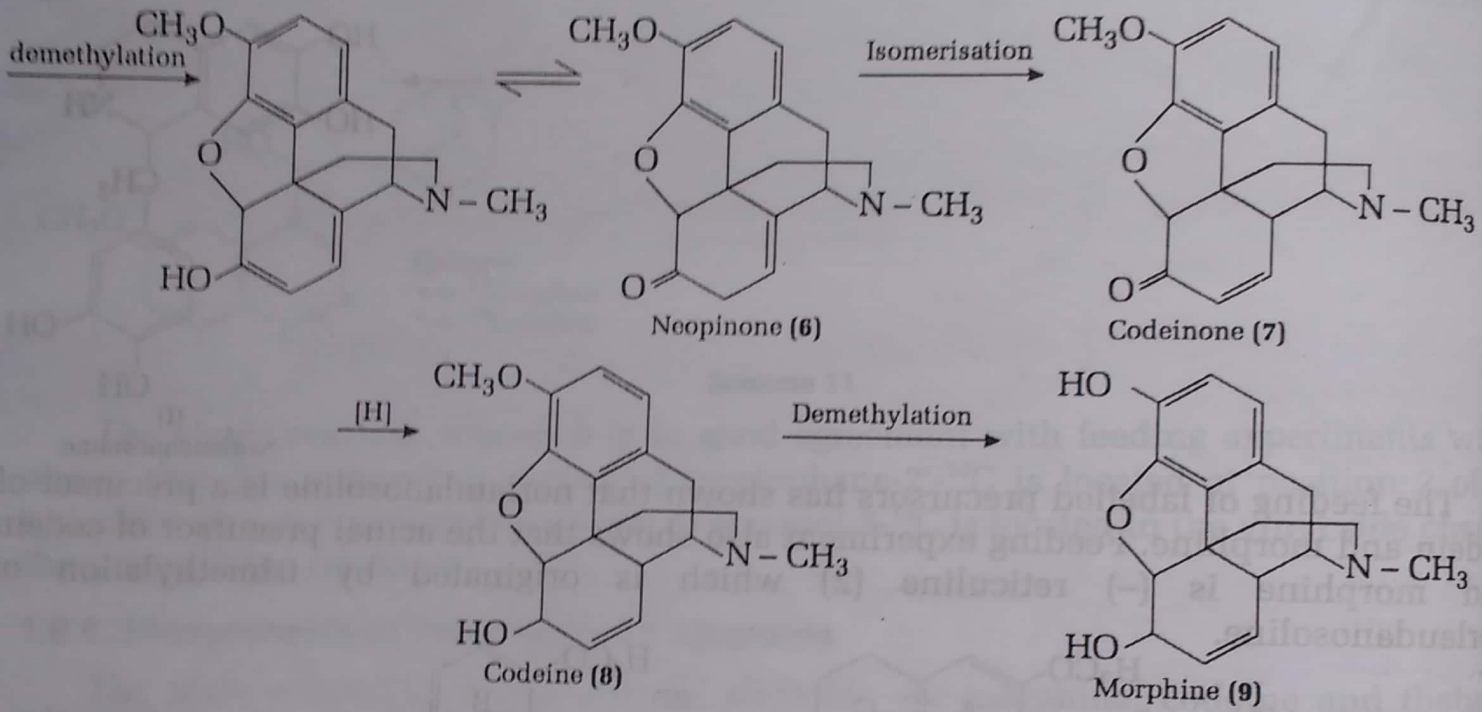


Biradical

(+) Salutaridine **(3)**

(4)

Thebaine
(5)



Scheme 12 : Biosynthesis of codeine and morphine