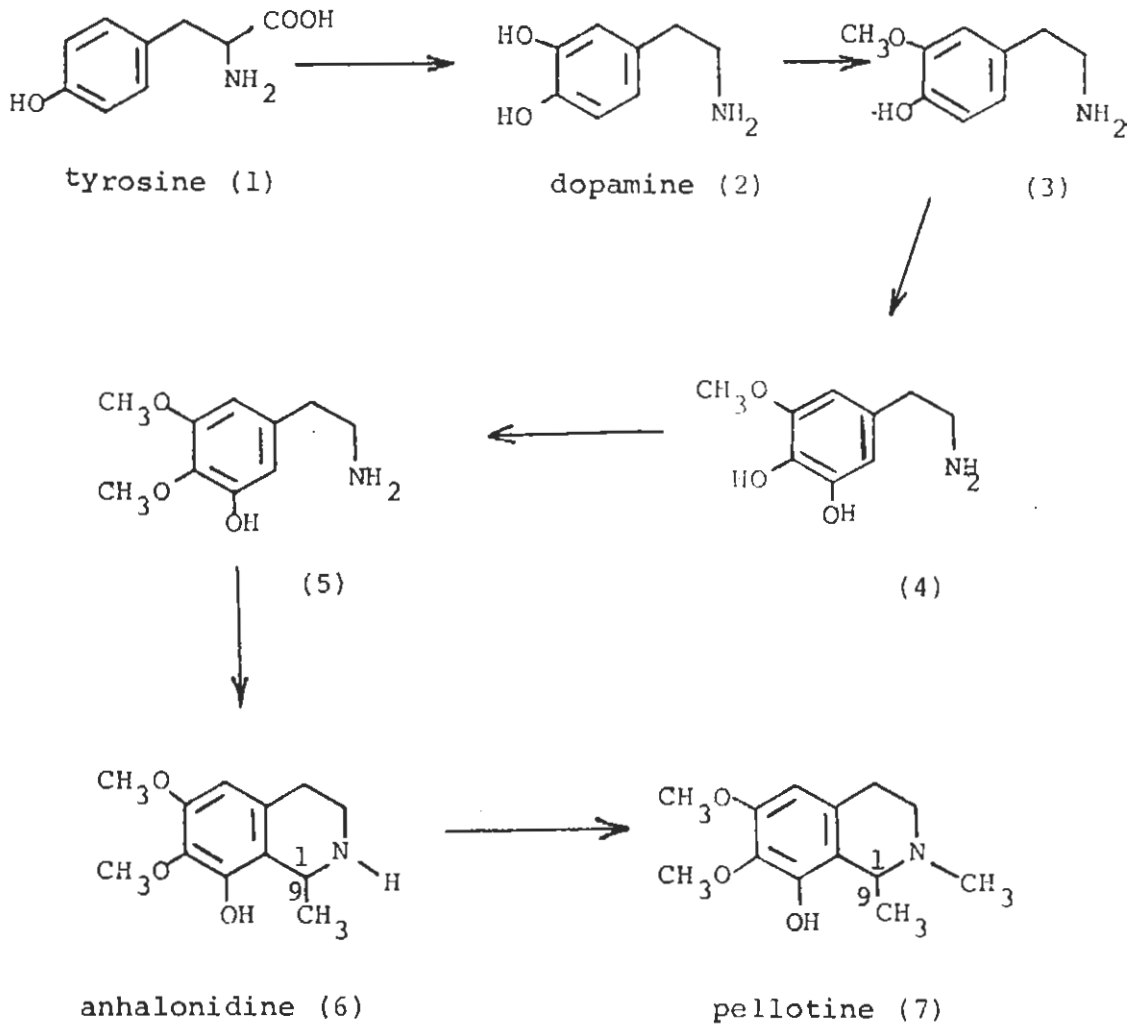


## 1.1 BIOSYNTHESIS OF ISOQUINOLINE ALKALOIDS

The isoquinoline alkaloids constitute one of the largest group of alkaloids, possessing a wide variety of structures. They occur most frequently in the Anonaceae, Berberidaceae, Fumariaceae, Papaveraceae and Ranunculaceae families.

### i) Simple Tetrahydroisoquinoline Alkaloids

Biosynthesis of the simple tetrahydroisoquinolines starts with the conversion of the amino acid tyrosine (1) to dopamine (2). This is O-methylated to 4-hydroxy-3-methoxyphenylethylamine (3),<sup>1,2</sup> which is a key intermediate from which the various tetrahydroisoquinoline alkaloids such as anhalonidine (6), pellotine (7) etc. arise (Scheme 1). It was originally assumed that the two-carbon unit which is incorporated in Cactaceae alkaloids such as anhalonidine (6) and pellotine (7) was derived from acetic acid. However, after feeding acetic acid labelled at C-1 to the Peyote cactus, *Lophophora williamsii* (Lemaire) Coult, pellotine (7) was isolated with the activity equally divided between C-1 and C-9 carbons, suggesting that acetic acid is not a direct precursor of the two carbon unit.<sup>1,3,4</sup>

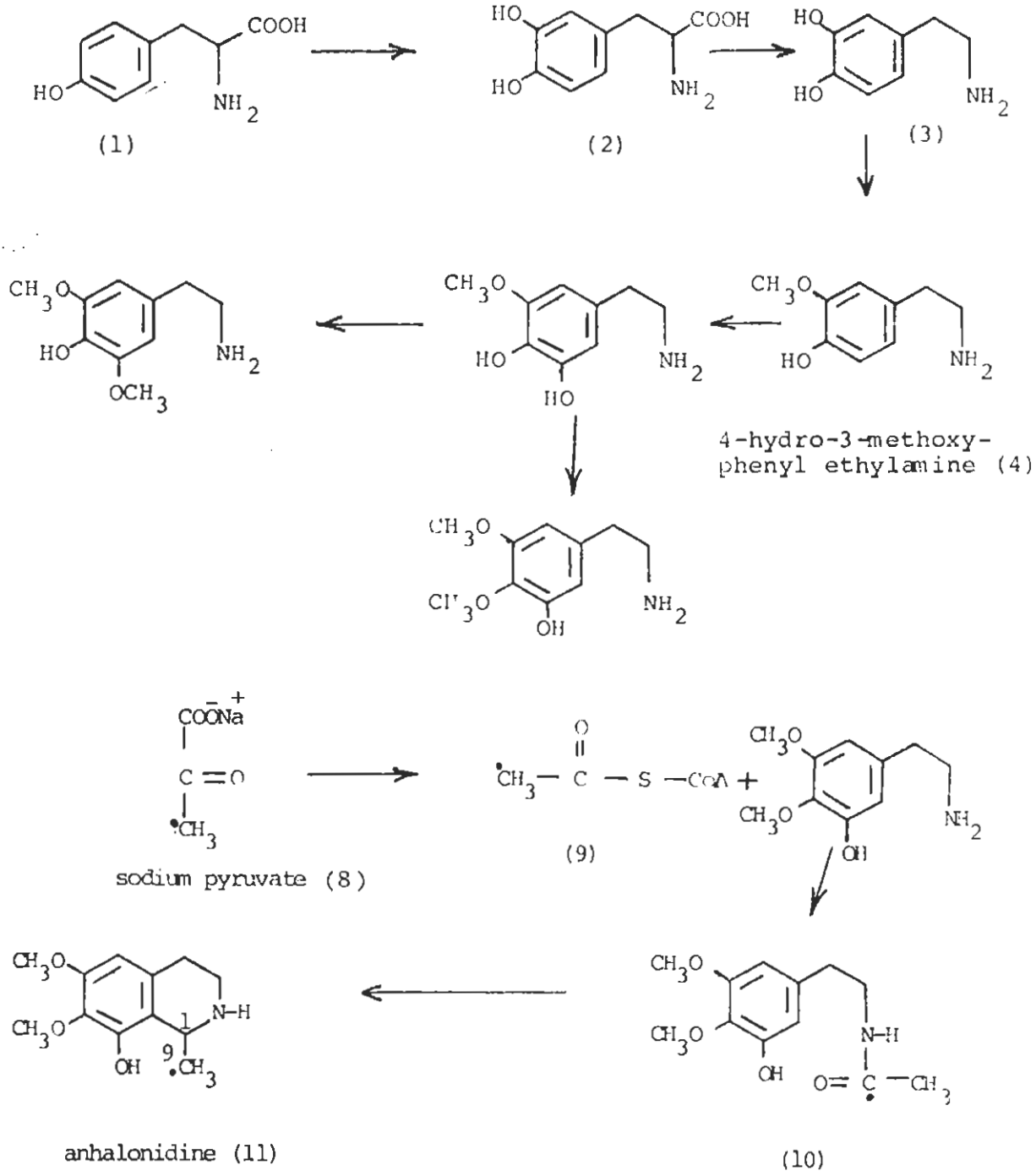


Scheme-1

The biosynthesis of anhalonidine (11) in *Lophophora williamsii* (Lemaire) was followed by feeding labelled sodium pyruvate (8), and the C-3 of pyruvate was found to be incorporated into C-9 of anhalonidine (11). The tetrahydroisoquinoline alkaloids having a methyl group at C-1 of anhalonidine are formed through the intermediacy of acetyl co-enzyme-A (9) and N-acetyl phenethyl amine (10)<sup>4</sup> (Scheme 2).

Anhalamine (19) and anhalonidine (11) are biosynthesized from the amino acid peyoxylic acid (18) and peyoruvic acid (20) respectively.<sup>6</sup> Thus administration of labelled peyoxylic acid and peyoruvic acid to the plant *Lophophora williamsii* led to the specific incorporation of the labels in anhalamine (19) and anhalonidine (11), respectively (Scheme 3).

The biosynthesis of another tetrahydroisoquinoline alkaloid, lophocerine (17) in *Cactus lophocereus Schottii* (Engelm) Britt.et.Rose,<sup>5</sup> has been studied by feeding labelled precursors. It has been shown that racemic leucine (15) and racemic mevalonic acid (12) act as precursors for the isoprenoid moiety of lophocerine (17) (Scheme 4), while racemic tyrosine (1) acts as the precursor



Scheme-2



peyoxylic acid (18)

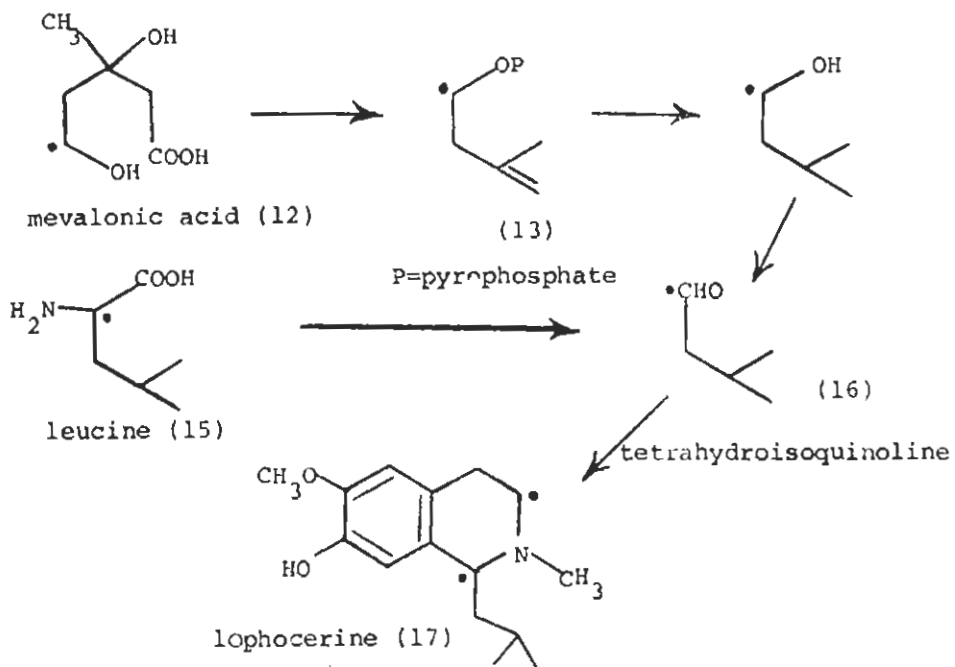
anhalamine (19)



peyoruvic acid (20)

anhalonidine (11)

Scheme-3



Scheme-4

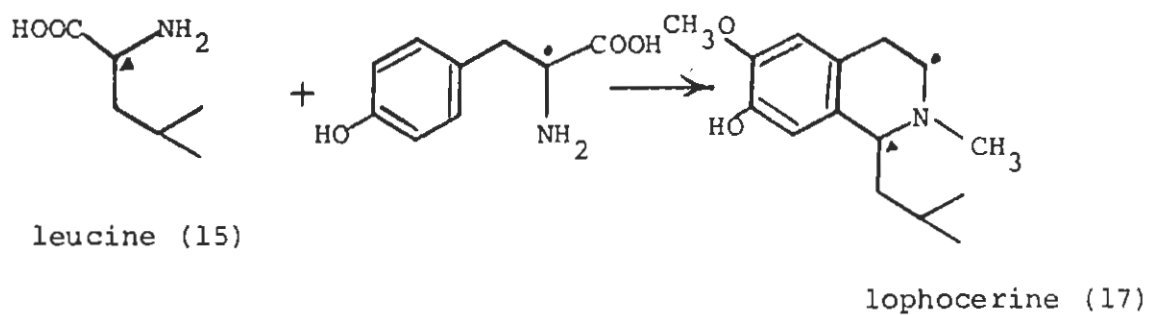
for the phenylethylamine portion of the tetrahydroisoquinoline nucleus (Scheme 5).

ii) Benzylisoquinoline Alkaloids

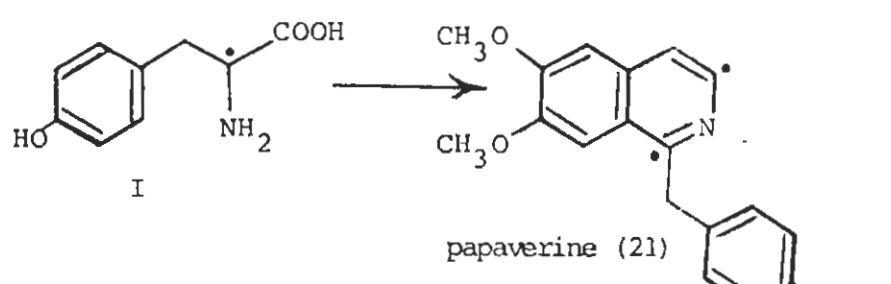
The benzylisoquinoline alkaloids are biosynthesized from two molecules of tyrosine (1). Thus when (+)-tyrosine labelled at C-2 was fed to *Papaver somniferum* L. carbons C-1 and C-3 of papaverine were found to be radioactive indicating that papaverine is derived from two units of tyrosine<sup>15</sup> (Scheme 6). Similarly labelled (+)-N-norlaudanosoline (22) has been shown to be the precursor of reticuline (23) in *Papaver somniferum* L. (Scheme 6a)

iii) Protoberberine Alkaloids

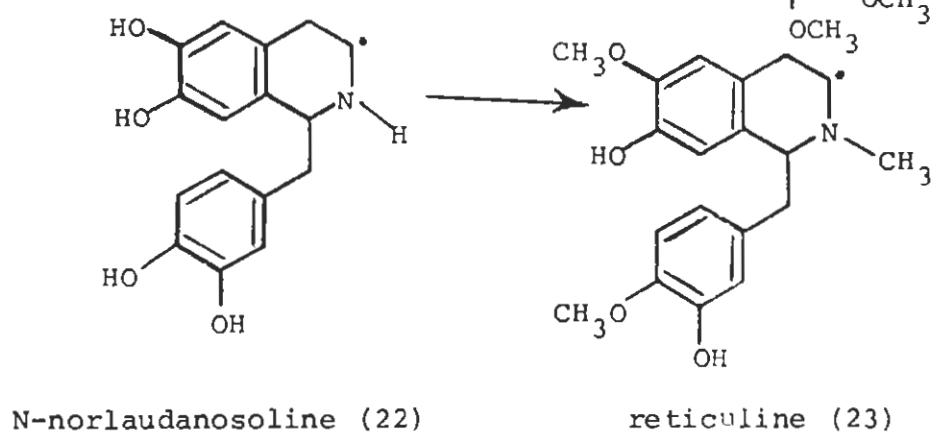
The biosynthesis of berberine (24) has been investigated by Spenser and co-workers<sup>17</sup> by feeding labelled C-2 tyrosine into *Hydrastis canadensis* L. Carbon atoms C-6 and C-14 of berberine were found to be radioactive, which indicated that berberine was biosynthesized from two units of tyrosine (1) (Scheme 7). The biosynthesis of berberine (26) was also investigated by feeding labelled (+)-laudanosoline (25) to *Berberis japonica*<sup>18</sup> Lindl. (Scheme 8).



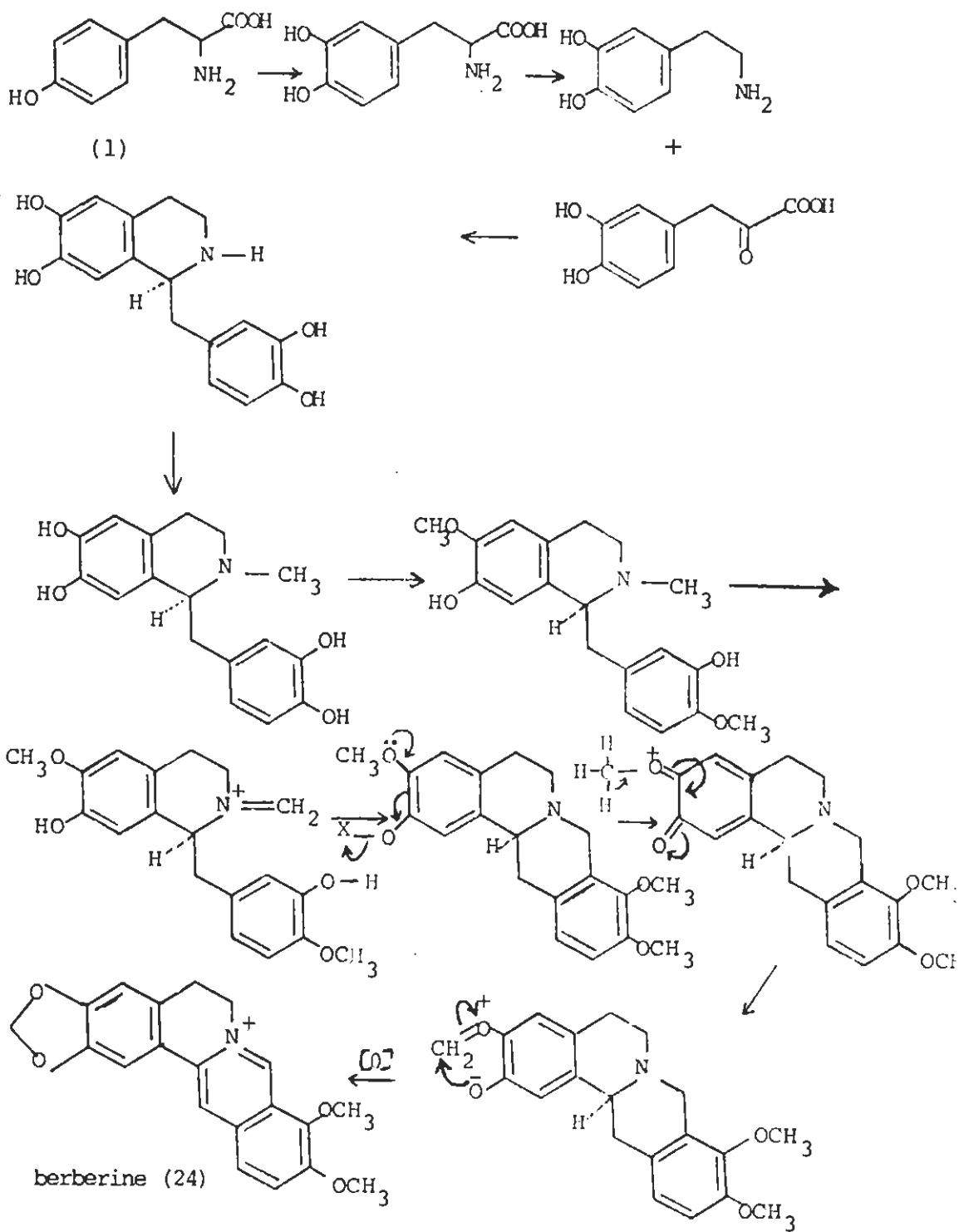
Scheme-5



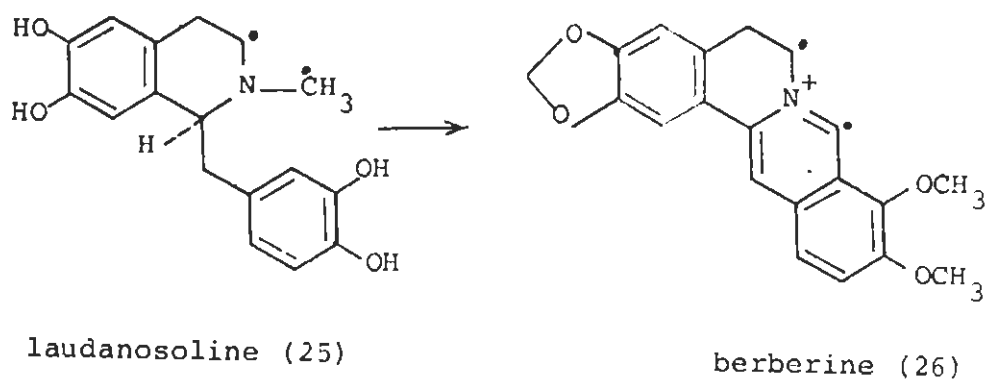
Scheme-6



Scheme-6a



Scheme-7



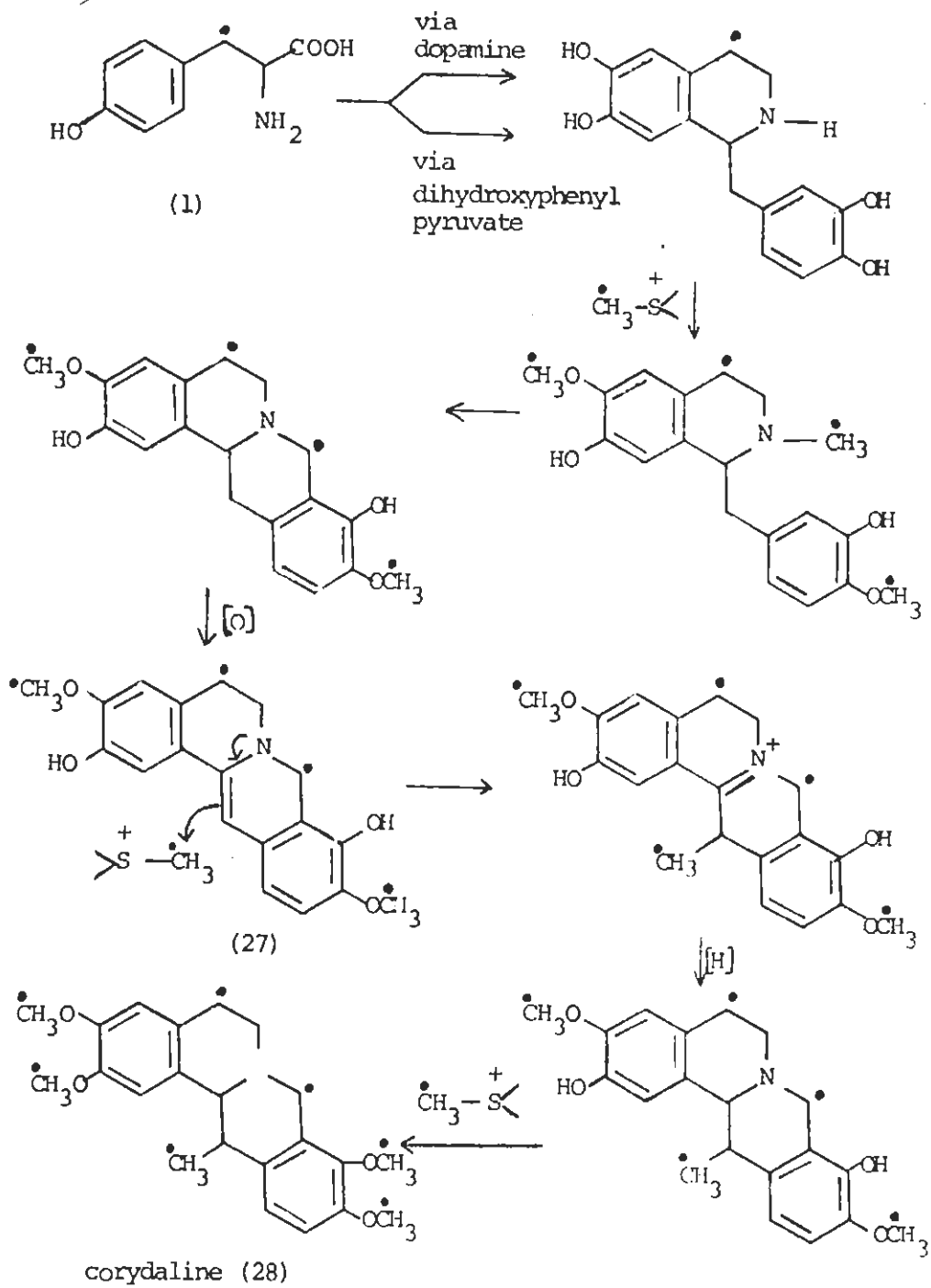
Scheme-8

iv) Corydaline and Ochotensimine Alkaloids

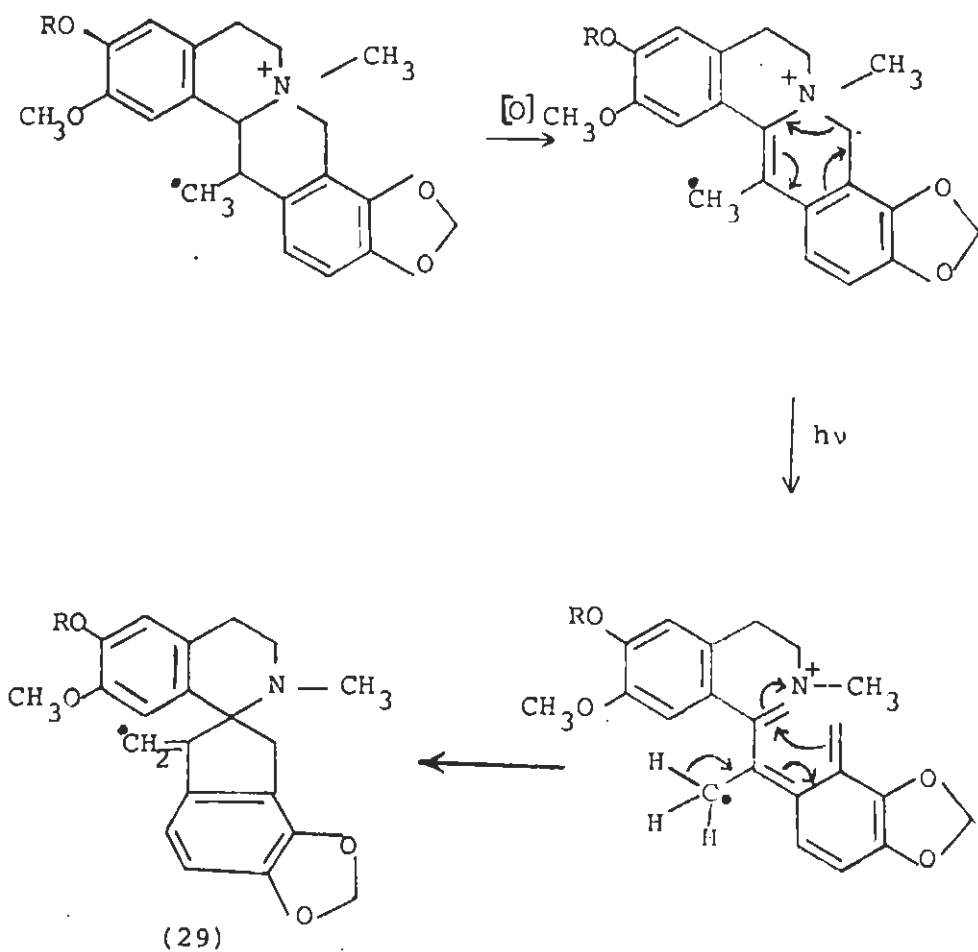
The corydaline skeleton is generated through the intermediacy of protoberberine system (27). It has been shown that the C-methyl group of corydaline (28) arises from a one-carbon unit which is introduced into C-13 of a preformed protoberberine system (27). The methyl group of methionine supplies the C-methyl group of corydaline. This was demonstrated by Holland et.al.<sup>19</sup> by feeding tyrosine labelled at C-3 and methionine having C-14 methyl into *Corydalis solida* sw (Fumariaceae) (Scheme 9). The exocyclic methylene groups of spirobenzylisoquinoline alkaloid ochotensimine (29) also arise from the same source (Scheme 10).

v) Phthalideisoquinoline Alkaloids

The biosynthesis of phthalideisoquinoline alkaloid narcotine (32) was studied<sup>7,10,11</sup> by feeding labelled tyrosine (1) into plant *Papaver somniferum* L. (Scheme 11). Narcotine (34) labelled at C-1 was obtained by feeding the benzylisoquinoline alkaloid (+)-norlaudanoline (33) labelled at C-1<sup>8</sup> (Scheme 12). Radioactive narcotine (31) was also formed by feeding the protoberberine alkaloid (-)-scoulerine (30) into the plant<sup>7-9</sup> (Scheme 13), which showed



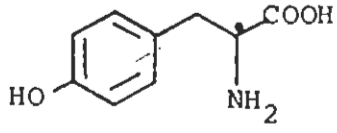
Scheme-9



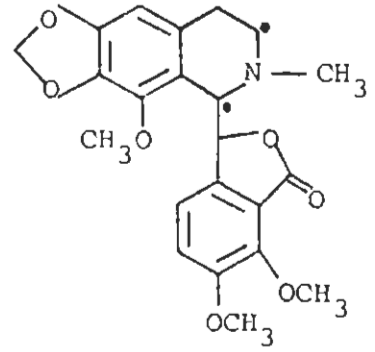
$\text{R}=\text{H}$ , ochotensine

$\text{R}=\text{CH}_3$ , ochotensimine

Scheme-10

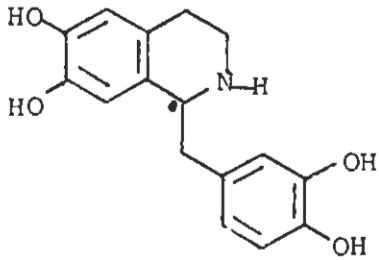


(1)

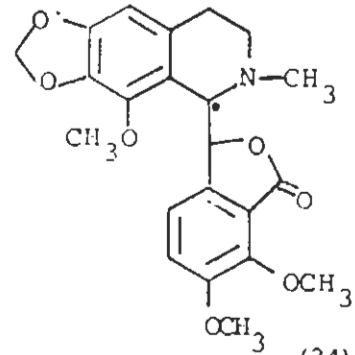


narcotine (32)

Scheme-11

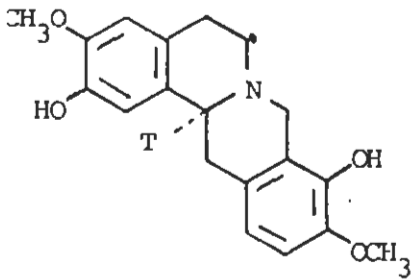


norlaudanosaline (33)

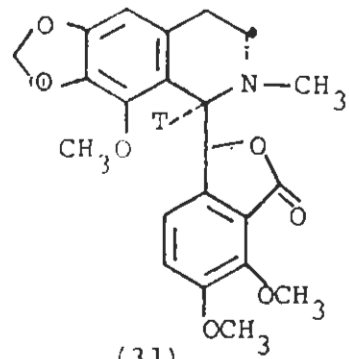


(34)

Scheme-12



scoulerine (30)



(31)

Scheme-13

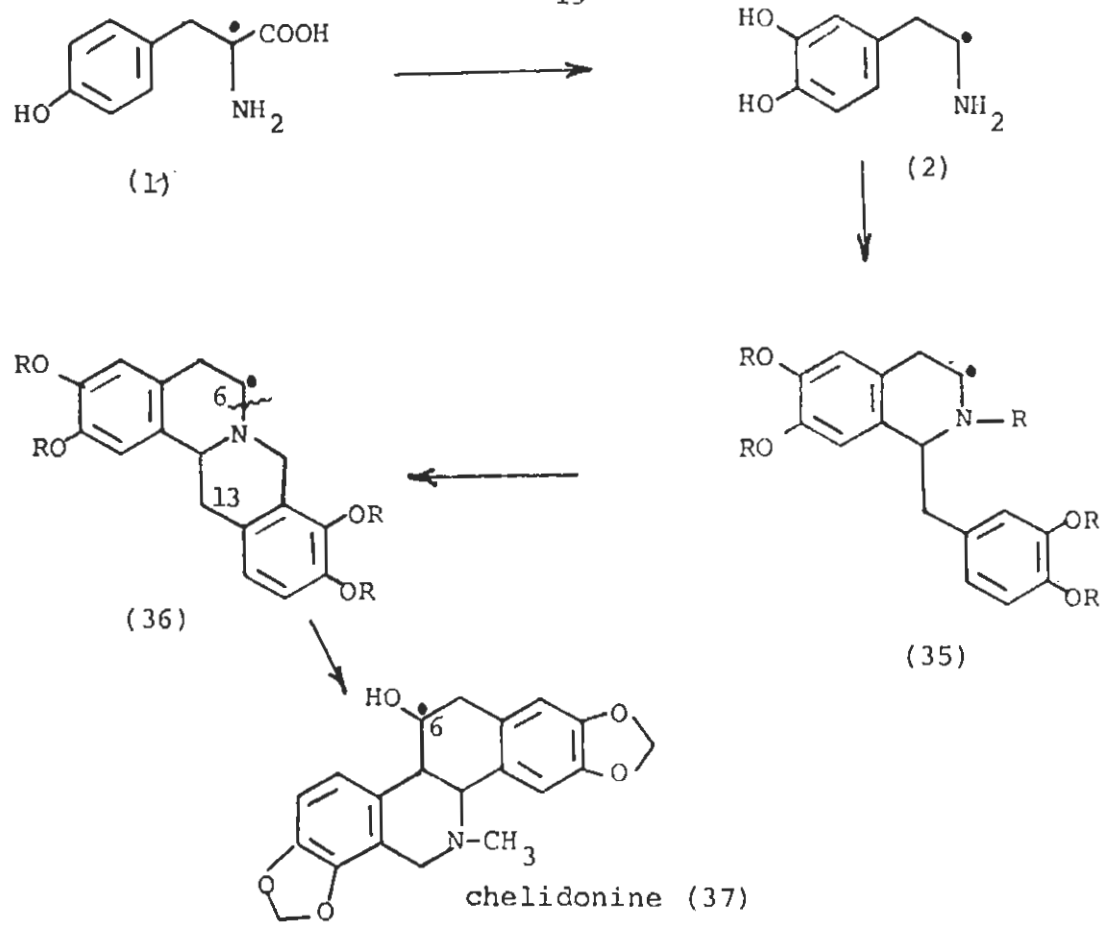
that protoberberine alkaloids are precursors for the phthalideisoquinoline alkaloids.

vi) Benzophenanthridine Alkaloids

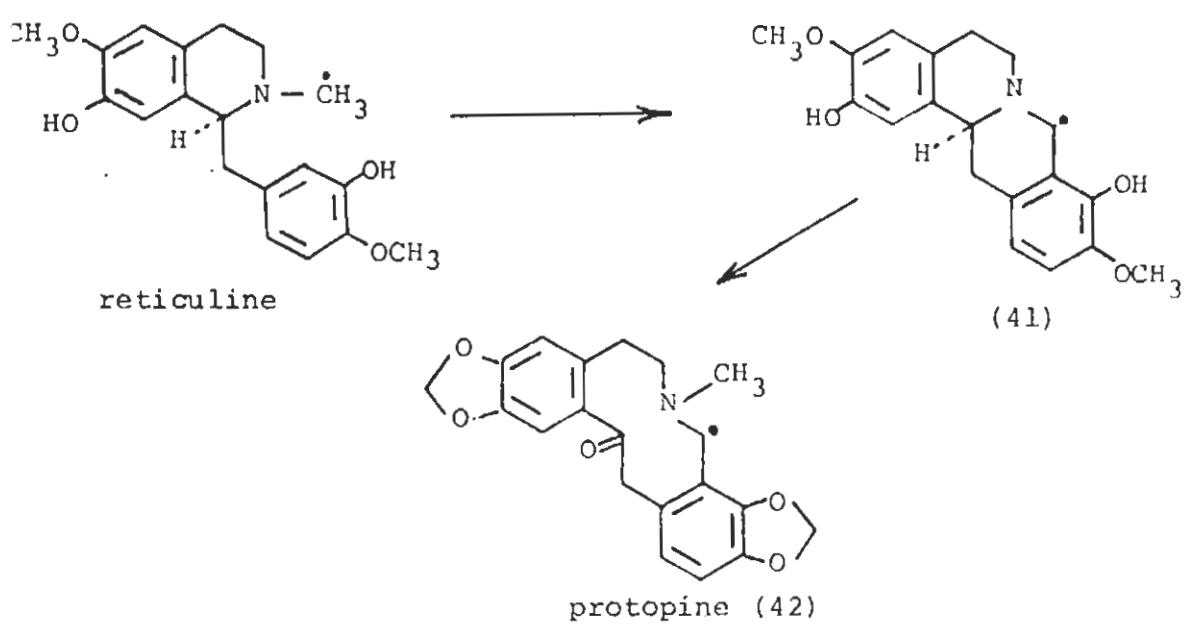
The benzophenanthridine alkaloids are formed in plants through cleavage of the 6,7 bond of protoberberine alkaloids which is followed by the joining of C-6 to the C-13. This has been proved by feeding labelled tyrosine (1) to *Chelidonium majus* L. (Papaveraceae) which resulted in the formation of a protoberberine alkaloidal system (36) which is then converted to radioactive chelidonine (37) labelled at C-6<sup>12</sup> (Scheme 14).

vii) Protopine Alkaloids

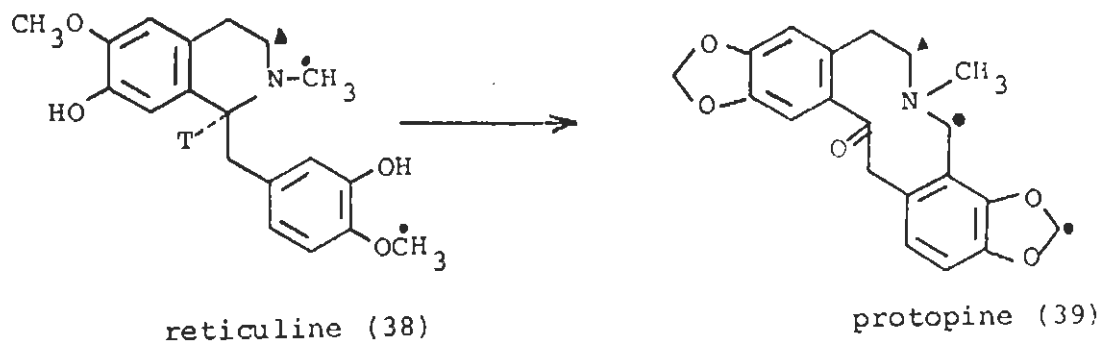
The protopine alkaloids are formed in plants by oxidation of protoberberine alkaloids. This was shown by feeding labelled (+)-reticuline hydrochloride to *Dicentra spectabilis* Lem (Fumariaceae) which afforded labelled protopine (42)<sup>13</sup> (Scheme 15). The biosynthesis of protopine (39) was also studied<sup>14</sup> by feeding multi-labelled reticuline (38) into *Chelidonium majus* L (Papaveraceae) (Scheme 16).



Scheme-14



Scheme-15



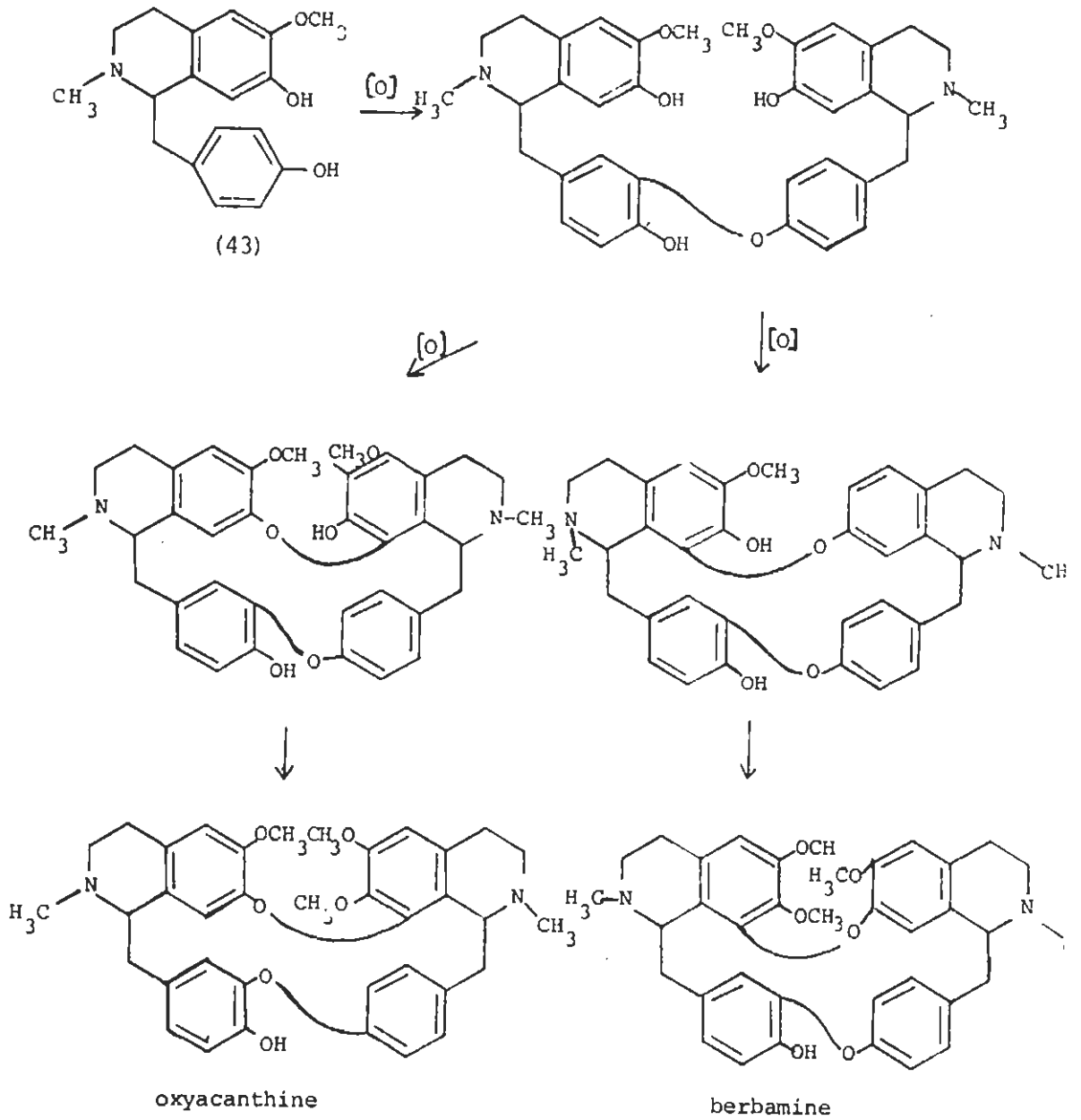
Scheme-16

viii) Bisbenzylisoquinoline Alkaloids

Bisbenzylisoquinoline alkaloids are formed in nature through the phenolic oxidation coupling of simple benzylisoquinoline alkaloids such as coclaurine, norcoclaurine and N-methylcoclaurine (43) (Scheme 17). Enzymic phenol oxidation<sup>21</sup> 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 being oxidised by divalent copper to the phenoxy radical.

ix) Pseudobenzylisoquinoline Alkaloids

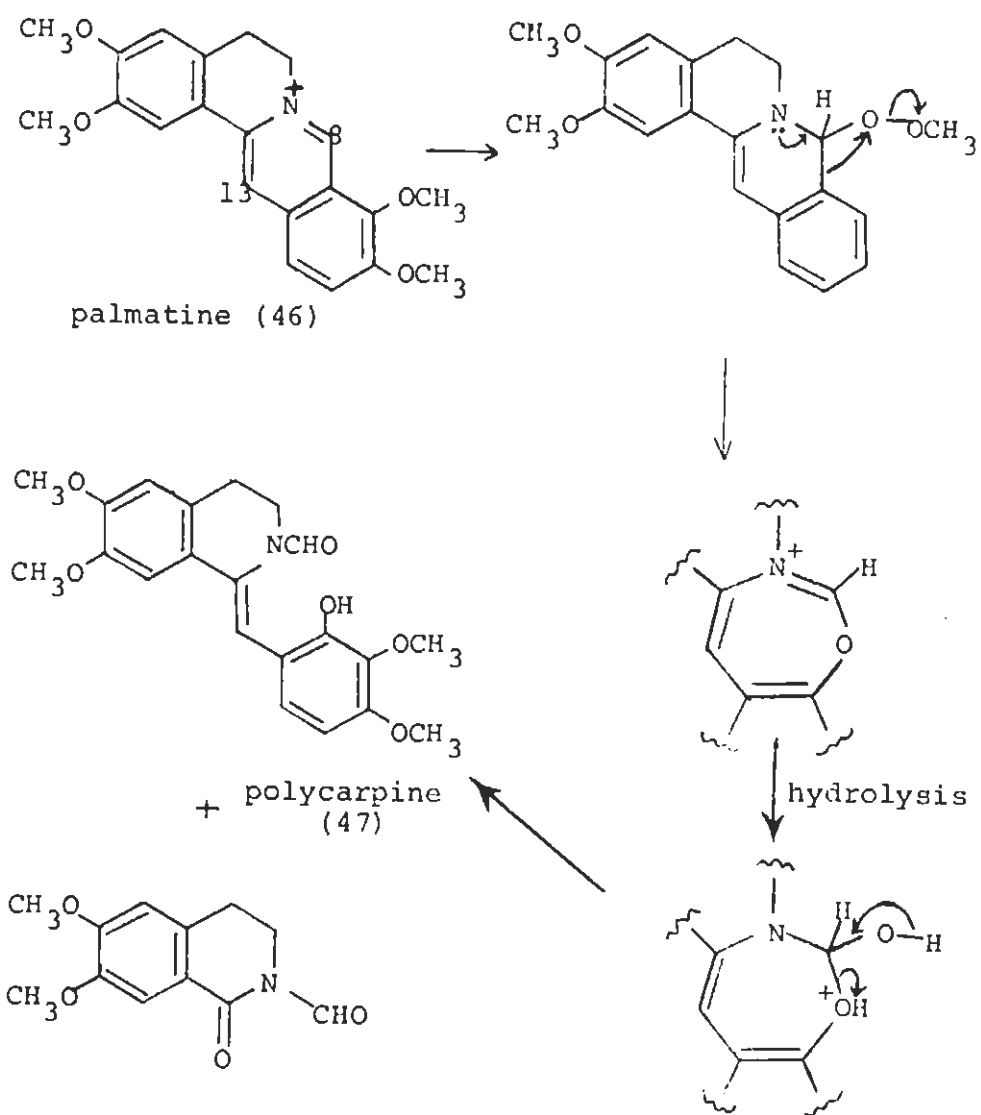
Benzylisoquinoline alkaloids which incorporate three oxygenated substituents in the bottom ring are called pseudobenzylisoquinoline alkaloids. Although no in vivo studies using labelled precursors have as yet been conducted to ascertain their biogenesis, the pseudobenzylisoquinoline alkaloids most probably originate from the oxidation of protoberberinium salts.<sup>20</sup> It appears that polycarpine (47)



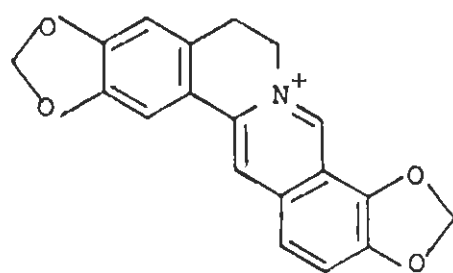
Scheme-17

is derived biogenetically from the protoberberinium salt palmatine (46) through hydroperoxide attack at the C-3 iminium site, followed by rearrangement and hydrolysis as mentioned in Scheme 18.

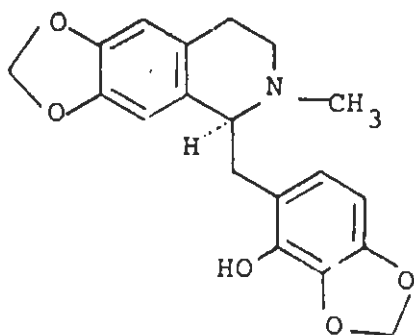
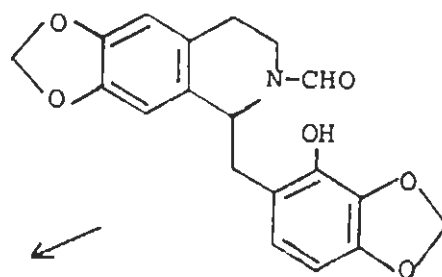
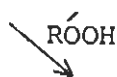
Another pseudobenzylisoquinoline alkaloid named (-)-ledecorine (49) is probably derived from the protoberberine alkaloid coptisine (48)<sup>19</sup> as shown in Scheme 19.



Scheme-18



coptisine (48)



leddecorine (49)

Scheme-19