CHAPTER II

HISTORICAL REVIEW

Alkaloidal Distribution in Genus *Annona*

Since 1930, the first study of Annona alkaloids from - A. *reticulata* Linn(50), there have been about 40 alkaloids of known structures from 11 out of 207 species. It is striking, that for its size the genus *Annona* is perhaps one of the chemically least known.

The alkaloidal distribution in the genus *Annona* is summarized in Table 2.

Table 2 Alkaloidal Distribution in genus *Annona*

Plant (Part)	Alkaloid	Structure No.	Type	Reference
Annona acuminata Saff.	Liriodenine	34	Oxoaporphine	10
	Lysicamine	35	"	51
	Homomoschatoline (O-methylmoschatoline Liridine)	32	"	52

Table 2 (continued)

Plant (Part)	Alkaloid	Structure No.	Type	Reference
Annona cherimolia Mill.	(-)-Anonaine	14	Aporphine	1
	Caffeine	40	Xanthine	53-55
(Seeds, Twigs)	(+)-Corytuberine	17	Aporphine	72
	(+)-Isoboldine	20	"	
	Lanuginosine	33	Oxoaporphine	
	Liriodenine	34	"	
	(+)-Nornantenine	25	Aporphine	
	(-)-Norushinsunine (Michelalbine)	28	7-substituted-aporphine	
	(+)-Reticuline	8	Tetrahydro-benzylisoquinoline	
	(-)-Stepholidine	10	Tetrahydro - protoberberine	
Annona crassiflora Mart.	(-)-Anonaine	14	Aporphine	1
	Asimilobine	15	"	56
(Leaves, Stem-barks)	Liriodenine	34	Oxoaporphine	
	(+)-Reticuline	8	Tetrahydro - benzylisoquinoline	

Table 2 (continued)

Plant (Part)	Alkaloid	Structure No.	Type	Reference
Annona cristalensis (Aerial parts)	Liriodenine	34	Oxoaporphine	35
	(R)-Coclaurine	5	Tetrahydro - benzylisoquinoline	
Annona elliptica R.E. Fries (Leaves, Stems)	(-)-Annonelliptine	2	Tetrahydro - benzylisoquinoline	57
Annona glabra Linn. (Leaves, Seeds, Stem barks)	(-)-Anolobine	13	Aporphine	1
	(-)-Anonaine	14	"	58-60
	Asimilobine	15	"	
	(+)-Isoboldine	20	"	
	Liriodenine	34	Oxoaporphine	
	(-)-N-methylactinodaphnine	22	Aporphine	
	(-)-Nornuciferine	26	"	
	Norushinsunine (Michelalbine)	28	7-substituted-aporphine	
	(+)-Reticuline	8	Tetrahydro - benzylisoquinoline	
	(+)-Roemerine	30	Aporphine	

Table 2 (continued)

Plant (Part)	Alkaloid	Structure No.	Type	Reference
Annona montana Macfad.	Annomontine	41	Pyrimidine-β-carboline	1
(Stem barks, Root barks)	(-)-Anonaine	14	Aporphine	61,62
	Argentinine	39	Phenanthrene	
	Asimilobine	15	Aporphine	
	Atherosperminine	38	Phenanthrene	
	(-)-Coreximine	9	Tetrahydro - protoberberine	
	(-)-Isoboldine	20	Aporphine	
	Liriodenine	34	Oxoaporphine	
	Methoxyannomontine	42	Pyrimidine-β-carboline	
	(+)-Reticuline	8	Tetrahydro - benzylisoquinoline	
Annona muricata Linn.	Anomuricine	3	Tetrahydro - benzylisoquinoline	1
(Leaves, Root-barks, Stem-barks)	Anomurine	4	"	63-65
	Atherosperminine	38	Phenanthrene	
	Coclaurine	5	Tetrahydro - benzylisoquinoline	

Table 2 (continued)

Plant (Part)	Alkaloid	Structure No.	Type	Reference
Annona muricata Linn.	Coreximine	9	Tetrahydro - protoberberine	
(Leaves, Root-barks, Stem barks)	(+)-Reticuline	8	Tetrahydro-benzylisoquinoline	
	(+)-Stepharine	12	Proaporphine	
Annona purpurea Linn.	(+)-Glaziovine	11	Proaporphine	1
	(-)-Isocorydine	21	Aporphine	36
(Leaves, Stems)	Norpurpureine	27	"	
	O-Demethylpurpureine	18	"	
	Oxoglaucine	36	Oxoaporphine	
	Oxopurpureine	37	"	
	Purpureine	29	Aporphine	
	(+)-Stepharine	12	Proaporphine	
Annona reticulata Linn.	(-)-Anonaine	14	Aporphine	1
	Coclaurine	5	Tetrahydro - benzylisoquinoline	66-68
(Root barks, Stem barks)	Liriodenine	34	Oxoaporphine	
	(-)-Norushinsunine (Michelalbine)	28	7-substitute aporphine	

Table 2 (continued)

Plant (Part)	ALkaloid	Structure No.	Type	Reference
Annona reticulata Linn.	(+)-Reticuline	8	Tetrahydro - benzylisoquinoline	
(Root barks, Stem barks)	Salsolinol	1	Simple Tetrahydro-isoquinoline	
Annona squamosa Linn.	(-)-Anolobine	13	Aporphine	1-9
	(-)-Anonaine	14	"	
(Stems, Leaves,	(+)-Corydine	16	"	
Roots, Barks,	(-)-Isocorydine	21	"	
Seeds)	(+)-Glaucine	19	"	
	Higenamine	6	Tetrahydro - benzylisoquinoline	
	Lanuginosine (Oxoxylopine)	33	Oxoaporphine	
	Liriodenine	34	"	
	(+)-Norcorydine	23	Aporphine	
	(+)-Norisocorydine	24	"	
	(-)-Norushinsunine (Michelalbine)	28	7-substituted-aporphine	
	(+)-O-methylarmepavine	7	Tetrahydro - benzylisoquinoline	

Table 2 (continued)

Plant (Part)	Alkaloid	Structure No.	Type	Reference
Annona squamosa Linn.	(+)-Reticuline	8	Tetrahydro - benzylisoquinoline	1-9
(Stems, Leaves,	(-)-Roemerine	30	Aporphine	
Roots, Barks,	(-)-Xylopine	31	"	
Seeds)				

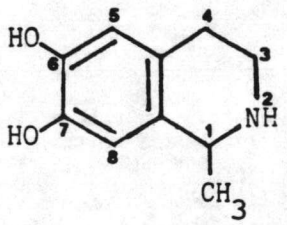
Chemistry of *Annona* Alkaloids

The majority of alkaloids found in *Annona spp.* possess an isoquinoline derived structure (39 out of 42 alkaloids). They are simple tetrahydroisoquinolines, tetrahydrobenzylisoquinolines, protoberberines, proaporphines, aporphines, oxoaporphines and phenanthrenes. Only three alkaloids found in *Annona spp.* are non-isoquinoline. The figure in square bla following the name of alkaloid type indicating the number of alkaloid in that type.

The numbering and structure of the alkaloids are as follows.

1. Simple Tetrahydroisoquinoline [1]

Although many of the simple tetrahydroisoquinolines have been found in Cactaceae and are also present in some members of the Papaveraceae and Fumariaceae (69), one of them, salsolinol (#1), surprisingly found in *Annona reticulata* Linn., together with dopamine, its biogenetic precursor (1).

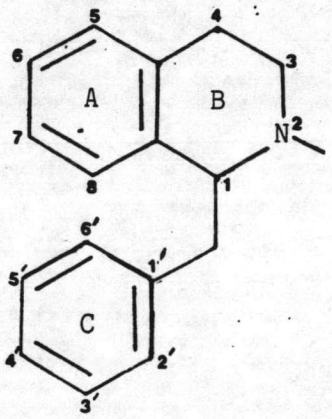


#1 Salsolinol

2. Benzylisoquinolines [7]

Seven tetrahydrobenzylisoquinolines were isolated from some species of *Annona* as shown in Table 3. The most frequently occuring tetrahydrobenzylisoquinoline is reticuline (#8). The alkaloid isolated by Meyer in 1941 from *Annona muricata* Linn, under the name " muricinine ", was later identified to be reticuline by Santos *et al.* (1).

Anomuricine (#3), anomurine (#4) from *Annona muricata* Linn. (63), and annoelliptine (#2) from *Annona elliptica* R.E. Fries (57), are special in that they are substituted at C-5 (1).

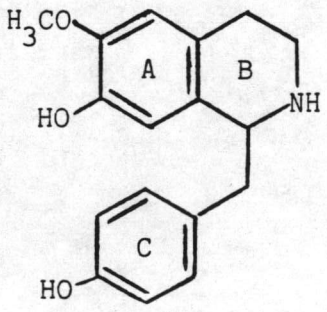


Tetrahydrobenzylisoquinoline

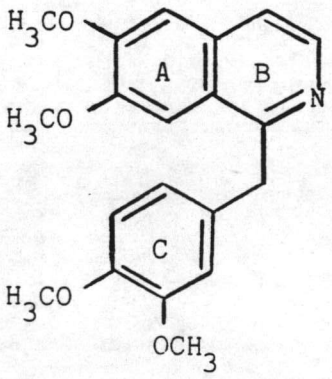
Table 3 Tetrahydrobenzylisoquinolines isolated from *Annona spp.*

Structure No.	Alkaloid	Substitutions					
		2	5	6	7	3'	4'
2	Annoelliptine	CH_3	OCH_3	OCH_3	OH	-	OH
3	Anomuricine	H	OH	OCH_3	OCH_3	-	OCH_3
4	Anomurine	H	OCH_3	OCH_3	OCH_3	-	OCH_3
5	Coclaurine	H	-	OCH_3	OH	-	OH
6	Higenamine	H	-	OH	OH	-	OH
7	O-methylarmepavine	CH_3	-	OCH_3	OCH_3	-	OCH_3
8	Reticuline	CH_3	-	OCH_3	OH	OH	OCH_3

The benzylisoquinoline alkaloids are either of the 1,2,3,4, - tetrahydroisoquinoline type, such as coclaurine (#5), or of the completely aromatic type, as in the case of papaverine (#43).



#5 Coclaurine



#43 Papaverine

Ring A in the benzylisoquinoline alkaloids may possess two or three oxygenated substituents, while ring C has only one or two substituents. No C-4 hydroxylated benzylisoquinoline has yet been isolated from nature, although it is more than probable that they do exist (70).

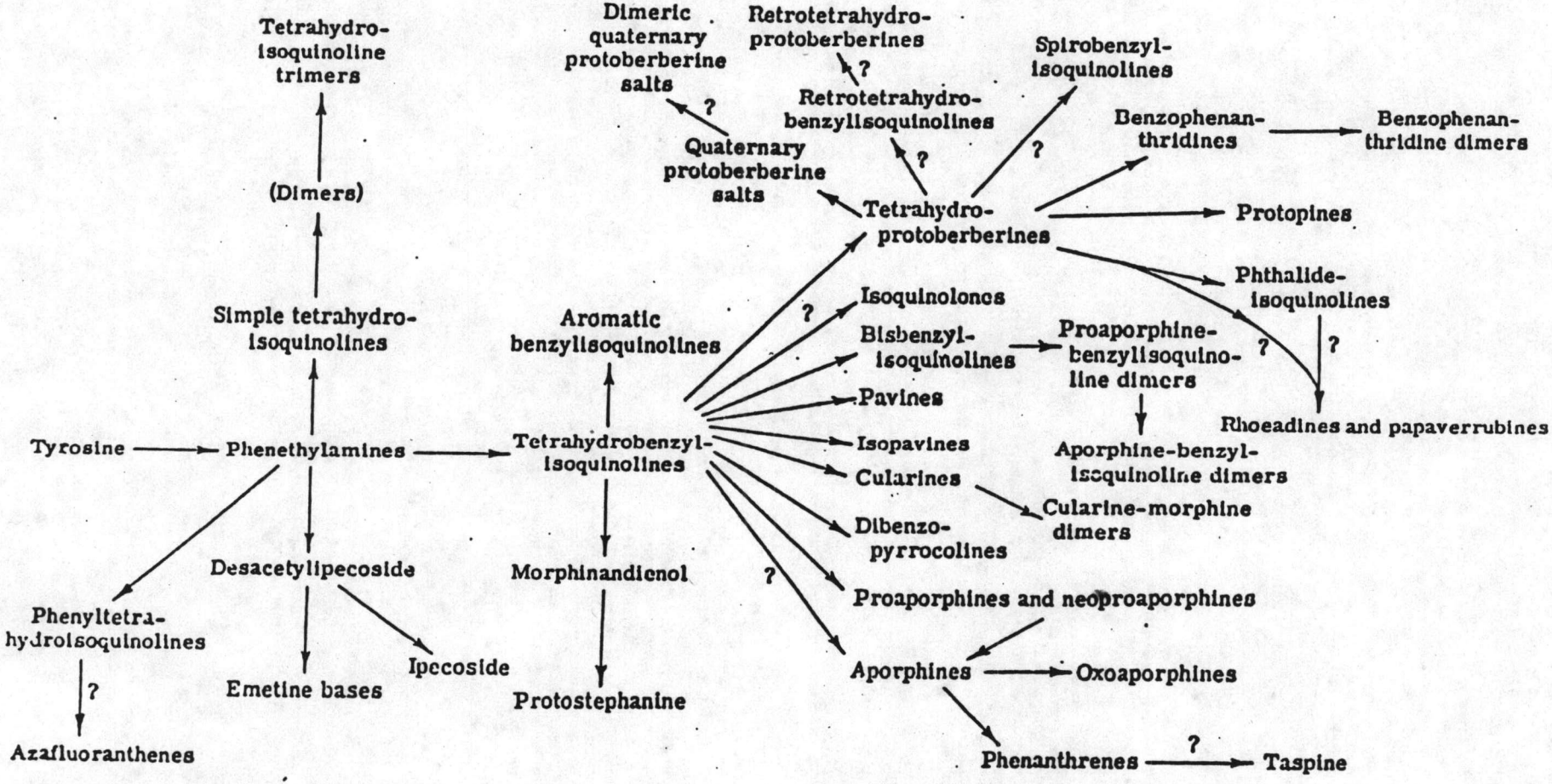
The alkaloids of the benzylisoquinoline type, are a vast and complex group of alkaloids (77). They occupy a paramount position in alkaloid chemistry because they act as *in vivo* precursors to so many of the other natural occuring isoquinolines: isoquinolones, pavines, isopavines, bisbenzylisoquinolines, cularines, dibenzopyrrocolines, morphines, cularine-morphine dimers, proaporphines, aporphines, protoberberines and others (70). Some of proven or probable biogenetic loci for the formation of the isoquinoline alkaloids are illustrated in Scheme I (71). (Page 26)

In addition the biogenetic relationship of the major alkaloid groups derived from a tetrahydrobenzylisoquinoline precursor are shown in Scheme II (77). (Page 27)

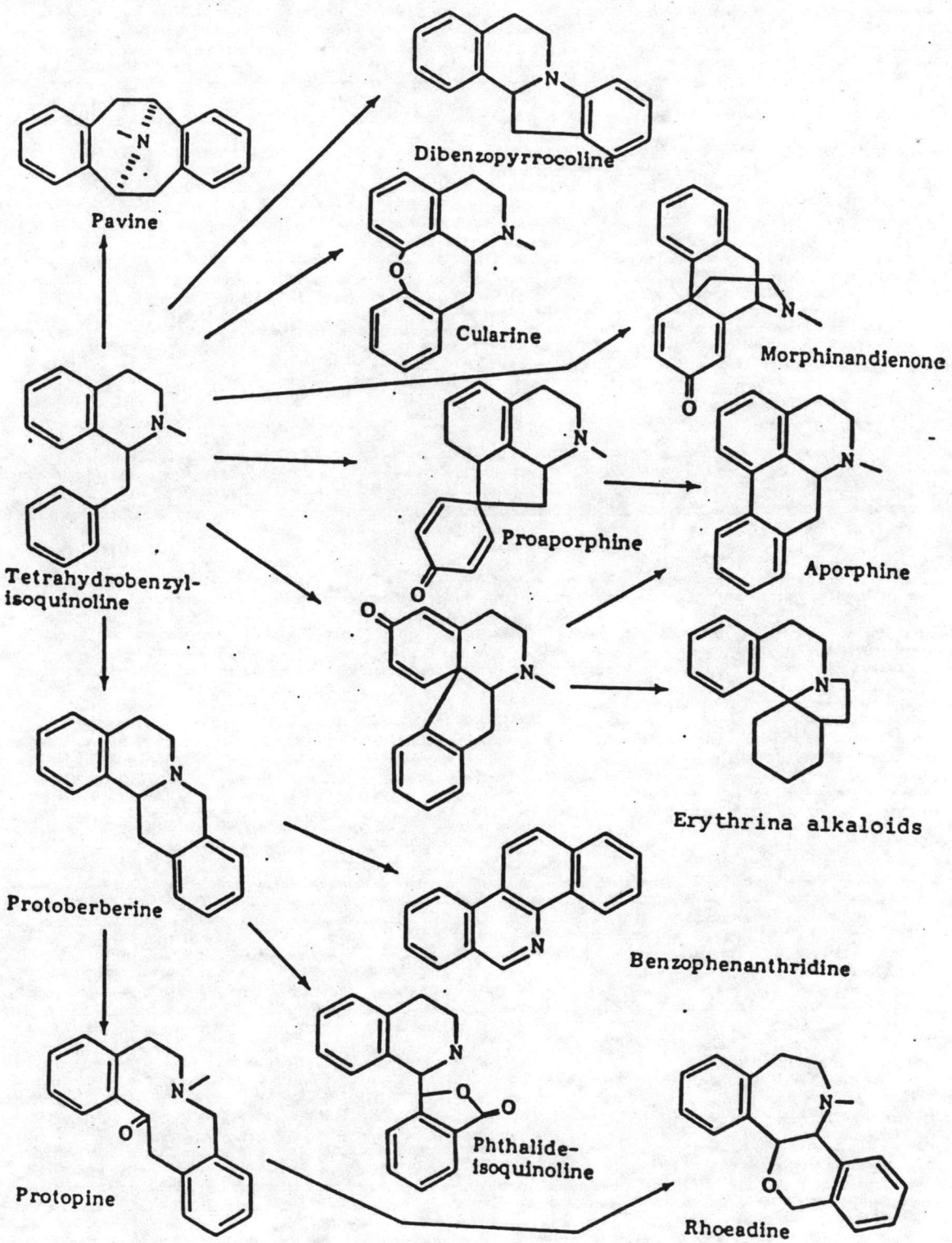
3. Protoberberines

Tetrahydroprotoberberines [2]

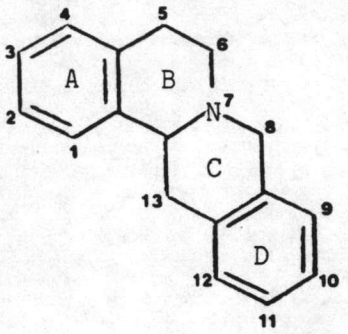
Only two tetrahydroprotoberberines described in *Annona* species. They are coreximine (#9) from *Annona montana* Macfad. and *Annona muricata* Linn. , and stepholidine (#10) from *Annona cherimolia* Mill. These alkaloid structures are shown in Table 4.



Scheme I Proven or Probable Biogenetic Loci for the Formation of the Isoquinoline Alkaloids



Scheme II Biogenetic relationships of the major alkaloid groups derived from a tetrahydrobenzylisoquinoline precursor

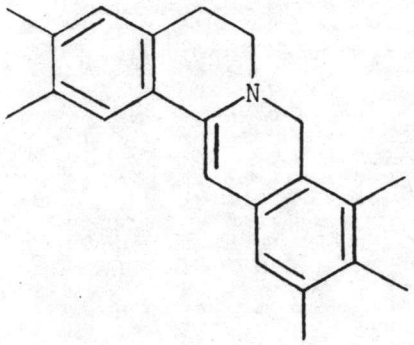


Tetrahydroprotoberberines

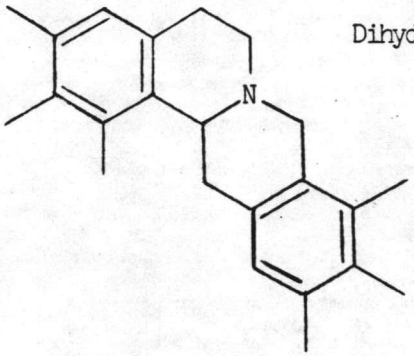
Table 4 Tetrahydroprotoberberines isolated from *Annona spp.*

Structure No.	Alkaloid	Substitutions				
		2	3	9	10	11
9	Coreximine	OH	OCH_3	-	OCH_3	OH
10	Stepholidine	OH	OCH_3	OCH_3	OH	-

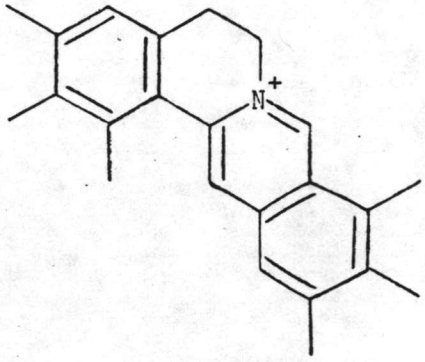
Most protoberberine alkaloids exist in nature either as tetrahydroprotoberberines or quaternary protoberberine salts, but some dihydroprotoberberines are also known. Substituents are usually present at C-2 and C-3 and either at C-9 and C-10 or at C-10 and C-11. In some instances a hydroxyl or methoxyl substituent may be present at C-1. A methyl group is sometimes found at C-13, while in a few cases an alcoholic hydroxyl is treated at C-13 or C-5 (72)



Dihydroprotoberberine



Tetrahydroprotoberberine

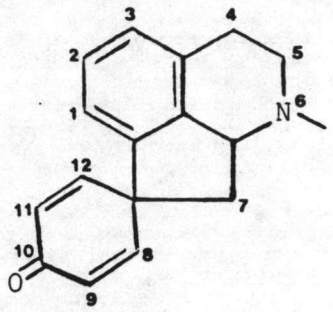


Quaternary protoberberine salts

The protoberberines are of the most widely distributed of the isoquinoline alkaloid groups, being present in at least nine plant families, particularly the Annonaceae, Berberidaceae, Lauraceae, Menispermaceae, Papaveraceae and Rutaceae (78). Over forty protoberberines are known but only two tetrahydroprotoberberines were isolated from *Annona spp.*

4. Proaporphines [2]

There are over 30 proaporphine alkaloids distributed in the plant families :- Annonaceae, Euphorbiaceae, Lauraceae, Menispermaceae, Monimiaceae, Nymphaeaceae and Papaveraceae (1,79). However, there seem to be few proaporphines in genus *Annona*. Only two representatives (#11,12), of this group have been reported in two species i.e. *Annona muricata* Linn., and A. *purpurea* Linn. They are shown in Table 5.

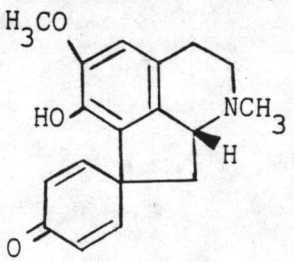


Proaporphine

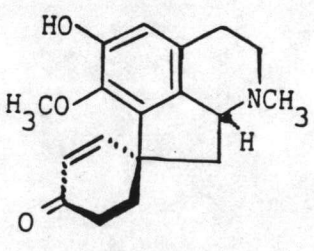
Table 5 Proaporphine isolated from *Annona spp.*

Structure No.	Alkaloid	Substitutions		
		1	2	6
11	(+)-Glaziovine	OH	OCH_3	CH_3
12	Stepharine	OCH_3	OCH_3	H

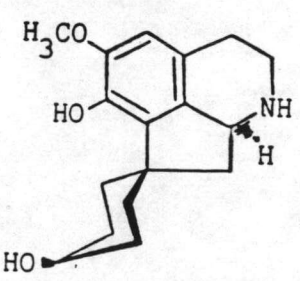
Fundamentally they are of two structural types, those with a dienone system, such as (+)-glaziovine (#11), and those in which the dienone system has been completely or partially reduced, such as - (+)-linearisine (#44) and (-)-oreoline (#45). Compounds having either stereochemistry at C-6 are known and the two sides of the cyclohexadienone system are not equivalent because of this asymmetry (79).



#11 (+)-Glaziovine



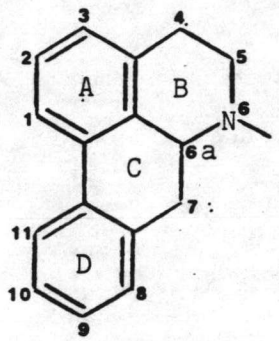
#44 (+)-Linearisine



#45 (-)-Oreoline

5. Aporphines [19]

Half of the alkaloids (19 out of 42) isolated from genus *Annona* are aporphines (#13-31), as shown in Table 6. They have very different structures and none is 8-substituted. Anonaine (#14) is the most common aporphine in this genus, since it has been reported in five species of *Annona*. Norushinsunine (michelalbine) (#28) is the only one 7-substituted aporphine found in *Annona* species (1).



Aporphine

Table 6 Aporphines isolated from *Annona spp.*

Structure No.	Alkaloid	Substitutions							
		1	2	3	6	7	9	10	11
13	Anolobine	OCH_2O		-	H	-	OH	-	-
14	Anonaine	OCH_2O		-	H	-	-	-	-
15	Asimilobine	OCH_3	OH	-	H	-	-	-	-
16	Corydine	OH	OCH_3	-	CH_3	-	-	OCH_3	OCH_3
17	(+)-Corytuberine	OH	OCH_3	-	CH_3	-	-	OCH_3	OH
18	O-demethylpurpureine	OCH_3	$OCH_3 \leftrightarrow OH$		CH_3	-	OCH_3	OCH_3	-

Structure No.	Alkaloid	Substitutions							
		1	2	3	6	7	9	10	11
19	Glaucine	OCH_3	OCH_3	-	CH_3	-	OCH_3	OCH_3	-
20	Isoboldine	OH	OCH_3	-	CH_3	-	OH	OCH_3	-
21	Isocorydine	OCH_3	OCH_3	-	CH_3	-	-	OCH_3	OH
22	N-methylactinodaphnine	OCH_2O		-	CH_3	-	OH	OCH_3	-
23	Norcorydine	OH	OCH_3	-	H	-	-	OCH_3	OCH_3
24	Norisocorydine	OCH_3	OCH_3	-	H	-	-	OCH_3	OH
25	Nornantenine	OCH_3	OCH_3	-	H	-	OCH_2O		-
26	Nornuciferine	OCH_3	OCH_3	-	H	-	-	-	-
27	Norpurpureine	OCH_3	OCH_3	OCH_3	H	-	OCH_3	OCH_3	-
28	Norushinsunine	OCH_2O		-	H	OH	-	-	-
29	Purpureine	OCH_3	OCH_3	OCH_3	CH_3	-	OCH_3	OCH_3	-
30	Roemerine	OCH_2O		-	CH_3	-	-	-	-
31	Xylopine	OCH_2O		-	H	-	OCH_3	-	-

The aporphines constitute the next to the largest group of isoquinoline alkaloids, being second only to the bisbenzylisoquinolines. They are distributed in at least 18 plant families, of which the most important are the Papaveraceae, Annonaceae, Lauraceae and Monimiaceae (80).

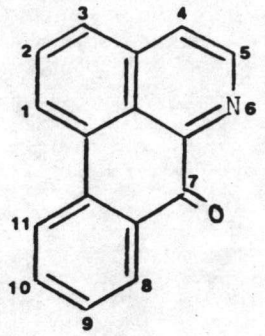
The nitrogen atom of aporphines is usually methylated, and although some noraporphines are known, they are not very stable and

are often characterized as their N-acetyl derivatives. Aporphines are known with the C-6_a stereochemistry either α or β.

The most diverse structural feature of the aporphines is the oxygenation pattern. Positions 1 and 2 are always oxygenated, either by hydroxy, methoxy or methylene dioxy groups. It is common to find further oxygen substituents at C-9, C-10 and C-11, and occasionally at C-8. It is rare to find oxygenation at C-7, except in oxoaporphines, and even rarer to find any oxygenation in ring B (80).

6. Oxoaporphines [6]

Six oxoaporphines (#32-37) were isolated from various species of *Annona*, liriodenine being ubiquitous. From the structural point of view, these oxoaporphines are rarely substituted at positions 3,9,10 and 11 (1). The oxoaporphines found in *Annona spp.* are shown in Table 7.



Oxoaporphine

Table 7 Oxoaporphines isolated from *Annona spp.*

Structure No.	Alkaloid	Substitutions				
		1	2	3	9	10
32	Homomoschatoline	OCH_3	OH	OCH_3	-	-
33	Lanuginosine	OCH_2O		-	OCH_3	-
34	Liriodenine	OCH_2O		-	-	-
35	Lysicamine	OCH_3	OCH_3	-	-	-
36	Oxoglaucine	OCH_3	OCH_3	-	OCH_3	OCH_3
37	Oxopurpureine	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3

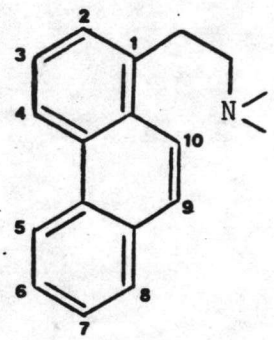
The oxoaporphines represent the most highly oxidized state of the aporphine skeleton. They commonly cooccur with aporphine alkaloids. Therefore, the oxoaporphines are most probably derived in plants by oxidation of the corresponding aporphines. The free bases possess a bright yellow or orange color which turns pink or red upon the addition of mineral acid (73,81).

Oxoaporphines are high melting and show a decomposition point rather than a melting point (73).

The numbering system of oxoaporphine is the same as that of the aporphines. Like the aporphines, beyond the 1,2-dioxygenation, they exhibit a variety of oxygen substitution patterns. In this series, however, there is a tendency toward 3-substitution and not 11-substitution (81).

7. Phenanthrenes [2]

Two members (#38-39), as shown in Table 8, belonging to the limited group of aminoethylphenanthrene derivatives ("open aporphine"), have been found in *Annona montana* Macfad. and *Annona muricata* Linn. None possess substituents on C-5 and C-6 (corresponding to positions 11 and 10 of the aporphines) (1).



Phenanthrene

Table 8 Phenanthrenes isolated from *Annona spp.*

Structure No.	Alkaloid	Substitutions			
		N	2	3	4
38	Atherosperminine	$(CH_3)_2$	-	OCH_3	OCH_3
39	Argentinine	$(CH_3)_2$	-	OH	OCH_3

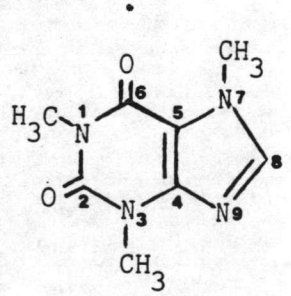
The phenanthrene alkaloids are a small group of optically inactive tertiary bases probably derived biogenetically from the Hofmann elimination of quaternary aporphine salts. They can, therefore, be included among the isoquinoline alkaloids.

The phenanthrene alkaloids are always substituted at C-3, C-4 since their precursors, the aporphines, are found with substituents at these two positions corresponding to C-2, C-1 of the aporphine skeleton (74).

8. Non-isoquinoline Alkaloids [3]

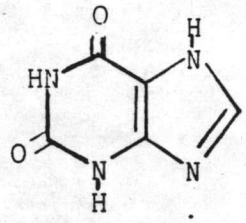
8.1 Purine [1]

Surprisingly, caffeine (#40) has been found to be one of the major constituents of *Annona cherimolia* Mill. seeds (1,54). Normally it was found in Coffee (*Coffea arabica* Linn.), Cola (*Cola nitida* (Vent.) Schott & Endl.), Maté (*Ilex paraguariensis* A.St-Hil.), Tea (*Camellia sinensis* (Linn.) O. Kuntze) and Cocoa (*Theobroma cacao* Linn.) (82).



#40 Caffeine

The most important purine alkaloids are derived from the xanthine nucleus (#46).

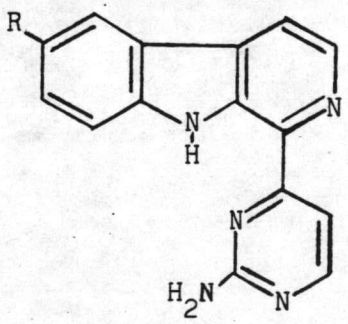


#46 Xanthine

Xanthine itself has not yet been found naturally, but several simple N-alkyl derivatives are of quite considerable significance. Prime among these is caffeine, which is 1,3,7-trimethylxanthine (82).

8.2 Pyrimidine-β-carboline [2]

Recently the isolation of two new alkaloids of an unusual type, namely annomontine (#41), and methoxyannomontine (#42), from the stem and root bark of *Annona montana* Macfad. was reported. They are the first examples of a new class of pyrimidine-β-carboline alkaloids, composed by an harman moiety linked to 2-aminopyrimidine (61,62).



Pyrimidine-β-carboline

#41 Annomontine R = H

#42 Methoxyannomontine R = OCH_3

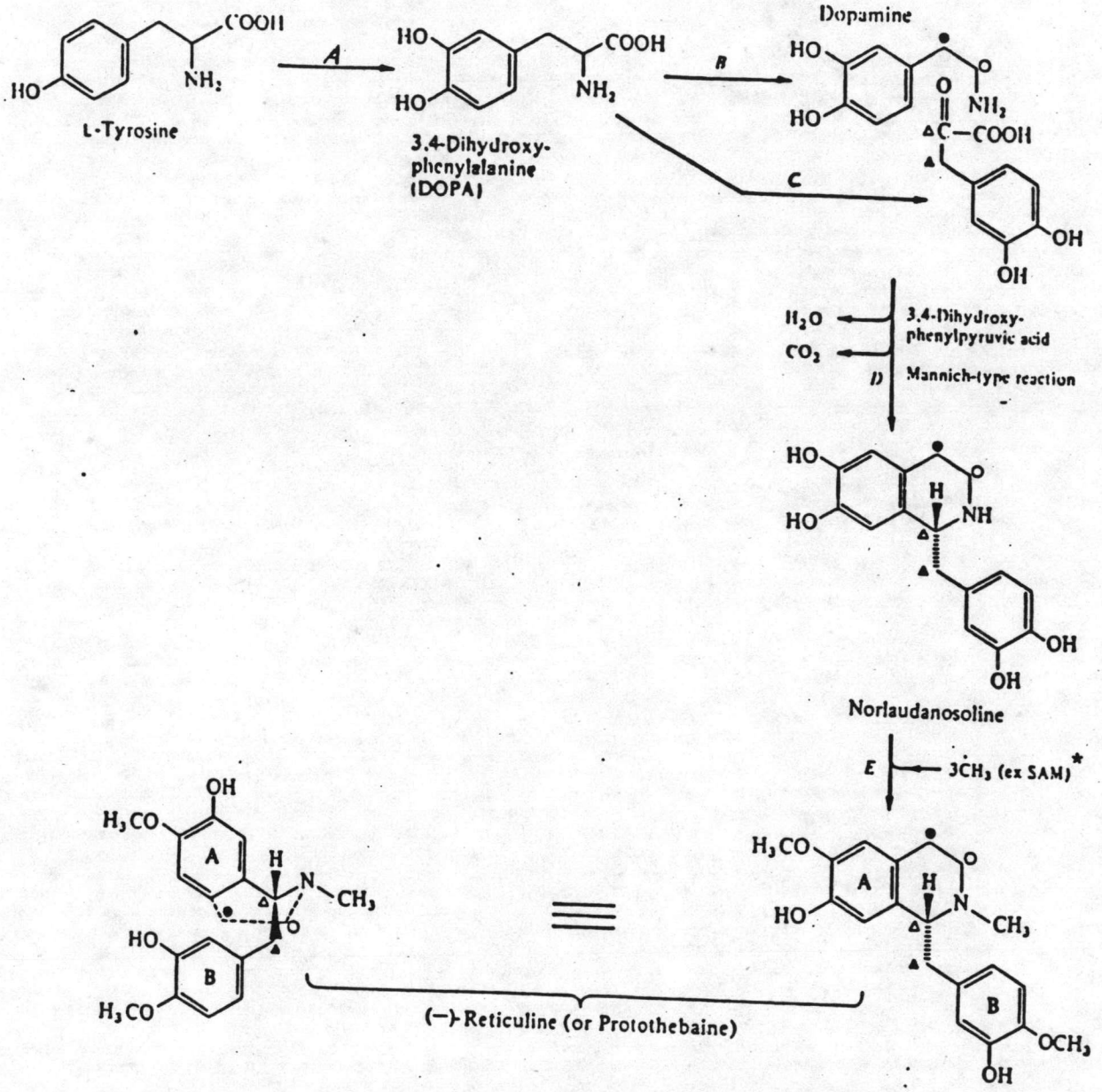
Biosynthesis of Aporphines

The biogenetic pathways leading to isoquinoline alkaloids are derived from tyrosine. Tyrosine is first elaborated to a suitable hydroxylated and derivatised phenethylamine which is then combined with a second building block. This second building block can vary widely to give various types of isoquinolines (85). The proven or probable biogenetic loci for the formation of the isoquinoline alkaloids is shown in scheme I (71). (Page 26)

The biosynthesis of isoquinoline alkaloids is conveniently treated in two parts, starting with the generation of benzylisoquinolines and then elaborating to more complicated structures (85).

Benzylisoquinolines derive from two molecules of L-tyrosine. They occupy a paramount position in alkaloid chemistry because they act as *in vivo* precursors to so many of the other naturally occurring isoquinolines. Reticuline is regarded as the key intermediate in the biosynthesis of the alkaloids based on the benzylisoquinoline nucleus, and as a result of the study of these alkaloids, much has been learned of the biosynthesis of reticuline (70,84).

The example of the formation of reticuline in *Papaver somniferum* Linn. is shown in Scheme 3 (86).



Scheme III The formation of 1-benzyl-1,2,3,4-tetrahydroisoquinolines

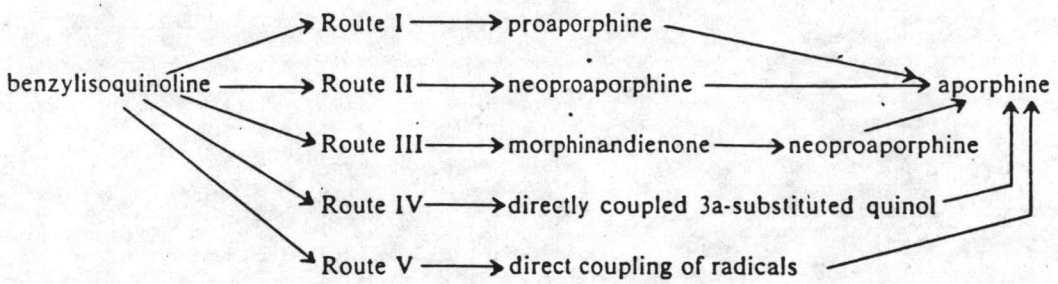
*SAM = S-adenosylmethionine

The first step (A) involves the conversion of two molecules of L-tyrosine into two molecules of DOPA. One molecule of DOPA is converted into dopamine (B) whilst the other is converted into 3,4-dihydroxyphenyl-pyruvic acid (C). These two compounds then combine with the elimination of water and carbon dioxide in a Mannich-type reaction to yield a molecule of norlaudanosoline (D). O- and N-methylation (E) then lead to (-)-reticuline (86).

More recent experiments have definitely show that benzylisoquinolines are natural precursor of aporphine alkaloids. For instance, reticuline occupied a key position in the biosynthesis of morphine alkaloids (66) and also was the precursor of other alkaloids such as boldine, isoboldine and bulbocapnine (15).

From some biogenetic results of aporphines, it would suggest that boldine is produced by two different pathways in two different plants. If this is a general trend, the biosynthesis of aporphine alkaloids may never be established. Clearly this is an area in need of considerable further study, and at this time it is not clear which, or how many, of the possible routes may be operating in order to produce the various aporphine alkaloids.

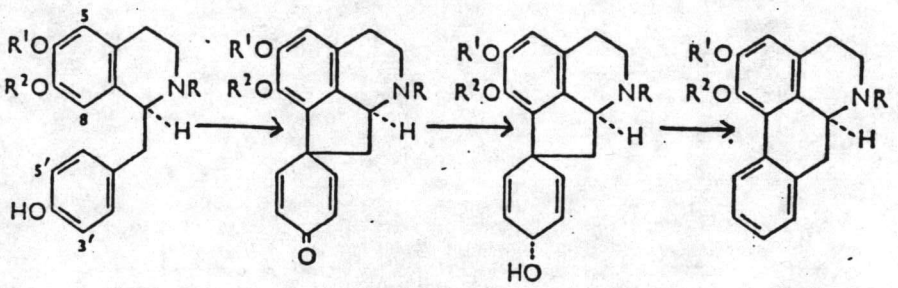
Hence, the discussion on the biogenetic synthesis of the aporphine alkaloids has raised a number of points concerning the biosynthesis of this group. In particular and depending on the orientation of phenolic and methoxy groups, we might envisage any of at least five routes being in operation from a benzylisoquinoline precursor (Scheme IV) (83).



Scheme IV Biogenesis of aporphines from benzylisoquinolines.

Route I : Benzylisoquinoline ⟶ Proaporphine ⟶ Aporphine

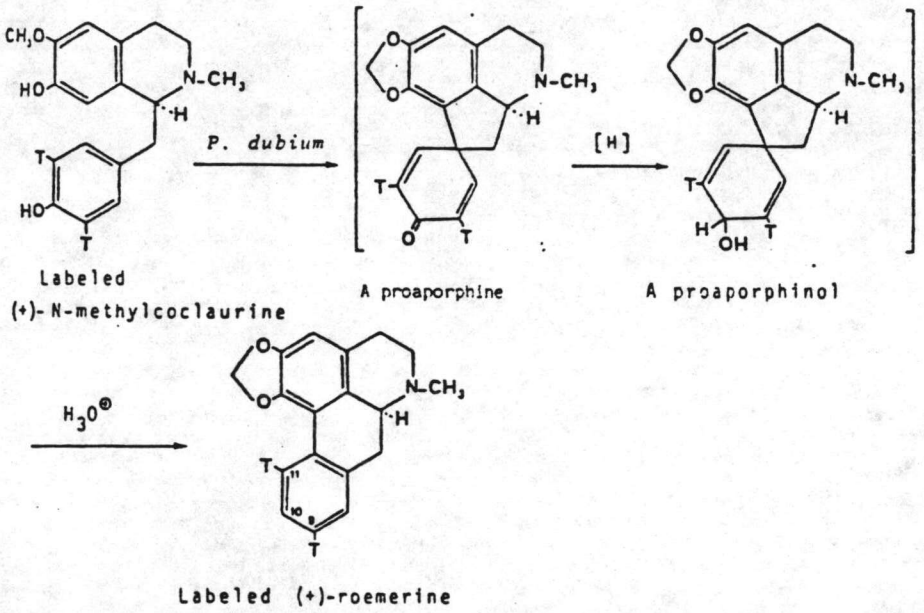
From Scheme V aporphine alkaloids lacking an oxygen substituent in ring D are derived from a benzylisoquinoline by oxidation to a dienone, reduction to dienol and dehydration with rearrangement to the fully aromatic compound (87).



Benzylisoquinoline Dienone Dienol Aporphine

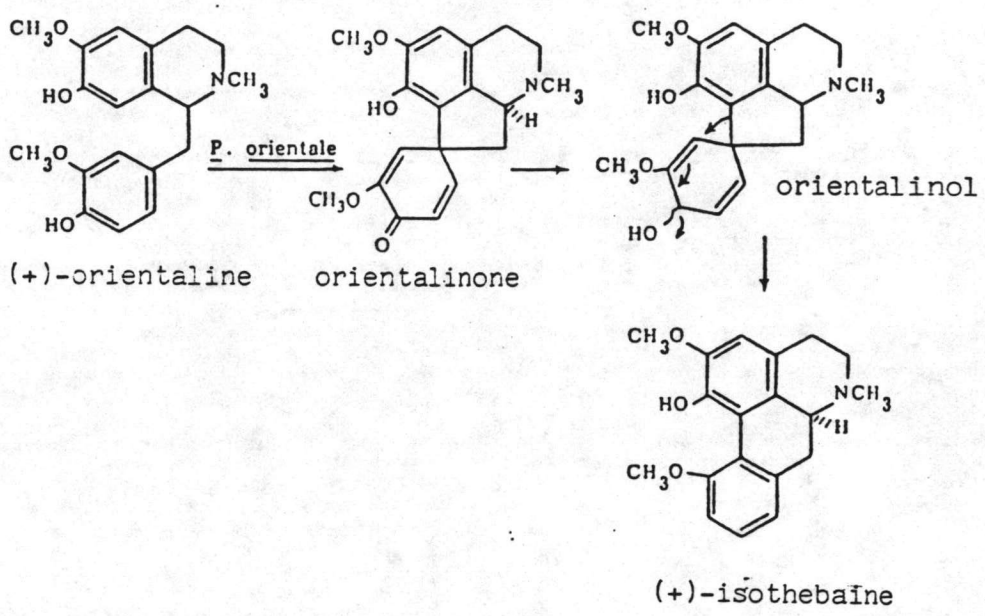
Scheme V Reaction of benzylisoquinoline to aporphine

Barton and co-workers (88) investigated the formation of (+)-roemerine in *Papaver dubium* Linn. and found that tritium-labeled (+)-N-methylcoclaurine was well incorporated. The position of the hydroxy group in the precursor suggests that a proaporphine intermediate is involved as in Scheme VI (75,83,89).



Scheme VI Biosynthesis of (+)-roemerine

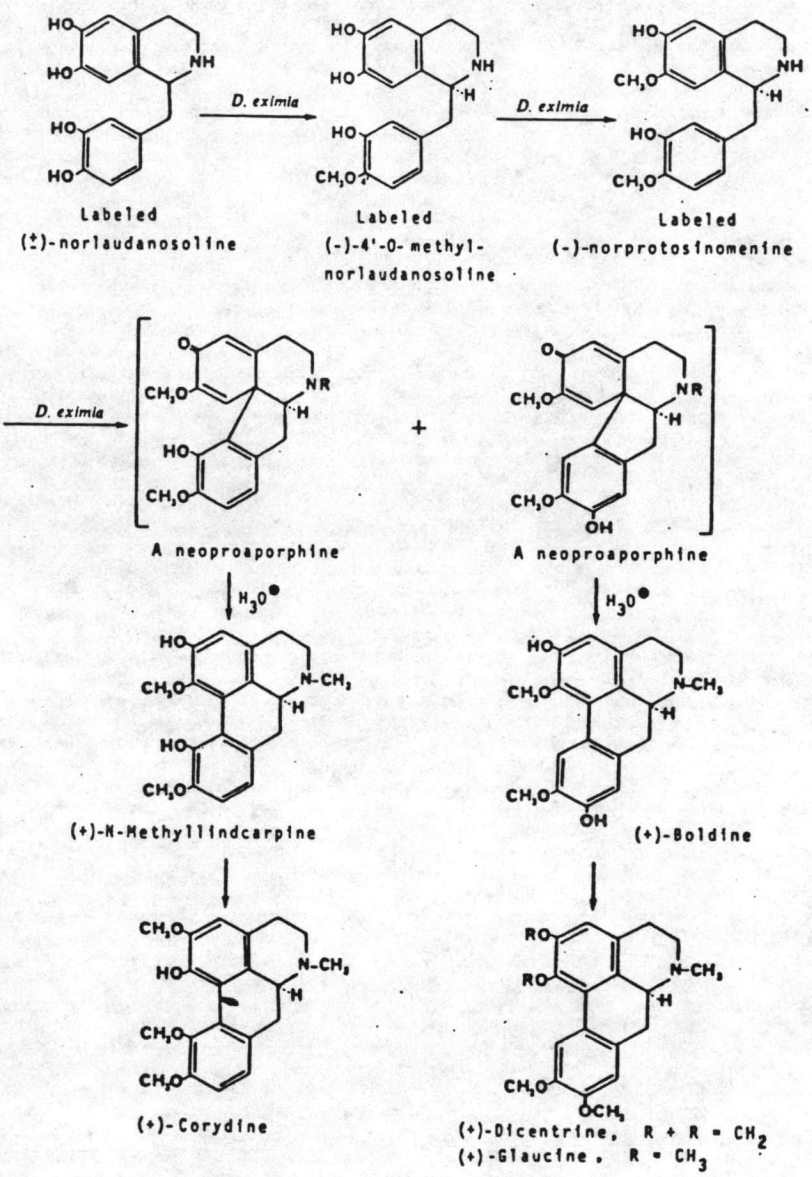
Similarly, Battersby and co-workers (90) showed that labeled (+)-orientaline, when fed to *Papaver orientale* Linn., was incorporated into the aporphine alkaloid (+)-isothebaine. The (+)-isothebaine can be envisaged as occuring through (-)-orientalinone, a co-constituent, as shown in Scheme VII (75,83,89,91).



Scheme VII Biosynthesis of (+)-isothebaine

Route II : Benzylisoquinoline ⟶ Neoproaporphine ⟶ Aporphine

More definitive results have been obtained by Battersby and co-workers (90) concerning the formation of corydine, dicentrine and glaucine in *Dicentra eximia* (Ker.) Torr. Reticuline and orientaline were not precursors, but 4'-O-methylnorlaudanosoline which originated from norlaudanosoline was effective precursor. 4'-O-methylnorlaudanosoline is converted into norprotosinomenine which must be incorporated into the three aporphine alkaloids by way of the two neoproaporphine intermediates as indicated in Scheme VIII (76,83,89).

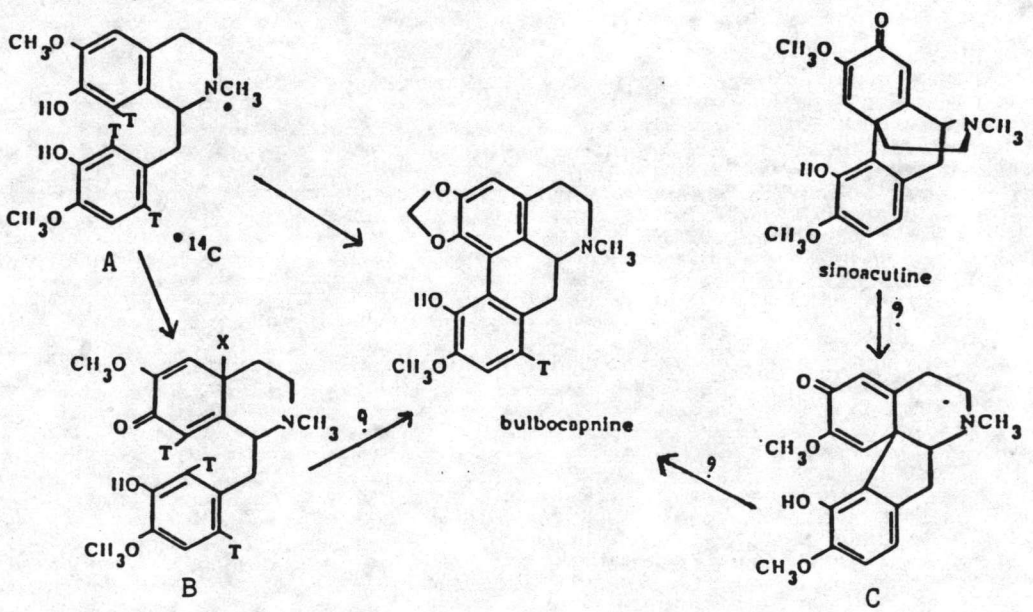


Scheme VIII Biosynthesis of Corydine, Dicentrine and Glaucine in *Dicentra eximia* (Ker.) Torr.

Route III : Benzylisoquinoline ⟶ Morphinandienone ⟶ Neoproaporphine ⟶ Aporphine

Route IV : Benzylisoquinoline ⟶ Directly coupled 3a - substituted quinol ⟶ Aporphine

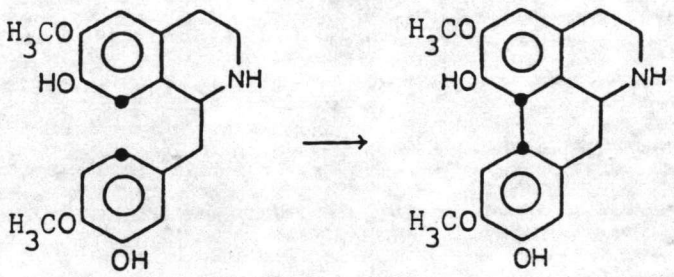
It is very difficult in some instances to say what the probable mechanism is unless variously methylated benzylisoquinoline precursors are used. For example, as in Scheme IX, N-methyl labeled (+)-reticuline (A) was a precursor of bulbocapnine in *Corydalis cava* Schweigg.et Korte, but is this evidence of direct phenol coupling ? Even if demethylation-remethylation is assumed not to occur, direct coupling of a 3α-substituted quinol not involving radicals is still a reasonable alternative (i.e. B). It is pertinent to note that the morphinandienone sinoacutine is also a constituent of this plant. Could sinoacutine be a key precursor *via* the intermediate neoproaporphine (C) ? (83)



Scheme IX Biosynthesis of bulbocapnine

Route V : Benzylisoquinoline ⟶ Direct coupling of radicals ⟶ Aporphine

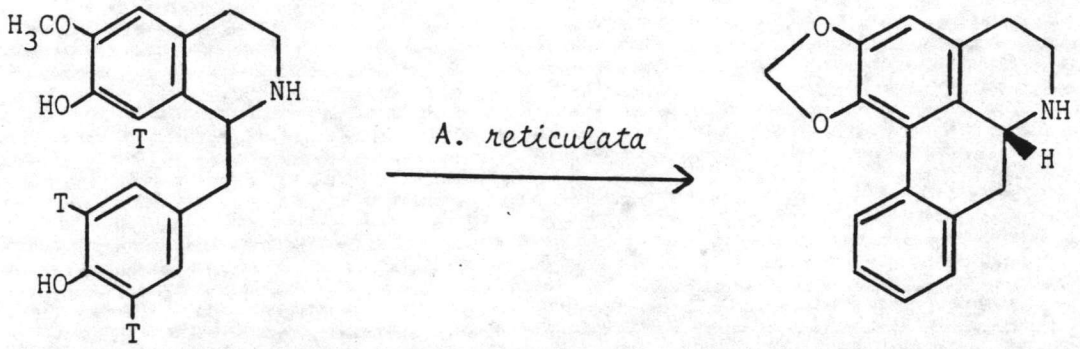
Aporphines are formed in plants by intramolecular phenolic oxidative coupling of benzylisoquinolines (92). Isoboldine has been shown to be formed in *Papaver somniferum* Linn. by a straightforward intramolecular oxidative coupling between the two aryl rings of reticuline. The site of coupling (marked by dots in Scheme X) both bear a hydrogen and therefore the two rings can rearomatise to give the biphenyl system characteristic of the aporphine alkaloids, though as we shall see the biosynthetic routes leading to members of this groups of alkaloids are not always so straightforward (86).



Reticuline Isoboldine

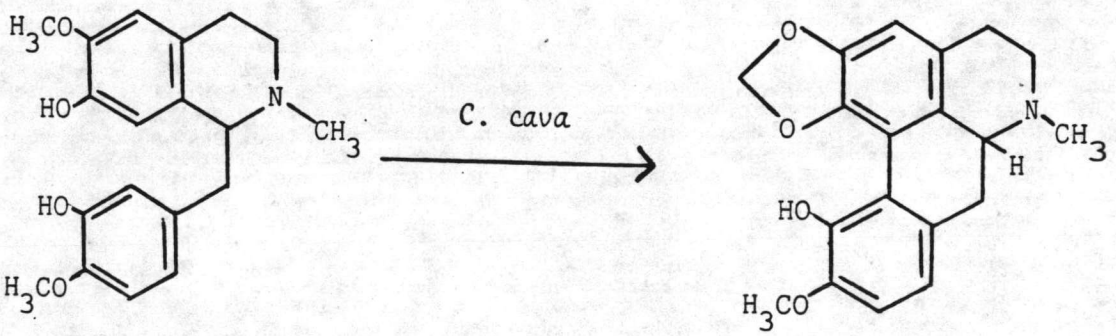
Scheme X Biosynthesis of Isoboldine

In other experiments, it was found that (±)-coclaurine could be a precursor for anonaine in *Anona reticulata* Sieber, ex. A.DC. (76).



labeled (±)-coclaurine — labeled (-)-anonaine

The evidence in favor of direct coupling of a benzylisoquinoline to an aporphine is more ambiguous. Blaschke has found that feeding (±)-reticuline labeled on the N-methyl group to the larkspur, *Corydalis cava* Schweigg.et Korte, had incorporated to labeled bulbocapnine as follows :-



labeled (±)-reticuline — labeled (+)-bulbocapnine

Benzylisoquinolines are not only the precursor of aporphines, but they are also the precursor of many other isoquinoline alkaloids which is summarized in Scheme II (Page 27) (77).

Biological and Pharmacological Activity of *Annona* Alkaloids

Considerable studies have been carried out to investigate the active principle for biological and pharmacological action of *Annona* alkaloids, as shown in Table 9.

Table 9 Biological and Pharmocological Activity of *Annona* Alkaloids

Alkaloid	Activity	Species found	Reference
Annomontine	weak sedative, antiamoebic.	*Annona montana* Macfad.	93
Anonaine	Parasiticide.	A. *cherimolia* Mill. A. *crassiflora* Mart. A. *glabra* Linn. A. *montana* Macfad. A. *reticulata* Linn. A. *squamosa* Linn.	1,9
Caffeine	increase central - nervous system activity	A. *cherimolia* Mill.	82

Table 9 (continued)

Alkaloid	Activity	Species found	Reference
Corydine	cytotoxic, antitumor, adrenolytic action, C.N.S. depressant, hypertensive, block nerve impulse-transmission.	*Annona purpurea* Linn. A. *squamosa* Linn.	3,5, 64, 82, 94
Corytuberine	respiratory stimulant secretion stimulant, slow the pulse.	A. *cherimolia* Mill.	82, 95
Glaucine	reduce blood pressure, inhibit respiration, antitussive, active adrenolytic, hypoglycemia.	A. *squamosa* Linn.	82, 94, 95
Glaziovine	antidepressant, Cytotoxic.	A. *purpurea* Linn.	63, 95

Table 9 (continued)

Alkaloid	Activity	Species found	Reference
Higenamine	effective β-adrenergic agonist (positive inotropic action)	*Annona squamosa* Linn.	2
Homomoschatoline	Cytotoxic	A. *acuminata* Saff.	10
Isoboldine	insect-feeding - inhibitor	A. *cherimolia* Mill. A. *glabra* Linn. A. *montana* Macfad.	96
Isocorydine	adrenolytic action	A. *squamosa* Linn.	94
Liriodenine	cytotoxic, antitumor, antibacterial, antifungal.	A. *acuminata* Saff. A. *cherimolia* Mill. A. *glabra* Linn. A. *montana* Macfad. A. *purpurea* Linn. A. *reticulata* Linn. A. *squamosa* Linn.	1,10, 57, 97

Table 9 (continued)

Alkaloid	Activity	Species found	Reference
Lysicamine	cytotoxic	*Annona acuminata* Saff.	10
Methoxyannomontine	weak sedative, antiamoebic	A. *montana* Macfad.	93
O-methylatheroline	cytotoxic	A. *purpurea* Linn.	63
Xylopine	sedative, analgesic	A. *squamosa* Linn.	95
Alkaloid from leaves and stem bark	analgesic, spasmolytic, antibacterial	A. *crassiflora* Mart.	52
Petroleum ether extract of root bark (C/M_2)	antineoplastic, antibacterial against *Staphylococcus aureus*, *Salmonella typhosa* (*in vitro*)	A. *senegalensis* Pers.	98, 99

Table 9 (continued)

Alkaloid	Activity	Species found	Reference
Aqueous and Ethanol extract	cardiorespiratory effect (cat), insecticidal, oxytocic, uterotonic, spasmogenic (guinea pig ileum), spasmolytic (rabbit duodenum)	*Annona squamosa* Linn.	10-14, 100