



CHAPTER II

HISTORICAL

Alkaloids Isolated from Species of *Papaver*

Papaver alpinum L.

alborine

alpinine

amurensine

amurensinine

amurine

cryptopine

muramine

nudaurine

oreophiline

papaverrubines

protopine

(Pfeifer and Doehnert, 1968)

Papaver apulum Ten.

coptisine

(Slavik and Applet, 1965)

Papaver arenarium Marsch.-Bieb.

rhoeadine

rhoeagenine

(Preininger *et al.*, 1962)

macrostomine

(Mnatsakanyan *et al.*, 1977b)

glycomarine

(Israilov *et al.*, 1980)

Papaver argemone L.

protopine

rhoeadine

rhoeagenine

(Preininger *et al.*, 1962)

coptisine

(Slavik and Applet, 1965)

Papaver armeniacum (L.) DC.

armepavine

coptisine

mecambrine

palmatine

protopine

sanguinarine

(Slavik and Applet, 1965)

1-benzyl-1,2,3,4-tetrahydroisoquinoline

papaverrubines

proaporheine

protoberberine

(Phillipson *et al.*, 1973)

thebaine

(Phillipson, 1973)

nuciferine

roemerine

(Phillipson *et al.*, 1981b)

Papaver atlanticum (Ball) Coss.

protopine

rheadine

rheagenine

(Preininger *et al.*, 1962)

coptisine

rheagine

sanguinarine

(Slavik and Applet, 1965)

cryptopine

papaverrubines

porphyroxine

(Pfeifer and Thomas, 1966)

Papaver bracteatum Lindl.

bractavine

isothebaine

thebaine

(Heydenreich and Pfeifer, 1965)

bracteine

mecambridine

salutaridine

(Heydenreich and Pfeifer, 1966)

bracteoline

(Heydenreich and Pfeifer, 1967)

alpinigenine

(Lalezari *et al.*, 1973)

oripavine

papaverrubines

proaporphines

protopine

(Kuppers *et al.*, 1976)

alpigenine

alpinine

bractamine

coptisine

epialpinine

oxysanguinerine

(Sariyar and Phillipson, 1977)

14- β -hydroxycodeine

14- β -hydroxycodeinone

N-methylcorydaldine

(Theuns *et al.*, 1977)

N-methylflavinantine

(Meshulam and Lavie, 1980)

corypalline

O-methylcorypalline

(Theuns *et al.*, 1983)

Papaver commutatum Fisch. & Mey.

papaverine

(Mnatsakanyan and Yunusov, 1961)

coptisine

(+)-isocorydine

rhoeadine

rhoeagine

(Slavik *et al.*, 1965a)

(-)-N-methylstyloponium chloride

(Preininger *et al.*, 1973b)

roemerine

(Mnatsakanyan *et al.*, 1977b)

Papaver cylindricum Cullen

armepavine

narcotine

oripavine

papaverine

rhoeadine

salutaridine

thebaine

(Sariyar, 1980)

cheilanthifoline

floripavidine

N-methylasimilobine

scoulerine

(Sariyar, 1982)

Papaver decaisnei Hochst. & Steud.

codeine

coptisine

corytuberine

morphine
 narcotine
 papaverine
 papaverrubine A, C, D & E
 protopine
 rhoeadine
 thebaine

(Slavik, 1980)

Papaver dubium L.

coptisine
 dubirheine
 mecambrine
 (Slavik, 1963)
 allocryptopine
 aporheine
 aporheinemethohydroxide
 corydine
 corysamine
 corytuberine
 isocorydine
 papaverrubine A, C, D & E
 protopine
 scoulerine

(Slavik and Slavikova, 1981)

Papaver fugax Poir.

armepavine

013126

18047385

coptisine

mecambrine

palmatine

pronuciferine

protopine

(Kuehn *et al.*, 1964)

papaverrubine B & D

roemerine

sanguinarine

(Kuehn and Pfeifer, 1965)

floripavine

fugapine

d-isoroemerine

(Yunusov *et al.*, 1965)

fugapavine

glaziovine

(-)-N-methylcrotonosine

papaverrubine C

salutaridine

(Kuehn and Pfeifer, 1967)

homolinearisine

papaverrubine A & E

(Pfeifer and Kuehn, 1968)

narcotine

rhoeadine

thebaine

(Phillipson *et al.*, 1973)

floripavidine

(Israilov *et al.*, 1976)

(+)-remrefidine

(Manushakyan and Mnatsakanyan, 1977)

Papaver glaucum Boiss. & Hausskn.

coptisine

glaudine

isorhoeadine

papaverrubine B, C & D

sanguinarine

(Pfeifer, 1964)

glaucamine

(Pfeifer and Mann, 1965 and Slavik *et al.*, 1965b)

epiglaucamine

glaupavine

(Slavik and Applet, 1965)

Papaver gracile Auch.

rhoeadine

(Preininger *et al.*, 1962)

Papaver hybridum L.

coptisine

(Slavik and Applet, 1965)

Papaver lasiothrix Fedde

mecambridine

orientaridine

salutaridine

thebaine

(Sariyar and Baytop, 1978)

Papaver macrostomum Boiss. & Huet.

protopine

rhoeadine

(Preininger *et al.*, 1962)

macrostomine

sevanine

(Mnatsakanyan *et al.*, 1974)

dehydronormacrostromine

(Mnatsakanyan *et al.*, 1977a)

Papaver monanthum Trautv.

protopine

rhoeadine

(Preininger *et al.*, 1962)

Papaver oreophilum F.J. Rupr.

N-methyl oreoline

oreodine

oreogenine

oreoline

oreophiline

papaverrubine F

(Pfeifer and Mann, 1968)

alborine

allocryptopine



berberine
 chelirubine
 coptisine
 corydine
 corysamine
 N, O-dimethyloridine
 isooridine
 isorhoeadine
 magnoflorine
 mecambridine
 menisperine
 N-methyloridine
 O-methyloridine
 nuciferine
 oridine
 papaverrubine A, C, D, & E
 protopine
 rhoeadine
 sanguinarine

(Veznik *et al.*, 1981)

Papaver orientale L.

bractavine

isothebaine

(Heydenreich and Pfeifer, 1965)

tetrahydroprotoberberine

(Nemeckova *et al.*, 1966)

mecambridine
 nuciferine
 orientalidine
 oxysanguinarine
 salutaridine



(Preininger and Santavy, 1966)

papaverrubine C & D

(Delenk-Heydenreich and Pfeifer, 1969)

narcotine

protopine

thebaine

(Nyomarkay *et al.*, 1974)

oripavine

(Shafiee *et al.*, 1975)

macrantaline

(Sariyar, 1976)

oripavidine

(Israilov *et al.*, 1977)

alborine

bracteoline

dihydroorientalinone

orientaline

orientalinone

(Sariyar and Phillipson, 1977)

alpinigenine

(Phillipson *et al.*, 1981a)

Papaver persicum Lindl.

armepavine

mecambrine

nuciferine

papaverrubine B & D

pronuciferine

protopine

roemerine

sanguinarine

(Kuehn and Pfeifer, 1965)

coptisine

O-demethyl nuciferine

palmatine

(Preininger *et al.*, 1967)*Papaver pilosum* Sibth & Smith

protopine

rhoeadine

(Preininger *et al.*, 1962)*Papaver polychaetum* Schott & Kotschy

armepavine

mecambrine

nuciferine

palmatine

pronuciferine

roemerine

sanguinarine

(Kuehn and Pfeifer, 1965)

papaverrubines

protopine

(Phillipson *et al.*, 1981b)

Papaver pseudo-orientale (Fedde) Medw.

alborine

aryapavine

bracteoline

isothebaine

orientalidine

salutaridine

(Shafiee *et al.*, 1975)

macrantaline

macrantoridine

mecambridine

(Sariyar and Phillipson, 1977)

caavine

(Lalezari and Shafiee, 1977)

alpinigenine

alpinine

thebaine

(Phillipson *et al.*, 1981a)

Papaver radicum Pottb.

β -allocryptopine

amurensinine

amurine

berberine

cryptopine
 O-methyl thalisopavine
 papaverrubines
 protopine
 sanguinarine

(Boehm *et al.*, 1975)

Papaver rhoeas L.

chelerythrine
 coptisine
 glaudine
 papaverrubine A, B, D & E

(Pfeifer and Hanus, 1965)

papaverrubine C
 rhoeadine
 rhoeagenine

(Nemeckova *et al.*, 1966)

adlumiceine
 adlumidiceine

(Preininger *et al.*, 1973a)

(-)-N-methylstyloponium chloride

(Preininger *et al.*, 1973b)

allocryptopine
 berberine
 corydine
 isocorydine
 isorhoeagenine
 6-methoxy-2-methyl-1,2,3,4-tetrahydro- β -carboline

β -stylophine methohydroxide

(Slavik, 1978)

Papaver rupifragum Boiss. & Reut.

allocryptopine

coptisine

corysamine

cryptopine

isorhoeadine

magnoflorine

papaverrubine A, B, C, D & E

protopine

rhoeadine

rhoeagenine

(-)-stylophine

(Slavikova and Slavik, 1980)

Papaver somniferum L.

codamine

hydrocotanine

lanthopine

laudanidine

laudanine

laudanosine

meconidine

ψ -morphine

narcotoline

neopine

protopine

(Manske and Ashford, 1954)

α -acetyl dihydrosanguinarine

β -allocryptopine

bound morphine

canadine

choline

codeine

coreximine

cryptopine

dihydroprotopine

dihydrosanguinarine

16-hydroxythebaine

magnoflorine

6-methylcodeine

morphine

narceine imide

narcotine

normorphine

norsanguinarine

noscopine

orientaline

13-oxocryptopine

oxydimorphine

oxysanguinarine

pacodine

palaudine

papaveraldine

papaverine
salutaridine
sanguinarine
stepholidine
tetrahydroxypapaverine
thebaine
two-N-oxides of morphine, codeine and thebaine
(Santavy, 1979)

Papaver spicatum Boiss. & Bal.

amurine
dehydroroemerine
dihydrondaaurine
glaucine
flavinantine
mecambrine
(Sariyar and Oztekin, 1981)

Papaver strictum Boiss. & Bal.

amurine
dihydrondaaurine
glaucine
N-methyl laurotetanine
roemeramine
roemerine
(Sariyar and Oztekin, 1981)

Papaver strigosum (Bonningh.) Schur.

coptisine

protopine

rhoeadine

rhoeagine

(Slavik and Applet, 1965)

Papaver syriacum Boiss. & Blanche

berberine

coptisine

corysamine

isorhoeadine

(±)-mecambrine

papaverrubines

protopine

rhoeadine

rhoeagenine

(-)-stylophine

(-)-β-stylophine

thebaine

(Slavik and Slavikova, 1976)

Papaver tauricola Boiss.

1-benzyl-1,2,3,4-tetrahydroisoquinoline

papaverrubines

protoberberine

protopine

(Preininger *et al.*, 1962)

epiglaudine

glaucamine

glaudine

oreodine

oreogenine

proaporphine

rhoeadine

rhoeagenine

(Sariyar and Phillipson, 1980a)

amurensinine

scoulerine

sinactine

(Sariyar and Phillipson, 1980b)

Papaver triniaefolium Boiss

armepavine

coptisine

mecambrine

palmatine

protopine

sanguinarine

(Slavik and Applet, 1965)

nuciferine

papaverrubine B & D

pronuciferine

roemerine

(Kuehn and Pfeifer, 1965)

(+)-aporheine

N-methyl-6,7-dimethoxytetrahydro isoquinoline

muramine

(-)-N-norarmepavine

(Preininger and Tosnaro, 1973)

floripavine

N-methylasimilobine

O-methylsalutaridine

salutaridine

(Manushakyan and Israilov, 1980)

Chemistry and Biosynthesis of Alkaloids from *Papaver somniferum* L.

Isolation of morphine from *Papaver somniferum* L. by Derosne in 1803 was the beginning of research on the chemistry of *Papaver* alkaloids. During the past years the increasing interest and research in the isolation, chemistry, biochemistry and chemotaxonomy of the *Papaver* alkaloids had led to the publication of a great number of original communications and summarizing reports. Perhaps no other genus of higher plants has been investigated chemically so extensively as has *Papaver*. According to Santavy (1979) and Preininger *et al.* (1981), opium alkaloids are summarized into the following groups:

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1. Benzylisoquinoline Alkaloids1.1. Basic Structure

Table 1

Benzylisoquinoline alkaloids from *Papaver somniferum* L.

| Basic structure | Alkaloid | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ |
|-----------------|----------------------|-----------------|-----------------|--------------------|-----------------|-----------------|
| | Papaverine | CH ₃ | CH ₃ | CH ₃ | CH ₃ | |
| | Pacodine | CH ₃ | H | -CH ₂ - | | |
| | Palaudine | CH ₃ | CH ₃ | H | CH ₃ | |
| | Laudanosine | CH ₃ | CH ₃ | CH ₃ | CH ₃ | CH ₃ |
| | Laudanidine | CH ₃ | CH ₃ | CH ₃ | H | CH ₃ |
| | Tetrahydropapaverine | H | CH ₃ | CH ₃ | CH ₃ | CH ₃ |
| | Codamine | CH ₃ | CH ₃ | H | CH ₃ | CH ₃ |
| | Orientaline | CH ₃ | CH ₃ | H | CH ₃ | H |
| | Papaveraldine | | | | | |

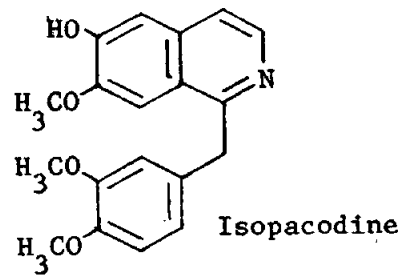
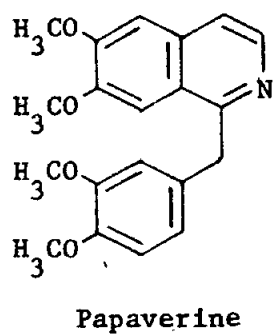
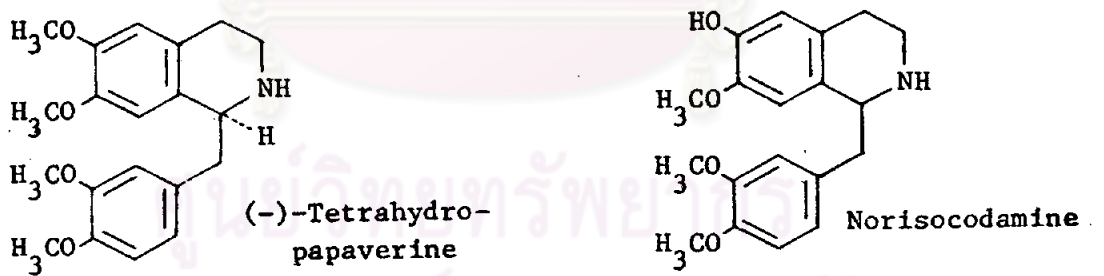
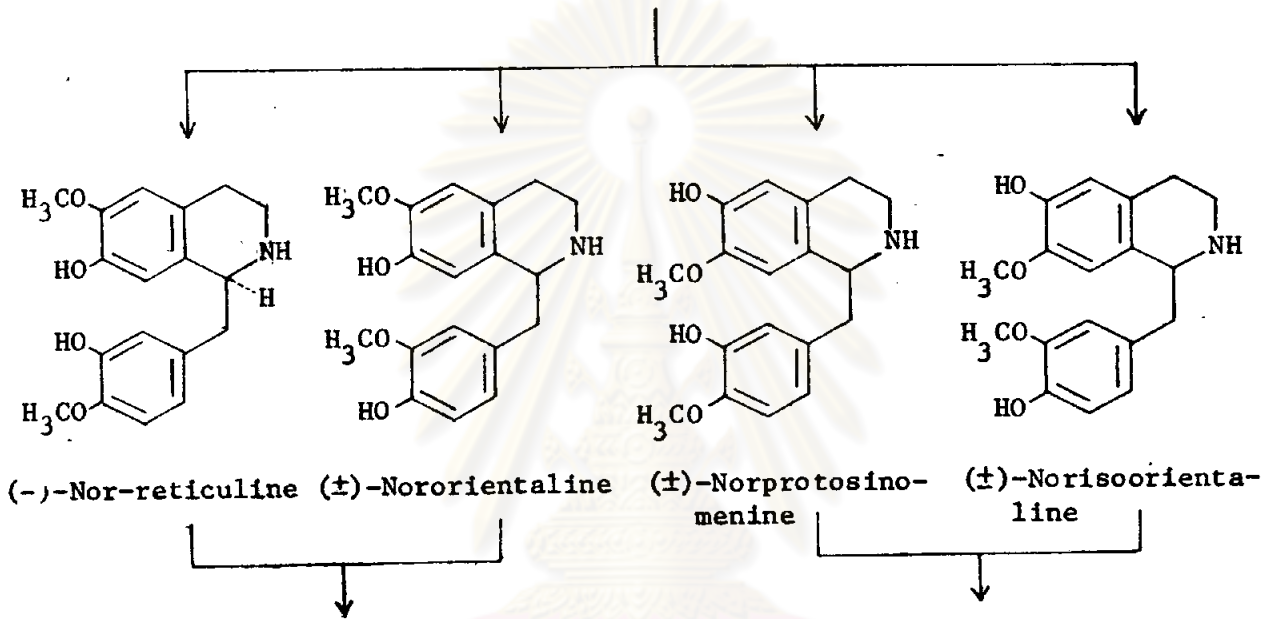
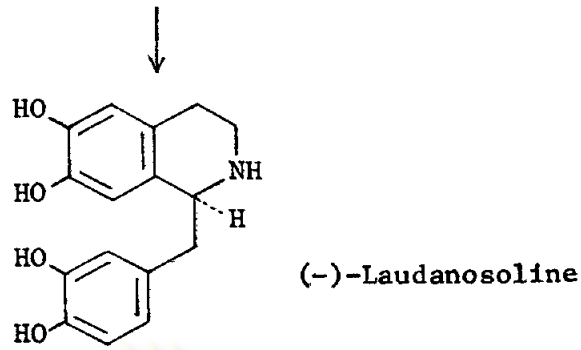
From a chemical structural view point, benzyloquinoline alkaloids may be divided into several groups. One comprises the opium alkaloids in which the aliphatic carbon atom of the benzyl group is connected only the position 1 and 1' (Burger, 1954). Structures of these are shown in Table 1 (Santavy, 1979).

Papaverine usually occurs to the extent of 0.5 to 1 % in opium and is found in all parts of *Papaver somniferum* L. especially in the unripe capsules. Oxidation of papaverine gives papaveraldine (Burger, 1954).

1.2. Biosynthesis of Papaverine

Alkaloids of benzyloquinoline structure results from the condensation of a phenylethylamine derivative with a phenylacetaldehyde derivative. Both of these moieties are derived from phenylalanine or tyrosine. Biosynthetic pathway of papaverine is shown below (Cordell, 1981):

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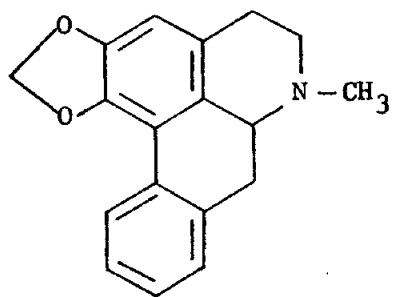


It is recently disclosed that the late stages in papaverine biosynthesis were investigated using partially methylated benzyltetrahydroisoquinoline. All four isomers are incorporated into papaverine, but only nor-reticuline and nororientaline are precursors of tetrahydropapaverine, itself a very good precursor of papaverine. Hence it was concluded that norisorientaline and norprotosinomenine are not normal precursors but are being incorporated into papaverine by way of an aberrant pathway involving norisocodamine and isopacodine. The main route to papaverine in *Papaver somniferum* L. is therefore from (-)-norlaudanosoline via (-)-nor-reticuline or (-)-nororientaline to (-)-norlaudanosoline or (-)-norcodamine to (-)-tetrahydropapaverine and thence papaverine (Cordell, 1981).

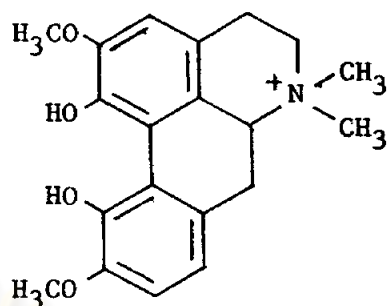
2. Aporphine Alkaloids

2.1. Basic Structure

The aporphine alkaloids are derived from the benzylisoquinoline by the abstraction of two hydrogens in such a manner that the two benzene nuclei now form part of a 4,5-dihydrophenanthrene. Since the biosynthesis of these alkaloids almost certainly proceeds from the benzylisoquinoline and since the later ones are derived from precursors in which the oxygen substituents are in the 10- and 11- positions, it follows that aporphine can have substituents only in the 1-, 2-, 9-, 10- or 11-positions (Manske, 1954a). The structures of aporphine alkaloids in *Papaver somniferum* L. are shown below:



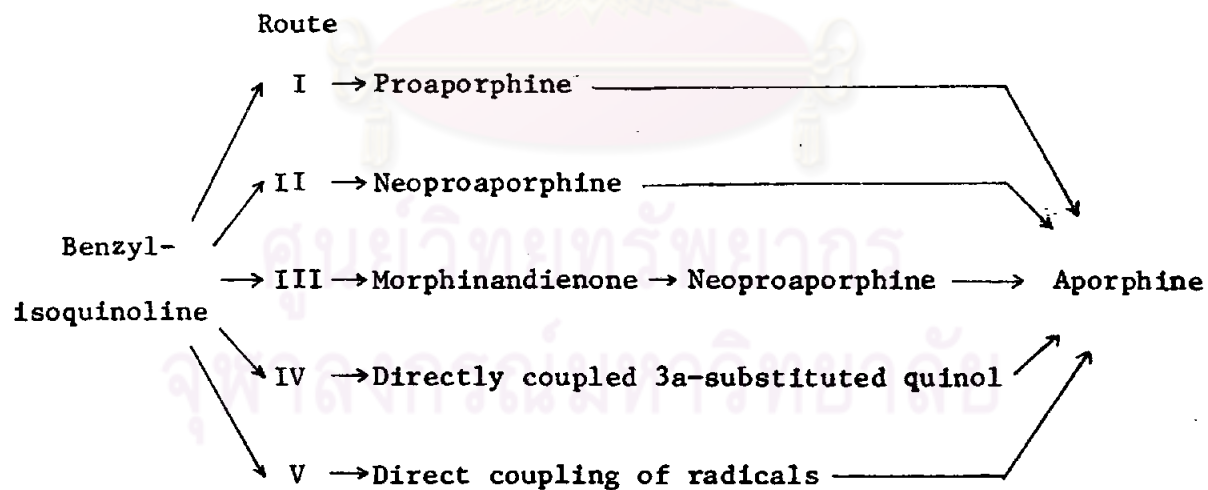
Aporheine



Magnoflorine

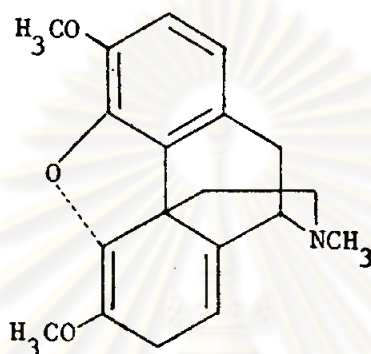
2.2. Biosynthesis

In particular and depending on the orientation of phenolic and methoxy groups, according to Cordell (1981), aporphine alkaloids are derived from any of the least five routes being in operation from a benzylisoquinoline precursor.



3. Promorphinane Alkaloids (Morphinandienone)

Promorphinane alkaloids are intermediates in biosynthesis of morphinane alkaloids, one of such intermediates is salutaridine (Santavy, 1979).



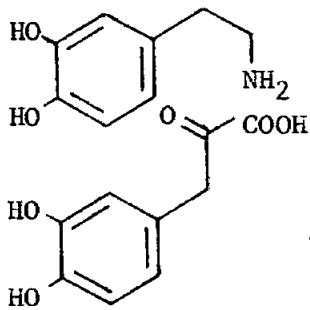
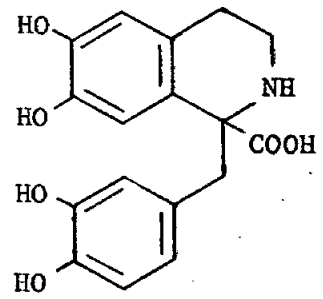
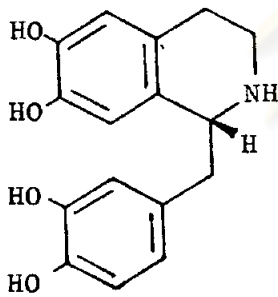
Salutaridine

3.1. Biosynthesis of Salutaridine

Salutaridine is derived from (-)-reticuline via incorporation of dopamine and 3,4-dihydroxypyruvic acid to norlaudanosoline l-carboxylic acid to (+)-norlaudanosoline as shown below (Cordell, 1981):

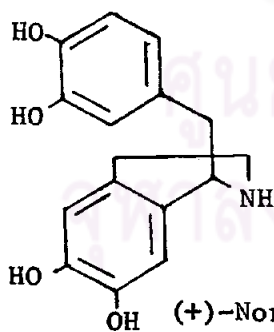
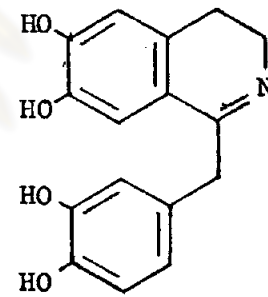
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Dopamine

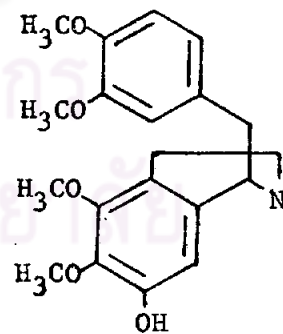
3,4-Dihydroxyphenyl-
pyruvic acidNorlaudanosoline
1-carboxylic acid

(+)-Norlaudanosoline

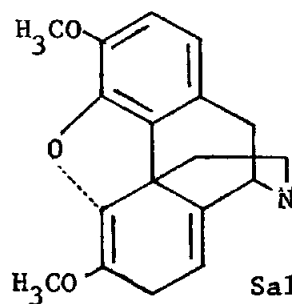
III



(+)-Norlaudanosoline



(-)-Reticuline

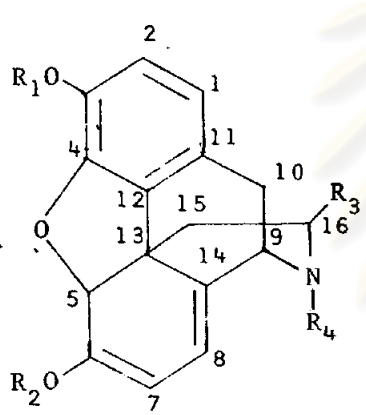
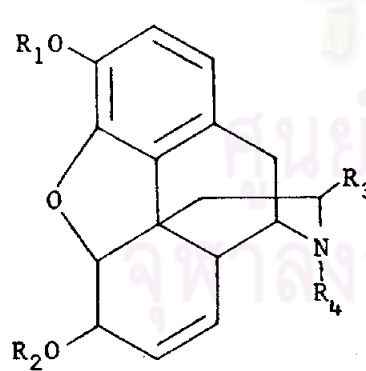


Salutaridinone

4. Morphinane Alkaloids4.1. Basic Structure

Table 3

Morphinane alkaloids from *Papaver somniferum* L.

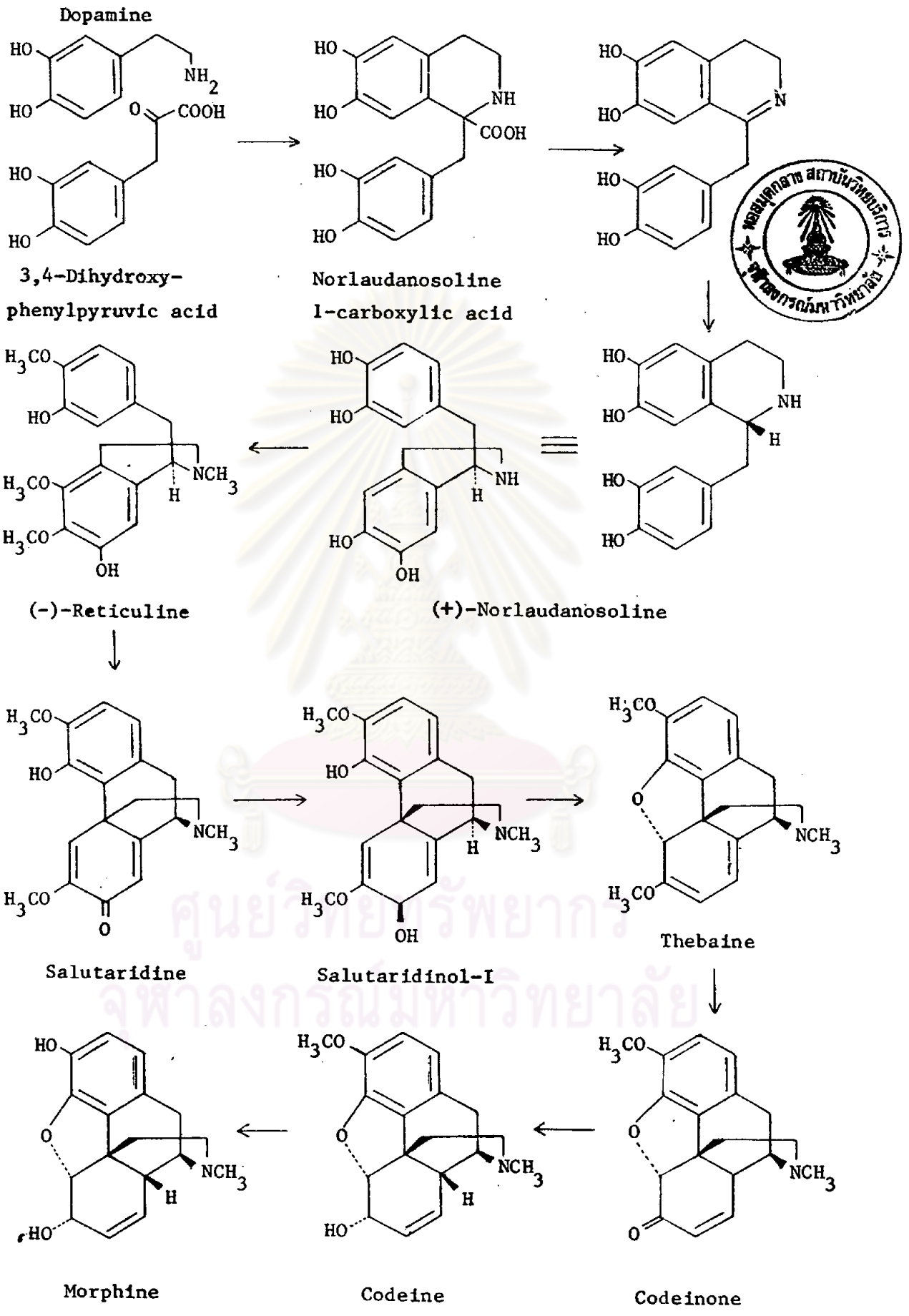
| Basic structure | Alkaloid | R ₁ | R ₂ | R ₃ | R ₄ |
|---|--------------------|-----------------|-----------------|----------------|-----------------|
|  | Thebaine | CH ₃ | CH ₃ | H | CH ₃ |
| | 16-Hydroxythebaine | CH ₃ | CH ₃ | OH | CH ₃ |
|  | Codeine | CH ₃ | H | H | CH ₃ |
| | 6-Methylcodeine | CH ₃ | CH ₃ | H | CH ₃ |
| | Morphine | H | H | H | CH ₃ |
| | Normorphine | H | H | H | H |

This group of alkaloids has a phenanthrene nucleus. The structure elucidation of these alkaloids stands as a monument to the brilliance of Robinson, but positive proof of the morphinane skeleton did not come until synthetic endeavors were successfully completed by Gates in 1952 (Cordell, 1981). The structures are shown in Table 2 (Santavy, 1979).

The prototype of morphinane alkaloids is morphine, which is the most important alkaloid in *Papaver somniferum* L.. Morphine exists to the extent of 4 to 21 %, codeine 0,8 to 2,5 % and thebaine 0,5 to 2,5 % (Tyler *et al.*, 1981).

4.2. Biosynthesis

Robinson, in 1931, first suggested that the alkaloids of the morphine group could be derived from two units of tyrosine, via benzyl-isoquinoline intermediates. The classic hypothesis for morphine alkaloid formation would be to place (+)-norlaudanosoline as the first dimeric intermediate. (+)-Norlaudanosoline is derivable from condensation of dopamine and 3,4-dihydroxypyruvic acid via amino acid. The next step, (+)-norlaudanosoline is incorporated to (-)-reticuline. (-)-Reticuline, but not (+)-reticuline is the precursor of morphinane alkaloids. The morphinanes are derived from (-)-reticuline via salutaridine to salutaridinol-I, thebaine, codeine and finally morphine (Cordell, 1981) as shown below:



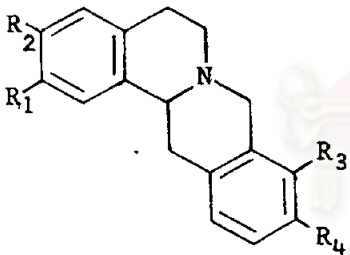
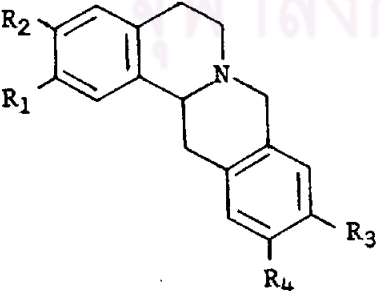
5. Berbene Alkaloids

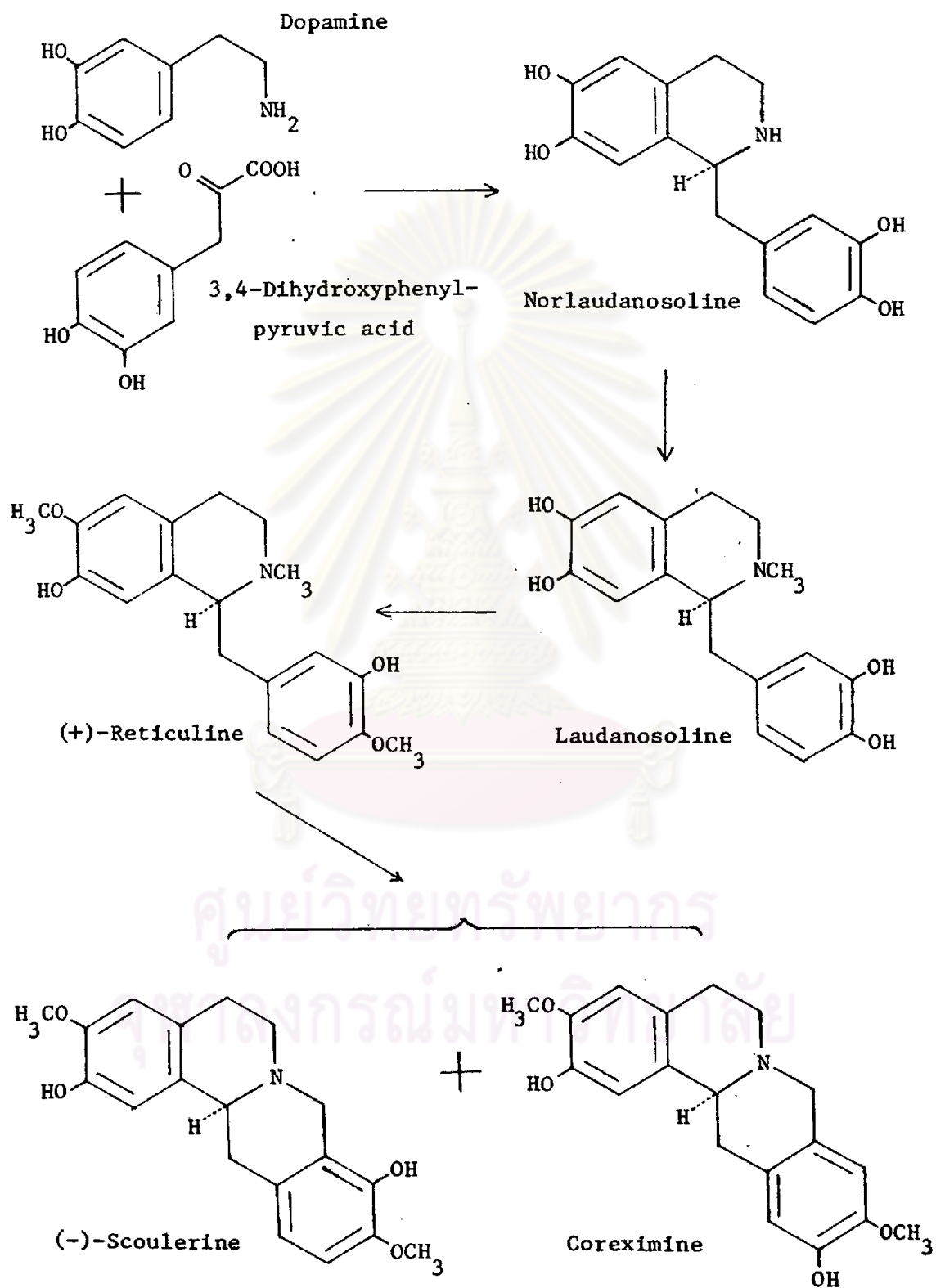
5.1. Basic Structure

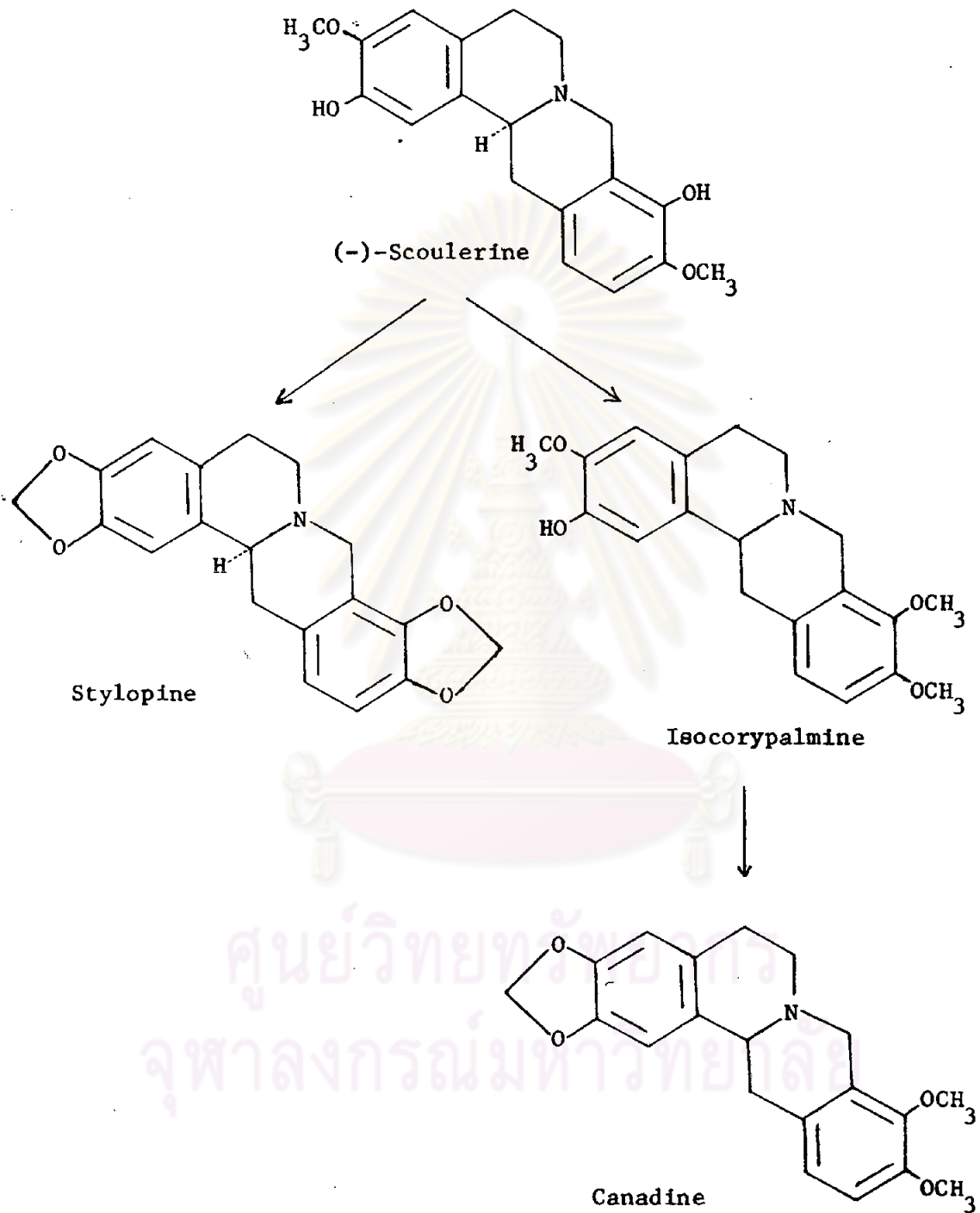
Santavy (1979) has included four types of alkaloids into berbene group. These are protoberberine, pseudoprotoberberine, corydaline and corytenchirine type. Alkaloids of *Papaver somniferum* L. in this group have structures of protoberberine and pseudoprotoberberine type which are shown in Table 3.

Table 3

Berbene alkaloids from *Papaver somniferum* L.

| Basic structure | Alkaloid | R ₁ | R ₂ | R ₃ | R ₄ |
|---|--------------|------------------------|------------------|------------------------|------------------|
| Protoberberine | | | | | |
|  | Stepholidine | OH | OCH ₃ | OCH ₃ | OH |
| | Canadine | -O-CH ₂ -O- | | OCH ₃ | OCH ₃ |
| | Stylophine | -O-CH ₂ -O- | | -O-CH ₂ -O- | |
| Pseudoprotoberberine | | | | | |
|  | Coreximine | OH | OCH ₃ | OH | OCH ₃ |

5.2. Biosynthesis



The fundamental units are those for the formation of the benzyl-isoquinoline alkaloids with the addition of a single carbon atom which becomes C-8 of the skeleton. Thus two molecules of tyrosine are involved, one proceeding to dopamine via dopa, and the second to 3,4-dihydroxyphenyl pyruvic acid. It has been firmly established that reticuline is a precursor of each of the alkaloids (Cordell, 1981).

6. Protopine Alkaloids

6.1. Basic Structure

Table 4

Protopine alkaloids from *Papaver somniferum* L.

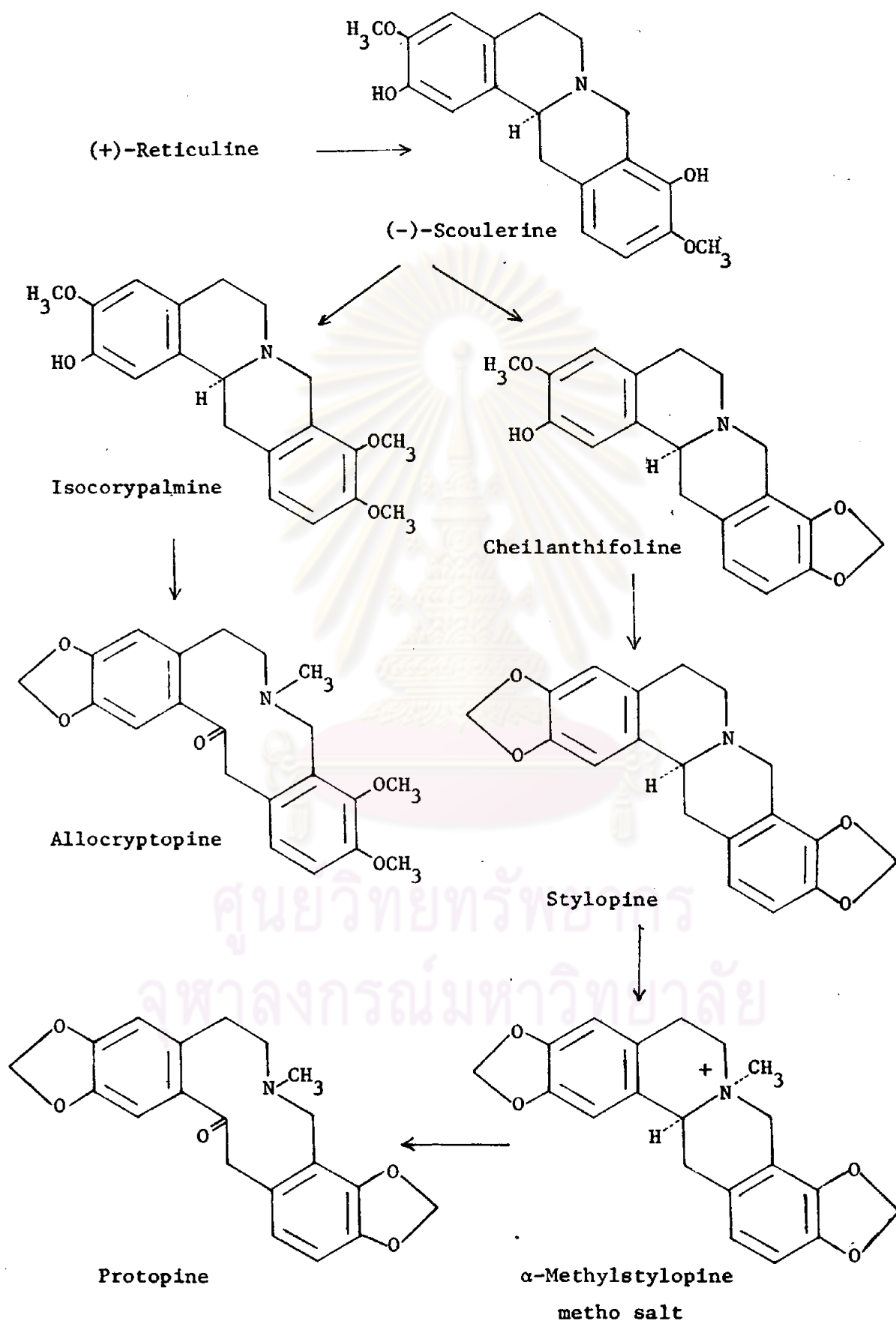
| Basic structure | Alkaloid | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ |
|-----------------|------------------|--------------------|-----------------|--------------------|-----------------|----------------|
| | Protopine | -CH ₂ - | | -CH ₂ - | | H ₂ |
| | Allocryptopine | -CH ₂ - | | CH ₃ | CH ₃ | H ₂ |
| | Cryptopine | CH ₃ | CH ₃ | -CH ₂ - | | H ₂ |
| | 13-Oxocryptopine | CH ₃ | CH ₃ | -CH ₂ - | | O |
| | Dihydroprotopine | -CH ₂ - | | -CH ₂ - | | |

The protopine alkaloids form a natural group which is characterized by the presence of a ten-membered N-heterocyclic ring containing one carbonyl group. The typical alkaloid is protopine, one of the most widely distributed of all benzylisoquinoline alkaloids (Manske, 1954c). The structures of this group of alkaloids from *Papaver somniferum* L. are shown in Table 4 (Santavy, 1979).

6.2. Biosynthesis

It has been shown that (+)-reticuline is a good precursor of protopine. .N-Methyl group of reticuline specifically enters C-8 of protopine. Finally, protopine is formed stereospecifically from the α -metho salt of stylophine, but not the β -metho salt. The biosynthetic pathway is shown below (Cordell, 1981):

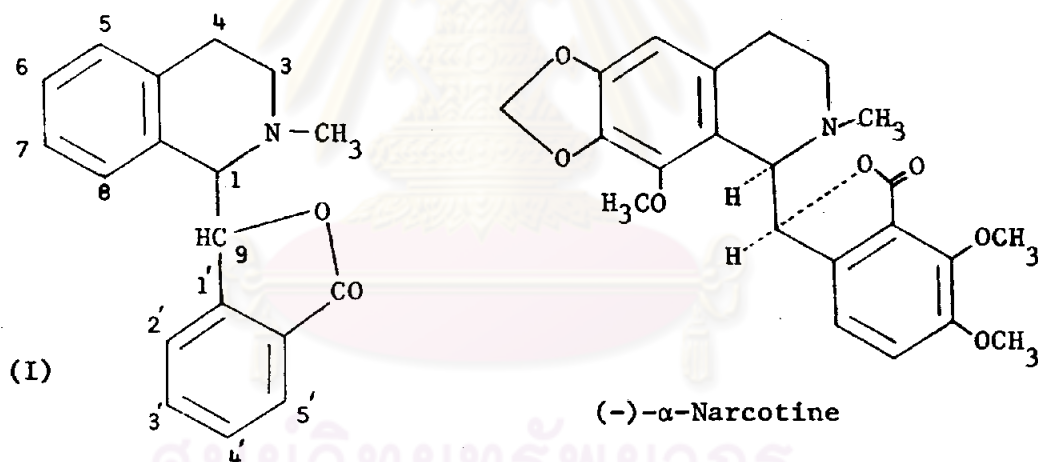
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จุฬาลงกรณ์มหาวิทยาลัย



7. Phthalideisoquinoline Alkaloids

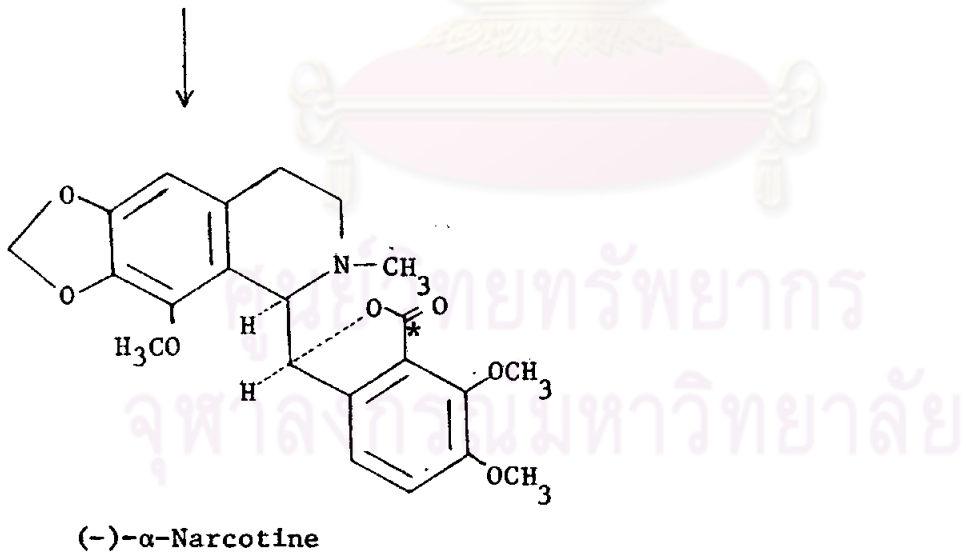
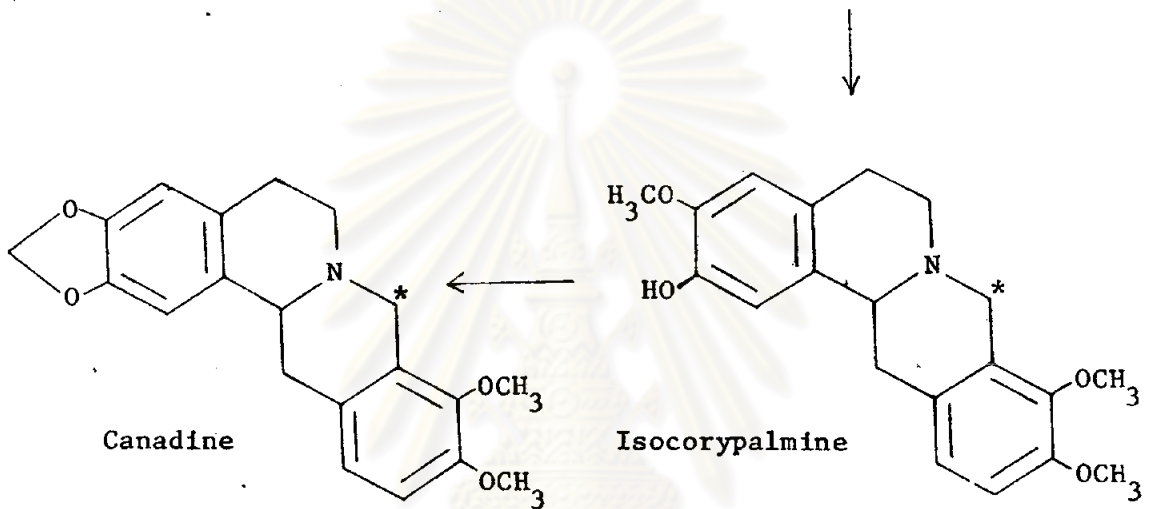
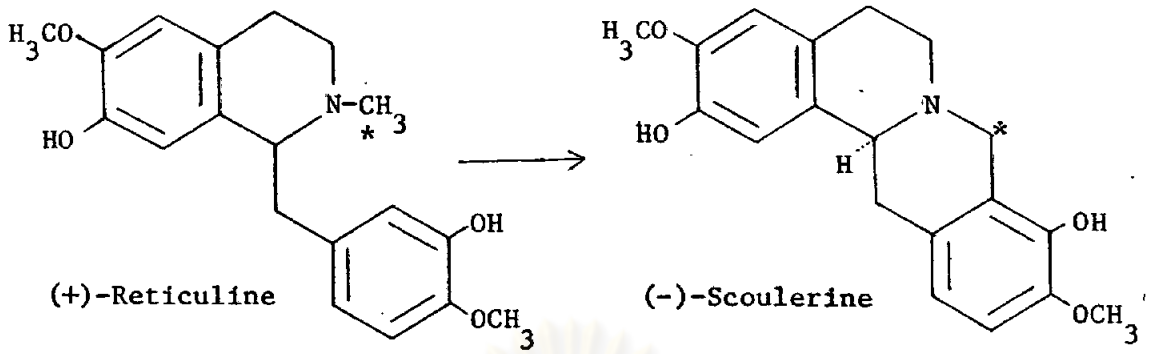
The term phthalideisoquinoline is applied to a group of alkaloids which are all derived from the parent substance (I) by the substitution of a hydroxyl at position 8 and/or methoxyl and methylenedioxy groups at position 6, 7, 4' and 5'. The nitrogen at position 2 always has a methyl group. Opium alkaloids of this group are (-)- α -narcotine and noscopine which is (\pm)- α -narcotine (Stanek and Manske, 1954).

The content of narcotine in opium is in the order of 0.7 to 6.4 %, although some Persian opium may contain as much as 11.2 % while a Chinese variety is started to be devoid of this alkaloid (Stanek and Manske, 1954).



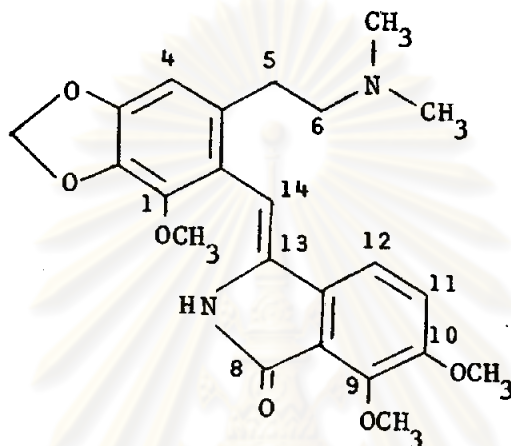
7.1. Biosynthesis

Simple benzyloisoquinoline such as norlaudanosoline and (+)-reticuline are also effective precursors. Narcotine is formed from the precursor via (-)-scoulerine to isocorypalmine and to canadine. It is significant to note that label from the N-methyl of (+)-reticuline is specifically incorporated into the carbonyl carbon of narcotine. The biosynthesis is shown below (Cordell, 1981):



8. Narceine Alkaloids

Alkaloids of this group are derived from narcotine by simple reactions but they are not phthalideisoquinolines (Stanek and Manske, 1954). Only narceineimide occurs in *Papaver somniferum* L. (Santavy, 1979).

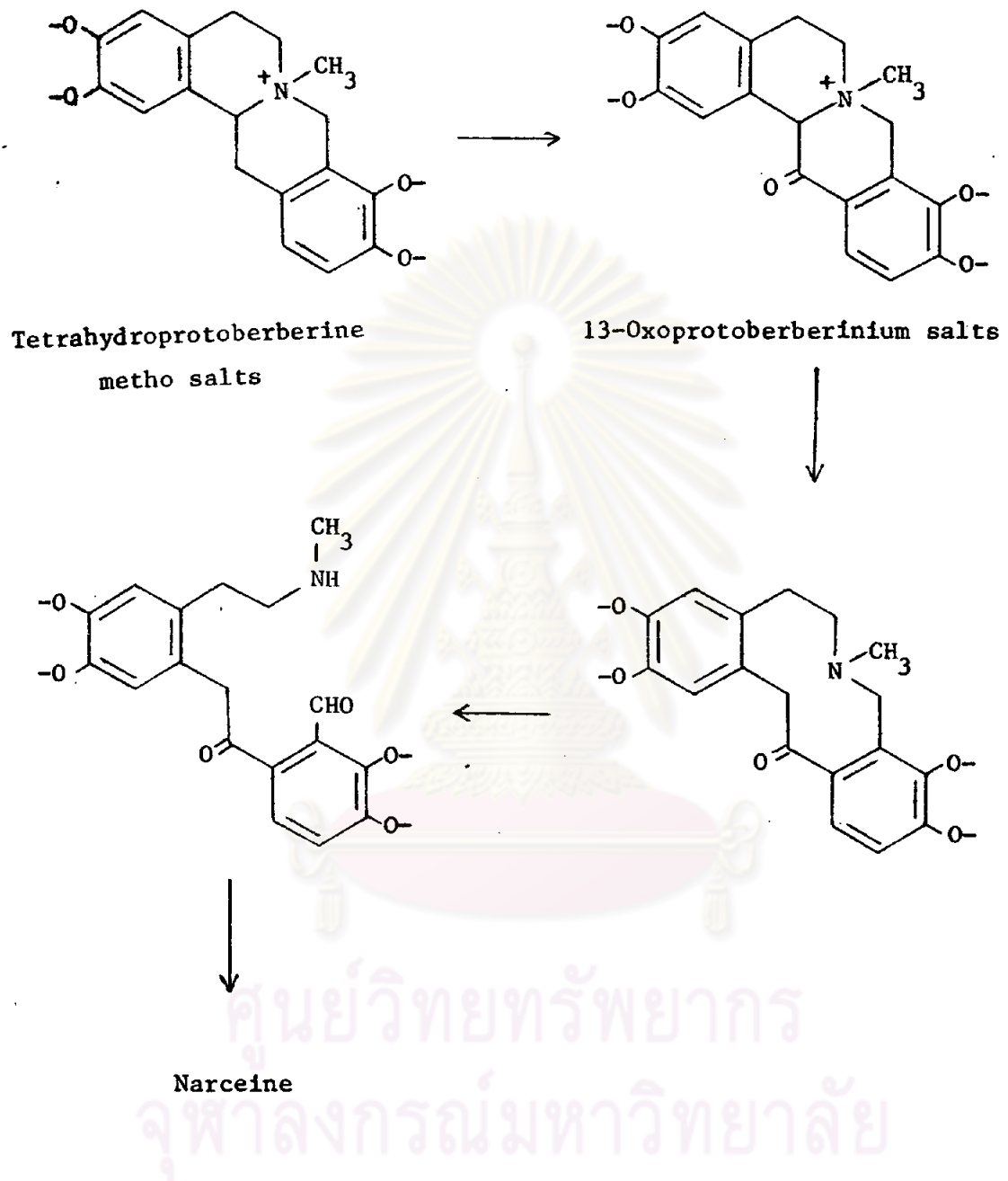


Narceineimide

It has three methoxyls, a methylenedioxy, two N-methyl groups and imide. Narceineimide compounds may not be true alkaloids, but artifacts formed during work up (Santavy, 1979).

8.1. Biosynthesis of Narceine Alkaloids

Nalliah *et al.* (1974) suggested that narceine alkaloids transformed from tetrahydroprotoberberine metho salts via 13-oxoprotoberberinium salts. The biosynthetic pathway is shown below:



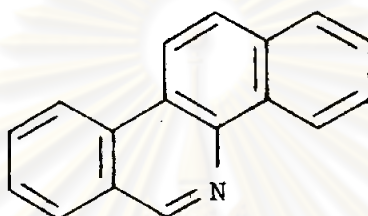
9. α -Naphthaphenanthridine Alkaloids9.1. Basic Structure

Table 5

 α -Naphthaphenanthridine alkaloids from *Papaver somniferum* L.

| Basic structure | Alkaloid | R ₁ | R ₂ |
|-----------------|------------------------------|----------------|-----------------------------------|
| | 6-Acetyldihydro-sanguinarine | H | CH ₂ COCH ₃ |
| | Dihydrosanguinarine | H | H |
| | Oxysanguinarine | -O- | -O- |
| | Sanguinarine | | |
| | Norsanguinarine | | |

The α -naphthaphenanthridine alkaloids are derived from the tetracyclic system (II) in which the terminal nuclei are fully aromatic, each having at least two alkoxy groups. The two central nuclei are either aromatic or fully reduced, in which latter case there is a hydroxyl on the non-nitrogenous ring. The nitrogen always carries a methyl group (Manske, 1954b).

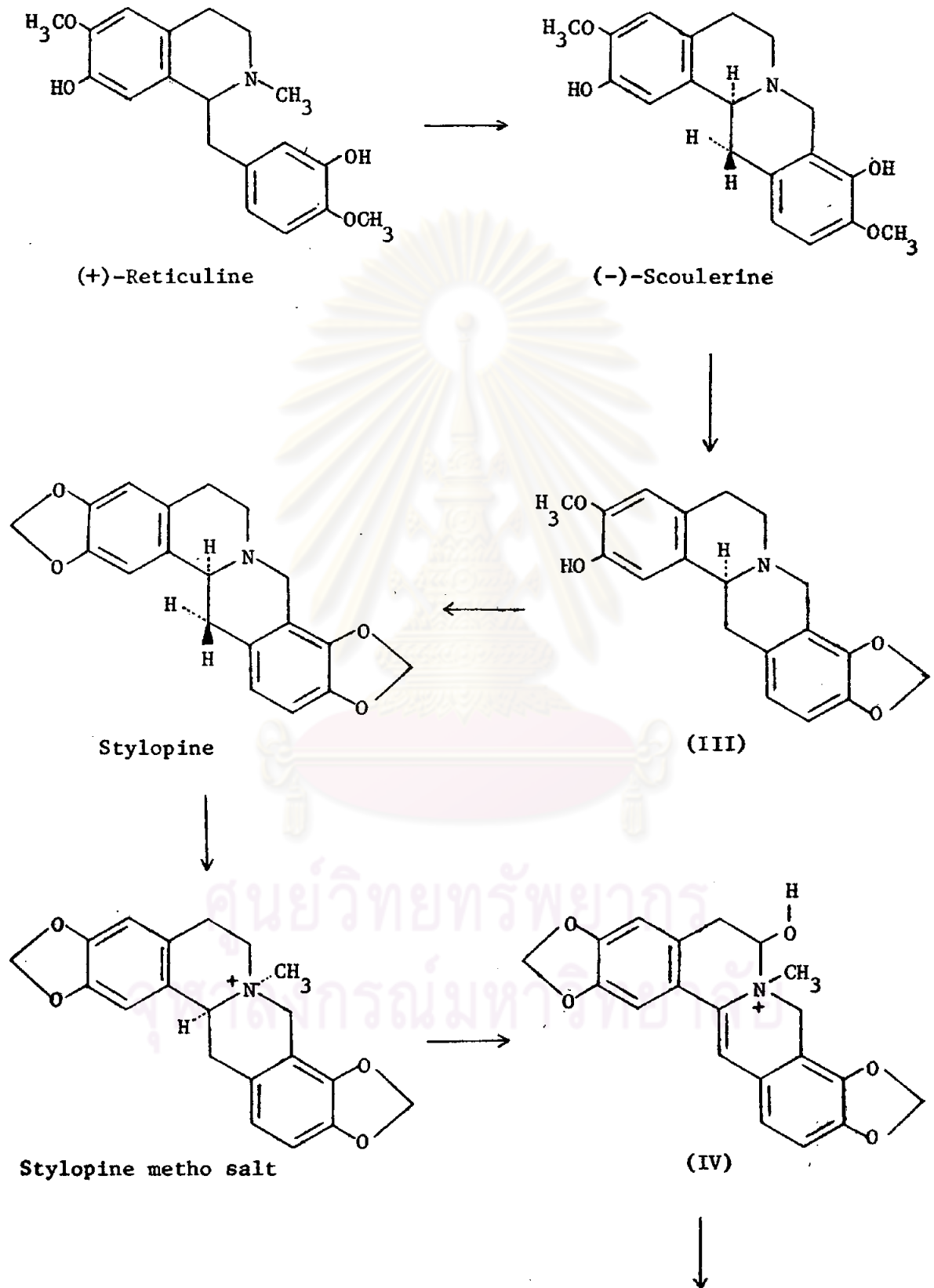


(II)

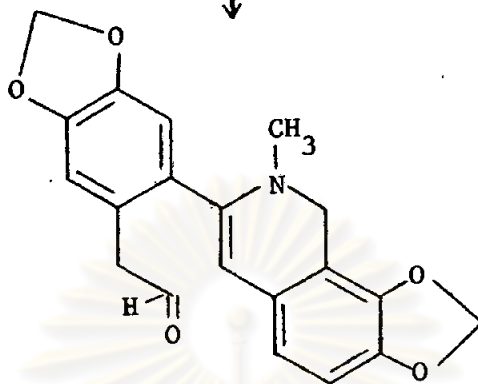
Opium alkaloids of this group are shown in Table 5 (Santavy, 1979).

9.2. Biosynthesis

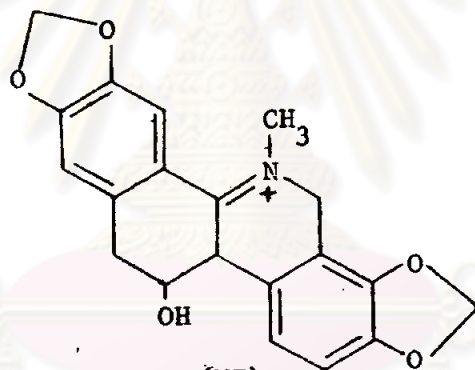
The key intermediate after dopamine is (+)-reticuline, which is cyclized oxidatively to (-)-scoulerine. The next step is formation of the two methylenedioxy groups to produce stylophine, probably via (III) (Battersby *et al.*, 1975). No intermediates have been isolated from the subsequent stages, which are thought to involve 6-hydroxylation of stylophine metho salt and 13,14-dehydrogenation to give (IV). Subsequent rearrangement affords chelidonine by cleavage to the enamine aldehyde (V) and reduction of the iminium species (VI) and sanguinarine by oxidative dehydration. The biosynthetic pathway is shown below (Cordell, 1981):



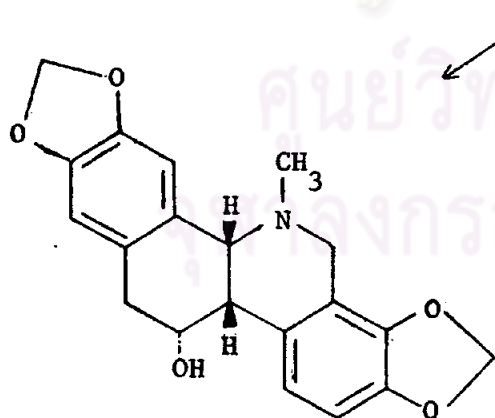
(IV)



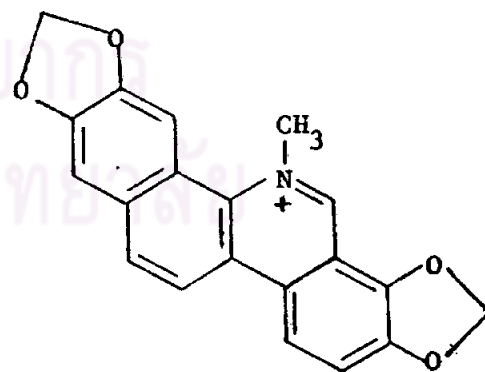
(V)



(VI)



Chelidonium



Sanguinarine

Biosynthetic Relationship Between the Alkaloids from *Papaver somniferum* L.

Although some opium alkaloids exhibit complex structures, the majority of alkaloids have the isoquinoline ring structure. All are derived from benzylisoquinoline intermediates which result from the condensation of a phenylethylamine derivative with a phenylacetaldehyde derivative. Both of these moieties are derived from tyrosine or phenylalanine. From norlaudanosoline, a benzylisoquinoline, four alternative pathways can then occur.

1. Papaverine, a benzylisoquinoline alkaloid, may be derived via (-)-nor-reticuline or (\pm)-nororientalinone which yields (-)-tetrahydropapaverine.

2. Aporphine alkaloids are formed from norlaudanosoline. This pathway has five routes.

3. Morphinane alkaloids are derived from (-)-reticuline via salutaridine, a promorphinane, to thebaine, codeinone, codeine and morphine respectively.

4. The fourth alternative pathway would proceed via (+)-reticuline to (-)-scoulerine, an intermediate of protopine, berbene, phthalideisoquinoline and α -naphthaphenanthridine alkaloids.

The biosynthetic relationship is shown in scheme below
(Staba *et al.*, 1982):

