CHAPTER 2

GENERAL CHEMICAL ASPECTS

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2.1 General definition

Alkaloids are basic natural secondary metabolites occurring primarily in plants. All parts of certain plants especially the seeds, leaves, bark and roots are believed to produce alkaloids. However, some alkaloids are also produced by animals, such as toxins in the skin of poison-dart frogs[13]. Alkaloids contain one or more heterocyclic nitrogen atoms and are usually found in the form of salts together with organic acids. They are originally defined as pharmacologically active due to their properties as bitter, alkaline and nitrogenous compounds that may have pronounced effects on the nervous systems of animals.

The term alkaloid was coined in 1819 by the pharmacist W. Meissner[14] and meant simply, *alkalilike* (Middle English *alcaly*, from Medieval Latin *alcali*, from Arabic *alqaliy* = ashes of stalwart, from *qualey*, to fry). The first modern definition by Winsterstein and Trier[15] described these substances in a broad sense as basic compounds of either plant or animal origin. The trivial names of alkaloids are based on those of the plants in which they were discovered and usually, closely related families often produce similar alkaloids. Although their biogenesis and metabolism[16] have been studied in many cases, the functions of alkaloids in plants are still unknown. Some of the suggested functions and their important are listed and described briefly as follow:-

a. Protection against animals: Their protective function against consumption by animals has been proven in a few cases. In fact, the insects cannot destroy a few plant species may be because of their alkaloid contents. However, explanation of the biological significance of the alkaloids cannot yet be given.

b. As storage reservoirs of nitrogen for protein synthesis.

c. As plant stimulants or regulators in such activities as growth, metabolism and reproduction.

d. Alkaloids are widely used therapeutically, as a combination of pure compounds, as extracts of total alkaloids or as synthetic analogues. These are due to the fact that many alkaloids have a strong and very specific effect on certain center of the nervous system.

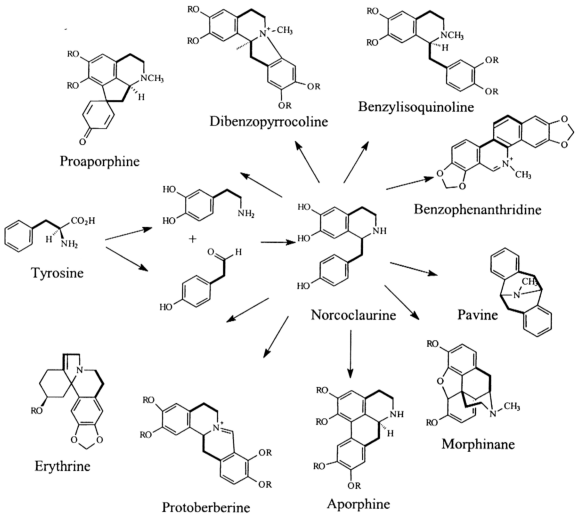
e. Many alkaloids serve as models for the chemical synthesis of analogues with excellent properties. Important examples are cocaine (*Erythroxylon coca*) as models for local anesthetics; morphine for analgesics and codeine for antitussive agent from *Papaver somniferum*[16].

2.2 Classification of isoquinoline alkaloids

Most of the alkaloids belong to the isoquinoline group, which can be classified into approximately twenty categories[17]. In terms of classifying alkaloids, several factor have to be considered. Although they have been simply classified by their origin, chemical, pharmacological and botanical properties, but some other factors such as biogenetic (biosynthetic pathway - the way they are produced in the plant i.e. an enzymatic synthesis) and spectroscopic criteria also important in classification of alkaloids.

Isoquinoline type is usually synthesized *in vivo* by a Mannich condensation between a phenylethylamine derivative and a carbonyl component[18]. Scheme 2.1 below shows various type of isoquinoline alkaloids started from tyrosine as an intermediate precursor of dopamine. This synthesis proved that, (*S*)-norcoclaurine[19] is the first and central intermediate of a vast majority of isoquinoline alkaloids. Various types of isoquinoline alkaloids found in Lauraceae: proaporphine, benzophenanthridine, pavine, morphinane, aporphine, protoberberine, erythrine and dibenzopyrrocoline can be derived from benzylisoquinolines.

In the following sections, the author will explain briefly the general spectral behaviors of proaporphine, proaporphine-tryptamine (a very rare group), aporphine (large group in isoquinoline), morphinandienone and bisbenzylisoquinoline type alkaloids including their sources in plant.

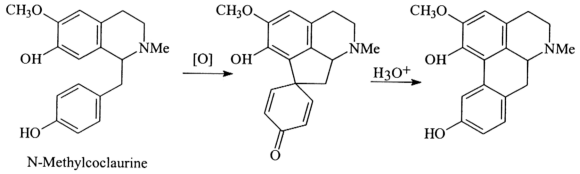


Sheme 2.1: Biosynthesis of various isoquinoline alkaloids from (*S*)-norcoclaurine

2.2.1 Proaporphines

Biosynthesis

The proaporphines possess a tetracyclic nucleus that incorporates a cyclohexadienone system in addition to the ubiquitous tetrahydroisoquinoline moiety[20]. Sometimes, one or both of the double bonds of the dienone system have been reduced. This group of alkaloids represents as an intermediate stage in the conversion of the benzylisoquinoline alkaloids by phenol oxidative coupling into the aporphines through acid catalyzed. In other words, proaporphine alkaloids can be considered to be the biogenetic precursor of the aporphines (Scheme 2.2).

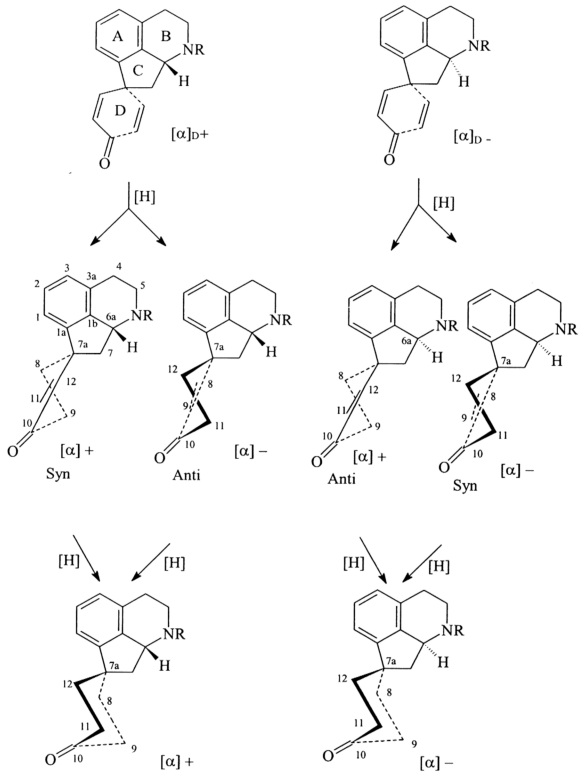


N-Methylcoclaurine

Scheme 2.2: Proaporphine alkaloids as biogenetic precursor of the aporphines

Absolute configuration

The absolute configuration[21] of a proaporphine may be determined simply by the sign of its specific rotation, since it is known that compounds of the C-6a *S* configuration possess a negative rotation or levorotatory, while those of the C-6a *R* series are positive rotation or dextrorotatory. In addition, a dependable method for the determination of absolute configuration is the acid catalyzed dienone-phenol arrangement of the proaporphine to yield the corresponding aporphines[22]. This method is usually stable and its specific rotation may be readily measured. Proaporhines can be reduced to yield the dihydro and tetrahydroproaporphine by using some catalysts such as H_2-Pd/C. Some interesting generalizations concerning the sign and magnitude of the spesific rotations for the proaporphines can be drawn and summarized in Scheme 2.3. The numbering system for the proaporphine alkaloids is shown below.

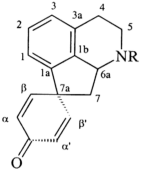


Scheme 2.3: The sign and magnitude of the specific rotations for the proaporphines and reduced proaporphines.

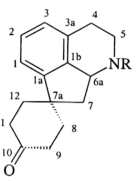
The NMR studies of proaporphines

^{1}H NMR of proaporphine and reduced proaporphine[23-25].

The ^{1}H NMR of proaporphines shows doublet doublet signal of the vinyl protons at about δ 6.25 and 6.60 for α and α' and δ 6.70-7.30 for β and β' respectively. The coupling constants of those two doublet doublet are ~10.5 Hz. Both of these signals show a further splitting of 2 Hz since each proton is coupled to another proton in a longer-range coupling. The β and β' protons are more downfield because they located at β to a carbonyl group. While the α and α' are less shielded.



Proaporphine



Reduced proaporphine

A singlet at about δ 6.65 is assigned to H-3. The presence of this signal shows that C-1 and/or C-2 are substituted. As in the aporphine alkaloids, the aliphatic protons will appear between δ 1.80-3.80 with a complex pattern and the *N*-methyl signal will resonate at $\delta \sim \delta$ 2.40 as a singlet with three protons.

From the reported ^{1}H-NMR data of reduced proaporphines possessing an enone moiety, the shift difference of the olefinic protons is about 0.70-0.76 ppm in the *anti* isomers such as amuronine **1** and about 0.9-0.95 ppm ($\Delta\delta_{8\text{-}9}$ of $\Delta\delta_{11\text{-}12}$) in the *syn*

isomers (H-6a and the double bond in ring D are on the same side) as in (+)-8,9-dihydrostepharine **2**.

^{13}C NMR of proaporphines

Analysis of ^{13}C NMR also shows significant chemical shifts for *syn* and *anti* isomers of reduced proaporphines[26-27]. The signal of C-7 in *syn* and *anti* reduced propaorphines bearing an allylic alcohol in ring D is observed around δ 50.2 and δ 45.0. However, in the *syn* and *anti* reduced enone proaporphines the signal for C-7 is observed around δ 49.0 and δ 43.0 respectively. The ^{13}C-NMR of selected propaorphine and reduced proaporphine is shown in Table 2.1 below.

The UV spectra of proaporphines[28]

The proaporphines show two main maxima at about 230 and 290 nm. The maximum at about 290 nm band shows a bathochromic shift in alkaline solution. For example litsericine shows maxima at 247 and 300 nm.

The mass spectra of proaporphines[29]

The molecular ion peak for proaporphines is usually observed as the base peak. Most of the compounds showed a large $[M-1]^+$ peak by losing 1 hidrogen atom from the carbon adjacent to the nitrogen atom and form a quaternary ammonium ion $[M-H]^+$. The most interesting fragmentation is the formation of the metastable peak from the retro-Diels-Alder at $[M-29]^+$ or $[M-43]^+$.

Table 2.1: ^{13}C NMR data of amuronine **1,** cryprochine **3,** isocryprochine **4,** (-)-*N*-methylcrotsparinine **5** and pronuciferine **6** in $CDCl_3$ (δ in ppm)

Position	**1**	**3**	**4**	**5**	**6**
1	143.7	144.7	152.8	140.8	143.7
1a	137.1	138.4	136.7	134.5	134.8
1b	126.8	134.2	135.4	121.5	127.5
2	152.6	153.2	144.4	147.9	152.7
3	111.3	110.9	110.9	110.2	111.9
3a	133.9	126.8	126.3	129.2	132.9
4	27.0	27.4	27.3	26.8	27.0
5	54.4	54.9	54.9	54.6	54.3
6a	65.0	65.1	66.4	64.6	65.0
7	43.2	50.2	39.5	48.8	46.9
7a	47.3	48.3	53.1	47.8	50.7
8	156.9	136.0	73.4	33.1	154.3
9	126.8	127.5	130.4	35.2	127.7
10	198.7	63.8	128.8	198.5	185.3
11	35.2	29.3	22.9	126.8	126.6
12	31.5	29.3	32.6	155.1	150.9
1-OMe	60.3	60.8	56.0		60.2
2-OMe	56.0	56.3	60.8	56.4	56.1
N-Me	43.2	43.3	43.4	43.4	43.2

2.2.2 Proaporphine alkaloids from plant species

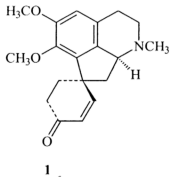
Proaporphine alkaloids can be found in several species especially from the family of Menispermaceae, Annonaceae, Papaveraceae and Lauraceae[30]. Some of the compounds showed interesting bioactivities[31].

(+)-Cryprochine **3**, a new proaporphine was isolated from the leaves and bark of *Cryptocarya chinensis* (Lauraceae) by Shoei-Sheng Lee and co-workers[32]. This alkaloid contains an allylic alcohol moiety. An oxidized cryprochine, isoamuronine **7** was then isolated from the wood of the same plant by Tian-Shung Wu and co-workers[33] together with four new proaporhines *i.e.* (+)-8,9-dihydrostepharine **2**. isocyprochine **4** and prooxcrytochine **8**.

Furthermore, pronuciferine **6** was previously isolated from *Stephania cepharantha* seeds (Menispermaceae)[34] as a known proaporphine. In continuing investigations of the alkaloidal constituents of the tubers of the same plant, Kashiwaba and co-workers[35] had isolated two proaporphine alkaloids, stepharine **9** and *N*-methylcrotsparine **10**. In addition, mecambrine **11** and pronuciferine **6** were isolated from *Papaver dubium* subsp. *laevigatum* (species collected in central Turkey) as minor alkaloids[36]. Cytotoxicity assay using *Artemia salina* (brine shrimp) was carried out on tertiary and quartenary extracts of *Papaver dubium* subsp. *laevigatum*. The presence of mecambrine in the extract has not decreased the cytotoxicity significantly since (+)-mecambrine **11** was previously reported to be moderately cytotoxic.

Annona glabra L. (Annonaceae)[37] is used in traditional medicines as an insecticide and a parasiticide can be found in the southern part of Taiwan and distributed mainly in Southeast Asia also contains proaporhine, (+)-stepharine **9**. On the other hand, the antiplatelet aggregation agent, glaziovine **12** was isolated from *Annona purpurea*[38].

In 1987, the Turkish *Roemeria hybrida* (L.) DC. (Papaveraceae)[39] had yielded nine proaporphines, i.e. (-) roemerialinone **13**, (-) isoorientalinone **14**, (-) isoroemerialinone **15**, (-)-11,12-dihydroorientalinone **16**, (+)-8,9-dihydroisoroemerialinone **17**, (-)-α-roemehybrine **18**, (-)-rohybrine **19**, (-)-mecambrine **20** and (-)-orientalinone **21**. Catalytic reduction of (-) isoorientalinone **14** yielded (+)-8,9-dihydroisoorientalinone **22,** which is originally obtained from *Papaver orientale*. Interestingly, the pairs of diastereomeric proaporphines, (-)-orientalinone **19** and (-)-isoorientalinone **14** together with (-)-roemerialinone **13** and (-)-isoroemerialinone **15**, were also isolated and determined their structures. The genus *Roemeria* is known to be rich in proaporphine and aporphine alkaloids[39].



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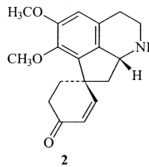

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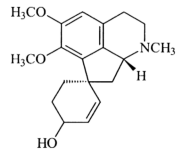

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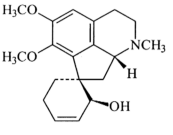

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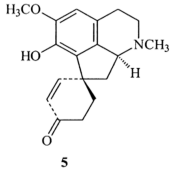

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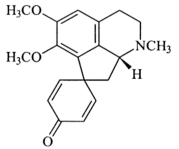

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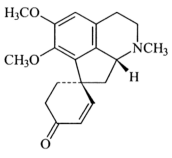

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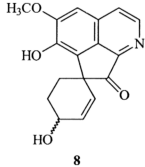

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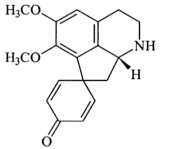

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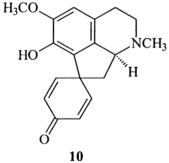

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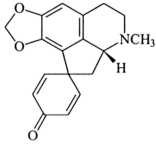

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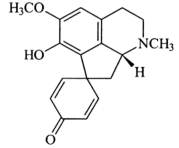

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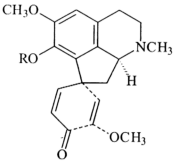
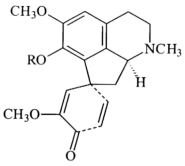
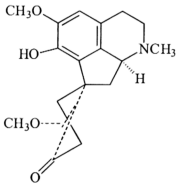


21: R=H
13: R= Me



14: R=H
15: R= Me



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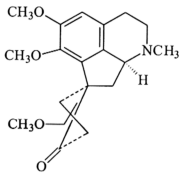

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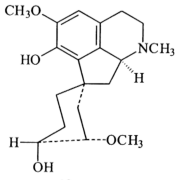

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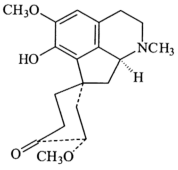

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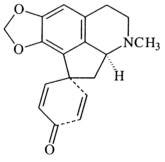

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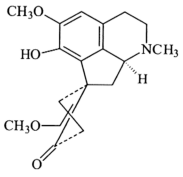
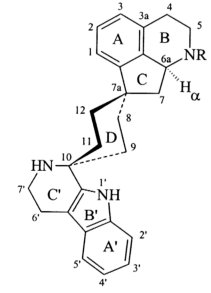


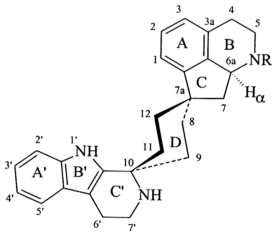
22

2.2.3 Proaporphine-tryptamine dimers

The proaporphine-tryptamine dimers are recognized as a group of heptacyclic alkaloids with nitrogen atom in the rings B, B' and C'. The dimers most probably formed biogenetically by Mannich-type condensation of a ketonic tetrahydroproaporphine with a tryptamine analogue[40]. Russian researchers were the first investigators of these dimer alkaloids in the 1950's. The species studied was *Roemeria hybrida* (L.) DC. (Papaveraceae)[41]. The alkaloid (-)-roemeridine was the first proaporphine-tryptamine isolated by the Russian team but its structure was not determined. The proaporphine-tryptamine dimers may be classified into two broad stereochemical series labeled *syn* and *anti* as exemplied by structures A and B. In the *syn* series, A, the proaporphine nitrogen atom and the non-basic nitrogen of the indole moiety are on the same side of ring D, whereas in the *anti* series, B, they lie on the opposite sides.



A



B

A further subdivision of the dimers is based upon the fact that some are dimethoxylated on ring A' at C-3' and C-4', while others are only monomethoxylated of ring A' specifically at C-3'. All dimers are oxygenated at C-1 and C-2 of ring A. This is also in line with the observation that all naturally occurring proaporphines and aporphines are also oxygenated at these two sites. In the case of the proaporphine-tryptamine dimers, the C-1 substituent may be hydroxyl or methoxyl groups, but a methoxyl seems to be preferred at C-2.

A total of fourteen known proaporphine-tryptamine dimers have been isolated from two different plant families (Papaveraceae and Lauraceae) in which 11 fall into the *syn* series, nine with axial and two with equatorial 9-methoxyl groups. The *anti* series includes only three compounds, all incorporating axial methoxyl substituents at C-9.

^{1}H NMR for proaporphine-tryptamine alkaloids[40-44].

In the ^{1}H NMR spectrum, two important features of proaporphine-tryptamine, are a relatively broad singlet at between δ 7.80-8.56, characteristic of the 1'-NH of the –carboline moiety, and ring A aromatic singlet at ~ δ 6.57 for H-3 of proaporphine moiety. All dimers are oxygenated at C-1 and C-2 on ring A and the ^{1}H NMR resonances of these methoxyl protons appear in the range of δ 3.80-4.00 as a sharp singlet. The chemical shifts of the 9-methoxyl group and H-9 are distinctly different for all three subgroups. These values are indicative of the stereochemistry at C-9 and C-10. For example, a singlet in the δ 3.33-3.38 range belongs to an aliphatic 9-methoxyl group of axial position, a caharacteristic substitution of the *Roemeria*

proaporphine-tryptamine dimers (Table 2.2). H-9 appears as a narrow ddd, spanning a width of 6 Hz, which is typical of equatorial hydrogen in a substituted cyclohexane structure in which normally resonates in the range of δ 3.43-3.46.

The chemical shifts of H-12 are also diagnostic for the *syn* or *anti* configuration as stated in Table 2.3. In the ^{1}H-NMR spectrum of the *syn* series, H-12 equatorial is always the most shielded proton in the range of δ 1.38-1.51. The difference in the chemical shifts of the axial and equatorial H-12 is approximately 1.7 ppm. On the other hand, the difference between chemical shifts of axial and equatorial H-12 in the *anti* compounds is approximately 0.6 ppm. Therefore, the chemical shifts of H-12 provide significant criteria for the assignment of the stereochemistry at C-10. The chemical shifts of H-12 of proaporphine-tryptamine dimers of the *Phoebe* species are also consistent with that of *Roemeria* species although there is no substitution at C-9. The chemical shifts of three proaporphine-tryptamine dimer alkaloids isolated from *Roemeria* species are shown in compounds **23**, **24** and **25**.

Table 2.2: Generalizations for the ^{1}H-NMR chemical shifts of H-9 and 9-OMe from *Roemeria* species

H	*Syn*/axial 9-OMe (δ)	*Syn*/equatorial 9-OMe (δ)	*Anti*/axial 9-OMe (δ)
H-9	3.43-3.46	3.79-3.80	3.63-3.80
9-OMe	3.33-3.38	3.08	3.20-3.25

Table 2.3: Generalizations for the ^{1}H-NMR chemical shifts of H-12 of proaporphine-tryptamine from *Roemeria* and *Phoebe* species.

H	*Syn* series (δ)	*Anti* series (δ)
H-12 axial	3.07-3.15	2.43-2.49
H-12 equatorial	1.38-1.51	1.85-1.90

The ^{13}C-NMR data in this type has not been fully documented. However, the quaternary spiro C-10 and C-7a appeared at δ 54.3 and δ 45.3 for (-)-roehybridine **23**[43]. Recent publication[44] of the ^{13}C NMR of two N-oxides, (-)-roehybridine α-N-oxide **26** and (-)-roehybridine β-N-oxide **27** is listed in Table 2.4 below.

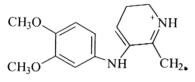
UV spectra for proaporphine-tryptamine alkaloids[40-42]

UV spectra of proaporphine-tryptamine dimers show maxima at 226, 290, 298 and 303 nm with a shoulder near 308 nm when the ring A' of tryptamine moiety were substituted by two methoxyl groups at position 3' and 4'. In contrast, for example (-)-roehybramine, which lacks the 4'-OMe group, exhibits in its UV spectrum a simpler pattern with maxima at 227 and 290 nm and a shoulder at 300 nm.

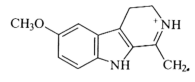
Table 2.4: ^{13}C-NMR data of (-)-roehybridine α-N-oxide **26** and (-)-roehybridine β-N-oxide **27** in $CDCl_3$ (δ in ppm)

Position	**26**	**27**
1	141.37	140.93
1a	133.84	133.73
1b	128.18	127.21
2	148.75	148.05
3	108.26	108.55
3a	118.39	119.78
4	26.89	24.11
5	69.83	66.04
6a	77.81	75.27
7	39.64	37.73
7a	45.14	45.48
8	28.87	29.47
9	82.58	83.15
10	54.28	54.17
11	29.27	29.19
12	31.02	30.11
1'a	129.96	136.35
1'b	137.42	137.66
2'	94.93	94.91
3'	146.61	156.10
4'	144.55	108.59
5'	100.42	118.63
5'a	119.44	121.44
5'b	108.35	108.55
6'	23.15	23.07
7'	39.63	39.57
2-OMe	56.39	56.52
9-OMe	57.32	57.12
3'-OMe	56.55	55.82
4'-OMe	56.30	
N-Me	46.76	56.71

Mass spectra of proaporphine-tryptamine alkaloids[40-43]



Ion C m/z 244



Ion D m/z 214

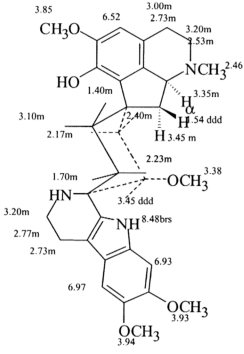
Proaporphine-tryptamine dimers with two methoxyls at position 3' and 4' usually show the base peak at m/z 244 and represents the tetrahydro- β-carbolinium ion C. In the case of *N*-Oxide, however, the molecular ion is very small due to facile loss of oxygen to provide $[M-16]^+$ ion. The base peak is still at m/z 244. On the other hand, if there is one substitution on ring A' of tryptamine moiety, the base peak is m/z 214 rather than 244 due to monomethoxylated ion D as in phoebegrandines A and B (**28**, **29**)[42].

2.2.4 Sources of proaporphine-tryptamine dimers.

In 1990, ten proaporphine tryptamine dimers were isolated in two different stereochemistry labeled *syn* and *anti* by Gozler and co-workers[43] from the Turkish *Roemeria hybrida*. Two known alkaloids are (-)-roehybridine **23** and (-)-roemeridine **24**, and the other eight have been divided into three subgroups based on the stereochemistry at C-9 and at the spiro C-10 center. The first subgroup is *syn* 9-OMe axial, includes (-)-roehybridine **23**, (-)-norroehybridine **30**, (-)-*O*-methylroehybridine **31**, (-)-roehybride-*N*-oxide **32** and (-)-roehybramine **33**. The second subgroup is *syn* 9-OMe equatorial, (+)-roehymine **25** and (+)-roebramine **34**. The third subgroup is

anti 9-OMe axial, (-)-roemeridine **24**, (-)-O-Methylroemeridine **35** and (-)-roemebramine **36**.

Recent study on the same species of *Roemeria hybrida* by Semith[44] yielded another two novel compounds of proaporphine-tryptamine *N*-oxides i.e. (-)-roehybridine-α-*N*-oxide **26** and (-)-roehybramine-β-*N*-oxide **27**.



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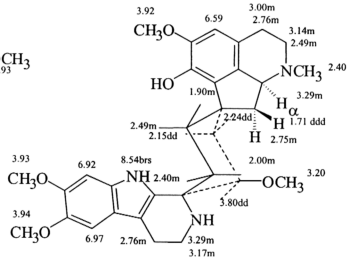

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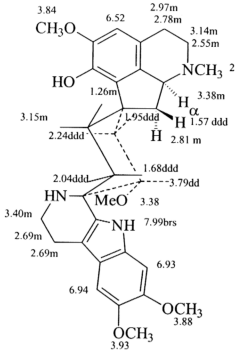
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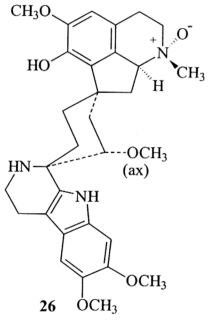
6.52
2.97m
2.78m
3.14m
2.55m
CH3O
NCH3 2.44
HO
1.26m
H α 3.38m
3.15m
1.95ddd
H 1.57 ddd
2.24ddd
H 2.81 m
1.68ddd
2.04ddd
3.79dd
HN
MeO 3.38
3.40m
NH 7.99brs
2.69m
2.69m
6.93
6.94
OCH3
3.88
OCH3
3.93

25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H
OCH3
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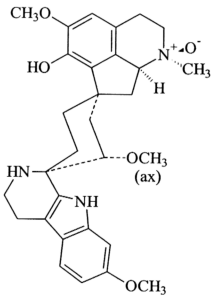
HN
NH
OCH3
OCH3

26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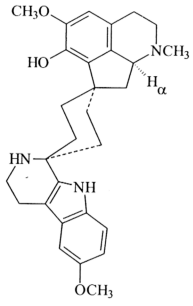
HO
N+ O-
CH3
H
OCH3
(ax)
HN
NH
OCH3

27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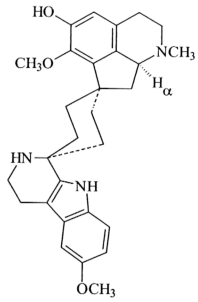
HO
NCH3
Hα
HN
NH
OCH3

28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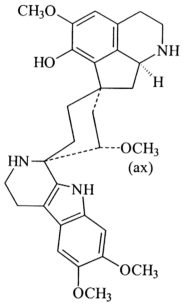
NCH3
Hα
HN
NH
OCH3

29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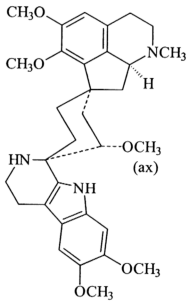
HO
NH
H
OCH3
(ax)
HN
NH
OCH3
OCH3

30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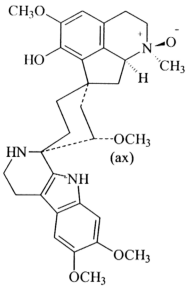
31



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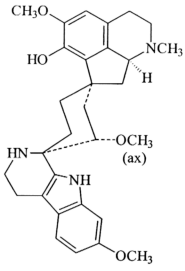

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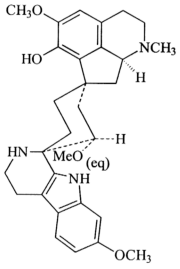

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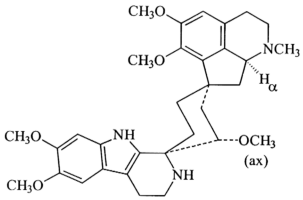

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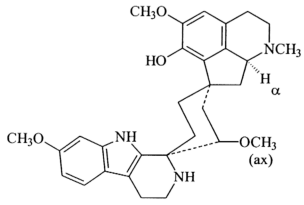
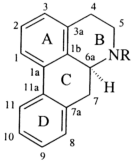


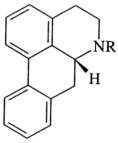
36

2.2.5 Aporphines

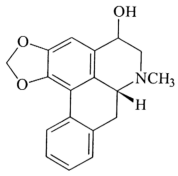
Aporphine alkaloids are the largest group within the isoquinoline alkaloids[45]. In the naturally occurring aporphine alkaloids, positions 1 and 2 are always oxygenated and frequently other positions are also substituted with hydroxyl, methoxyl or methylene dioxyl groups. In some cases a hydroxyl function is located at C-7 as in *R* (-)-ushinsunine **37**, while in the case of *R*-(-)-steporphine **38**, oxygenated at C-4. *S*-(+)-glaucine **39** and *S*-(+)-bulbocapnine **40** were among the first naturally occurring aporphines to have their structure elucidated and usually the natural alkaloids proved to be optically active, possessing either the *R* or *S* absolute configuration. The aporphine alkaloids contain a twisted biphenyl system. The molecule can exist in either the absolute configuration *S* series or its mirror image *R* series. The numbering of aporphine skeleton is generally represented by the structure below[46].



H-6a-(*S*)



H-6a-(*R*)



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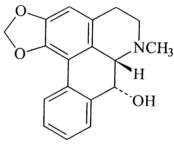

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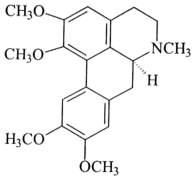

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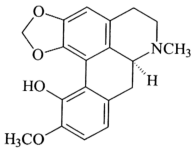


40

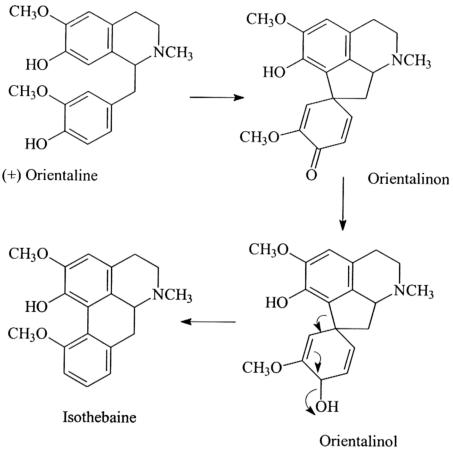
Absolute configuration[46]

Specific rotation is a good indicator of absolute configuration for the aporphine. If the alkaloid is strongly positive in rotation, then its absolute rotation is such as to possess an alpha C-6a hydrogen. However, dehydroproaporphines do not possess asymmetry and are optically inactive. In a few instances[46], the absolute configuration has been deduced from structural relationships with other aporphines of known stereochemistry.

In the case of 1,2-substitution, where ring D is unsubstituted, the trends is towards laevorotation. (+)-Nuciferine and (+)- roemerine are exceptions, and it is interesting to note that they both originate in the family Papaveraceae. In the case of C-1,2-substituted aporphines, the magnitude of the specific rotation is larger than 145° when the C-1 substituent is a methoxy group. Whereas the magnitude is less than 120° if a hydroxy or methylene dioxy group is present at C-1. In 1,2,9,10-substitution and 1,2,10,11-substitution almost all pattern exhibit dextrorotation. It should be noted that positions 1 and 2 are always substituted in aporphines and the spesific rotation will be large ~200° whenever C-11 is substituted.

Biogenesis

Aporphine alkaloids are derived from the corresponding phenolic tetrahydrobenzylisoquinolines by direct oxidative coupling or by the formation of dienone derivatives (proaporphine)[46]. These derivatives then rearrange into aporphines through dienone-phenol or dienol-benzene rearrangements. The possible biogenetic route for aporphines involves dienone intermediates is shown in Scheme 2.4. This pathway was postulated by the incorporation of (+)-orientaline into isothebaine *via* orientalinone and orientalinol. The dienol-benzene rearrangement involved in the biosynthesis resulted in the lost of one oxygen atom in its ring D (Scheme 2.4).



Scheme 2.4: The biogenetic pathway of aporphines.

^{1}H NMR of aporphines

The ^{1}H NMR spectroscopy shows an initial role in the success of determining the structures of aporphines. High field shift of methoxyl signals are found in the position of C-1 and C-11 due to the anisotropic character of the benzene ring. Position C-2 is also substituted when position of C-1 and C-11 are substituted. This affected the methoxyl groups at C-1 and C-11 would be sterically hindered. As a result, the methoxyl protons are pushed out of the aromatic plane, which is a shielded area. In addition, ring A dan ring D is facing each other. Hence the protons of the

metoxyl groups can arrange themselves on top of the adjacent ring, which happens to be a shielded zone, giving a more upfield shift[47].

As in proaporphine, the methylenedioxyl group of aporphines shows resonances at region of δ 5.87 - 6.02. Four possible locations for this group are C-1,2; C-2,3; C-9,10; and C-10,11. The presence of C-1,2 methylenedioxyl group is proven by an up field shift of the C-11 proton which appeared in the range δ 7.47 - 7.86. If C-1 is substituted by hydroxyl or a methoxyl group then the proton signal is further downfield, in region δ 7.80 and δ 8.21.

At positions C-9 and C-10, two protons reveal a singlet whereas at position C-1,2; C-2,3; and C-10,11, it gives two doublets with coupling constant of about 1.5 Hz. This in equivalences arises from the torsion caused by the twisted biphenyl system of ring A and D[48]. The appearance of the torsional effect on the methylenedioxy relies on their positions and at position C-9,10 the effect seems to be negligible[49]. The aromatic proton at C-11 is found downfield in the region of δ 8.74 - 7.68. The protons at C-3, C-8 and C-9 are located relatively upfield in the region of δ 7.00 - 6.38 and cannot be easily differentiated from one another. The *N*-methyl group resonates between δ 2.5 - 2.60 and the aliphatic protons of C-4, C-5 and C-7 displayed a complex pattern with absorption in the region of δ 2.4 - 4.4. If H-3 is ortho to hydroxyl or a methoxyl, it will resonate at a higher field. This is due to the induction effect.

On the other hand, H-11 usually resonates at a lower field with respect to the other protons because of the deshielding effect imposed by the facing aromatic ring and hydrogen bonding with the C-1 substituent.

Oxoaporphine[49]

The most characteristic features of oxoaporphines are the highly deshielded chemical shift values of the aromatic protons and the absence of the aliphatic proton signals. The oxoaporphines proved to have a carbonyl group at C-7 and a double bond between C-4 and C-5. A characteristic AB system signal at about δ 7.65 and 8.75 with a coupling constant of 6 Hz, which correspond to H-4 and H-5 is reffered to a double bond between C-4 and C-5. In addition, the methylenedioxyl gives a singlet at about δ 6.1 due to the planarity of the oxoaporphine skeleton. H-8 resonates at a lower field (δ 8.2 - 8.6) because of the neighbouring C-7 carbonyl.

Mass Spectrometry[49-50]

The principle fragmentation of the mass spectra of the aporphines is the loss of the hydrogen beside nitrogen (6a-H). The $[M-1]^+$ peak always serves at the base peak of the molecule. Additionally, peak occured at $[M-15]^+$ and $[M-31]^+$ respectively, probably due to the loss of methyl or methoxyl from one of the methoxyl substituents. If hydroxyl group is substituted, a $[M-17]^+$ peak will reveal.

Furthermore, the steric interactions that occurred between the C-1 and C-11 substituents in the second group of alkaloids are much larger than those, which occurred between the C-1 substituent and C-11 hydrogen in the first group. This

happened because of the steric hindrance to the coplanarity in biphenyls, which is caused by the presence of ortho-substituents.

Oxygen functions in the C-1 and C-11 positions of the twisted biphenyl ring system of aporphines considerably enhance the angle of twist. Hence, expulsion of one of these substituents or loss of methyl from a C-1 or C-11 methoxyl group would considerably reduce the steric hindrance to coplanarity of the biphenyl system. The differences in the intensities of the peaks $[M-1]^+$, $[M-43]^+$, $[M-58]^+$and $[M-74]^+$ ions in the two groups may be explained by based on the generation of the new double bonds in these ions. This would be favoured in the group A since the diphenyl is more coplanar.

The ultra-violet region for the aporphine skeleton is dependent on the position of the substituents rather than on the nature of the substituents. It is derived from the basic biphenyl system with the added influence of several auxochromes. The approximate absorption for various substitution patterns is listed in Table 2.5 [51]. The spectra of the other aporphines fall into two characteristic types having maxima at 220 nm and two in the region 270 - 310 nm. The shape of the curve and the intensity of the latter two maxima depend on the substitution in ring D. Furthermore, the mono phenolic aporphine position at C-3 and C-9 display a bathochromic shift at 315 nm and 350 nm in the alkaline environment[52-53].

Oxoaporphine showed three main absorption bands at 245 - 270 (log ε4.1), 309 (3.6) and 413 nm (3.8)[54]. In acid medium, the oxoaporphine reveals a bathochromic shifts with the maxima between 325 and 460 nm (log $\varepsilon \sim 3.5$).

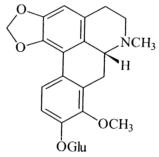
Table 2.5: UV-max of aporphines

Position of substituents	λ_{max} (nm)							
1,2		234		273				312
1,2,9		233sh				280		310sh
1,2,10	226		266		275		305	
1,2,9,10	220		282		305			
1,2,9,11	220		270		305			

Note : sh = shoulder

2.2.6 New aporphine alkaloids and their bioassay properties

Two new aporphine glycosides, stesakine-9-O-β-D-glucopyranoside **41**, and *N*-methylasimilobine-2-O- β-D-glucopyranoside **42** were isolated from the seeds of *Stephania cepherantha* Hayata (Menispermaceae) by Kashiwaba and co-workers[55] (2000), whereas the 6a,7-dihydroaporphine alkaloids dehydrostephanine **43** and dehydrocrebanine **44** from *Stephania venosa* (Menispermaceae)[56] showed potent activity with IC_{50} values of 40 and 70 ng/ml, respectively after these two compounds were tested for their antimalarial potential. Interestingly, these two dihydroaporphines showed 3-4 times more potent than their parent compounds, aporphine. The additional data obtained from the investigation suggested that introducing unsaturation to the C-6a and C-7 carbons for developing new natural product-based antimalarial could augment the antimalarial potential of this group of natural products.



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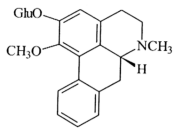

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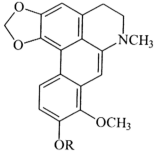
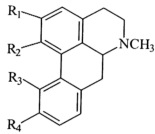


43: R= H

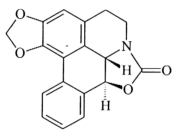
44: R= Me



45 : $R_1 = R_3 = R_4 = OCH_3$, $R_4 = OH$
46 : $R_1 = R_2 = R_4 = OCH_3$, $R_3 = OH$
47 : $R_1 + R_2 =$ -O-CH_2-O-, $R_3 = R_4 = H$

In the case study of chemical constituents and cytotoxic activity from *Papaver dubium* subsp. *dubium* and *P. dubium* subsp. L*aevigatum*[57], three aporphine alkaloids have been isolated i.e. corydine **45**, isocorydine **46** and roemerine **47**. Meanwhile, a novel oxazoloaporphine, artabonatine A **48** and a new 7-hydroxyaporphine, artabonatine B **49** were isolated and characterized from the fresh unripe fruits of *Artabotrys uncinatus* (Annonaceae)[58]. As a traditional folk medicine, the roots and fruits of *Artabotrys* are used for treatment of malaria. Further studies on chemical constituents of the same species by Tian and co-workers[59], afforded another two novel oxoaporphines, artabonatine C **50** and artabonatine D **51**, a new oxaloaporphine, artabonatine E **52**, and a new 7,7'-bisdehydroaporohine, artabonatine F **53**. The roots were used to treat Hepatocarcinoma and nasopharyngeal carcinoma (NPC), the most

important cancers in Taiwan. *Artabotrys uncinatus* was used for treatment of human NPC as a traditional folk medicine.



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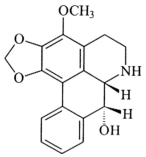

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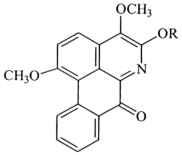
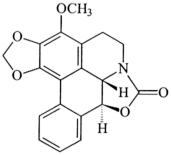


50 : R = OCH_3
51 : R = H



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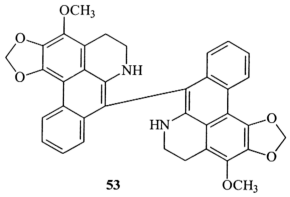
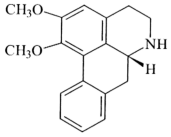


53

In addition, Fang-Rong Chang and co-workers[60] on the study of alkaloids from *Annona glabra* (Annonaceae) afforded five aporphines, (-)-nornuciferine **54**, (-)-anonaine **55**, (-)-*N*-Formylanonaine **56**, (-) asimilobine **57** and (+)-nordomesticine **58**.



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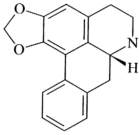

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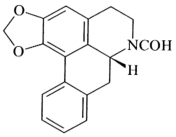

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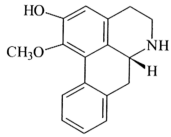

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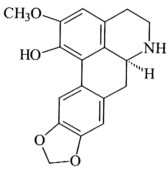

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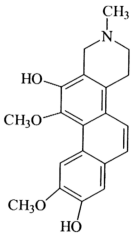
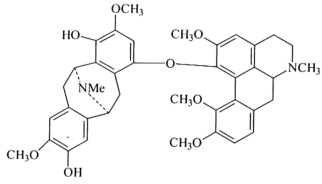


59

Some alkaloids also present in the barks of *Litsea cubeba* Persoon[61]. Continuing investigation on the alkaloids of the woods, a novel phenantrene, litebamine **59** was isolated. The litebamine is the first phenantrene alkaloid possessing an isoquinoline moiety. Biogenetically, it could be derived from boldine, an aporphine existing in the same plant, *via* secoboldine as intermediate. The latest study by Shoei-Sheng Lee and co-workers[62] on the species *Thalictrum fauriei* from the family Ranunculaceae also produced dimeric aporphine; fauripavine **60**, fauridine **61**, faurithaline **62** and 3-methoxylfaurithaline **63**.

In an ongoing effort to uncover bioactive and/or novel natural products Kithsiri and co-workers[63] investigated the constituents of the bark of *Phoenicanthus oblique* (Annonaceae). They isolated a new dimeric aporphine alkaloid phoenicanthusine **64** with hitherto unprecedented linkages between the two monomers, together with three known dimeric aporphines [7,7'-bis(dehydro-O-methylisopiline **65**, 7-dehydronuciferyl-7'-dehydro-O-methylisopiline **66** and urabaine **67**. In conclusion, all those alkaloids found from the different species and different families as described above have an aporphine unit with unique structural features.



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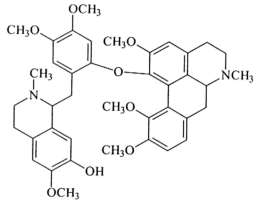

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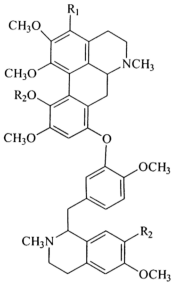
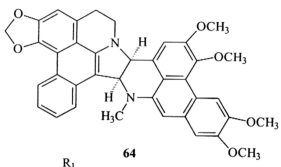
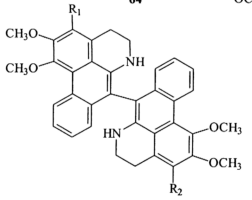


62: $R_1 = R_2 = H$
63: $R_1 = OMe$, $R_2 = H$



64

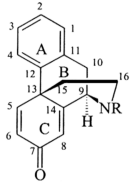


65: $R_1 = R_2 = OCH_3$
66: $R_1 = OCH_3$, $R_2 = H$
67: $R_1 = R_2 = H$

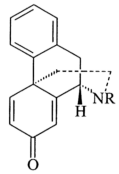
2.2.7 Morphinoid alkaloids

Absolute configuration

The molecule can exist in either the absolute configuration *S* series or its mirror image *R* series. The numbering of morphinandienone skeleton is generally represented by the structure below[64].



R



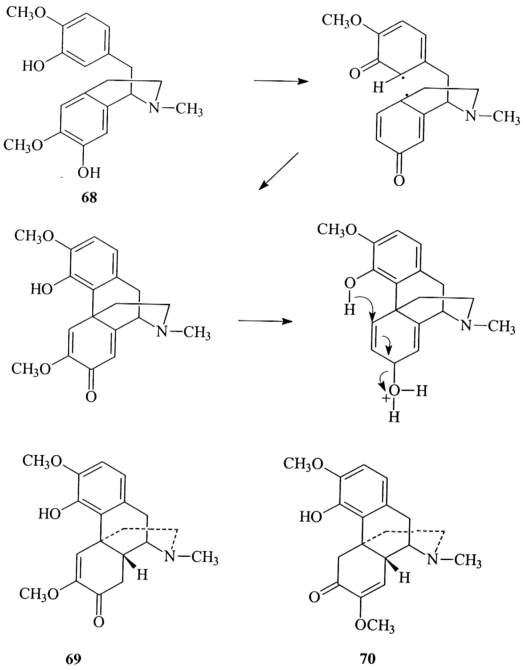
S

Biogenesis

Seven decades ago, Robinson suggested[64] laudanine **68**, a benzylisoquinoline type, might be a biogenetic precursor of morphinoid and its close relatives such as codeine and thebaine. The biogenetic pathways may involve ionic intermediates in the electrophilic attack of the benzene nucleus during cyclization to give the morphine skeletal structure. The possible route to morphine may involve both ionic and radical components.

Morphinandienones, recognized as intermediates in the biosynthesis of morphinan alkaloids were obtained *in vitro* by processes mimicking the plant

synthesis. The variety of morphinan alkaloids of this class is illustrated in Scheme 2.5. Ocobotrine **69** and 14-episinomenine **70** alkaloids are examples of the B/C trans-series alkaloids. The structure of 14-episinomenine **70** consists of one ketone functional group at C-6 whereas ocobotrine **69** contains carbonyl group at C-7.



Scheme 2.5: The biogenetic pathway and the types of morphinan alkaloids.

^{1}H NMR spectroscopy[65]

Several general features have been observed in the proton shifts of morphinandienones. Three to four singlets of aromatic ring and the cross-conjugated cyclohexadienone protons are observed at around δ 7.0 and methoxyl groups appeared at around δ 3.0-4.0. The C-9 proton appeared at around δ 2.5-4.0 as a doublet and not triplet due to the coupling of C-10 protons because the C-9 proton is out of planar of heterocyclic ring. Multiplets at around δ 1.0-2.0 and δ 2.0-3.0 are related to the protons of C-15 and C-16 respectively. Interestingly, one unique pattern 'doublet doublet' and 'one doublet' protons are observed at δ 2.0-3.5 (J = 18.0 Hz) corresponding to α and β C-10 protons, which are ABX system.

Mass spectra of morphinan alkaloids[66]

Common characteristic fragmentation patterns of morphinandienones are m/z $[M\text{-}Me]^+$, $[M\text{-}CO]^+$, $[M\text{-}COMe]^+$. The peak at $[M\text{-}15]^+$ due to the loss of –Me group is very intense in this type of alkaloid. Initial cleavage at an allylic or benzylic bond follow by the loss of methyl would give the conjugated even-electron ions.

UV and IR spectra[67]

The common UV spectra data of morphinandienones are the absorption bands at 209, 238 and 280 nm.

Three major peaks at around 1620-1670 cm^{-1} in IR spectrum revealed the presence of an α-methoxyl cross-conjugated cyclohexadienone system is the most general characteristic of the moephinandieneones type.

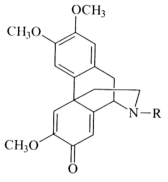
2.2.8 Sources of morphinoid alkaloids

Nordin and co-workers[68] worked on the species of *Alseodaphne perakensis* (Lauraceae), the Malaysian species that is widely distributed throughout peninsular Malaysia was found to be rich in morphinoid alkaloids. Initial chemical work on this species led to the isolation of the major alkaloid component, *N*-Methyl-2,3,6-trimethoxymorphinandien-7-one **71** along with a minor compound i.e. *N*-Methyl-2,3,6-trimethoxymorphinandien-7-one *N*-oxide **72**. The compound, an amorphous, pale yellow solid was isolated from leaves of *A. perakensis*.

Kashiwaba and his co-workers[69] in 1997 has reported 14 morphinoids from *Stephania cepharantha*. Full details of the isolation and characterization of 14 morphinoids obtained from the tubers of *S. cepherantha* Hayata (Menispermaceae) cultivated in Japan can be found in several journals since 1992[70-72]. These compounds are; cephamonine **73**, cephamuline **74**, cephasamine **75**, cephakicine **76**, cephatonine **77**, sinomenine **78**, tanngine **79**,14-episinomenine **70**, FK-3000 **80**, sinoacutine **81**; four hasubanane alkaloids, cepharamine **82**, aknadininen **83**, aknadicine **84**, and aknadiactam **85**. Prior to these reports, Brigitte Chanks and co-workers[73] had studied the alkaloid content on the same genus *Stephania zippeliana* and afforded six morphinans, while Amarendra Patra[74] from India, had studied the alkaloid content of the roots of the vine *stephania*, native to Thailand and commonly used in the country

for medicinal purposes under the local name "*Borapet Pungchang*". Further chemical investigation had led to the isolation of a new promorphinane, stephaphylline **86** and three hasubananes, nordelavaine **87**, stephanubine **88** and delavaine **89**. In addition, phytochemical studies on the genus *Platicapnos* by Rafael Suau and co-workers[75] had found to contain aporphinoid alkaloids and one morphinanedienone, (-)-sinoacutine **81**.

Only one species from family of Annonaceae, *Fissistigma oldhamii*[76], previously showed significant activity in bioassay. *Fissistigma oldhamii* (Hemsl.) Merr. is a folk medicine, which has been used for hepatomegaly, anti-inflammatory effects, anti-tumor action and rheumatism in Taiwan and southern China, also showed significant activity in antiplatelet aggregation. In order to understand the bioactive principles of this plant, Jin-Bin Wu and co-workers isolated two morphinanedienone alkaloids; *N*-Methyl-2,3,6-trimethoxymorphinandien-7-one **71** and *N*-nor-l-2,3,6-trimethoxymorphinandien-7-one **90** from the methanolic extract of stem *F. oldhamii.*



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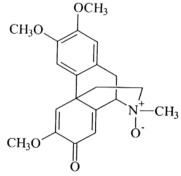

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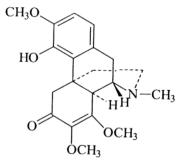

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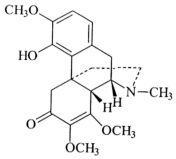

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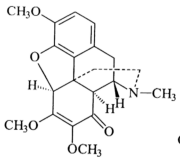

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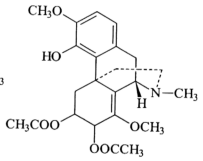

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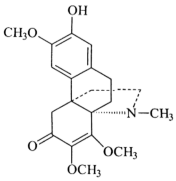

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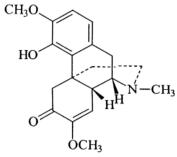

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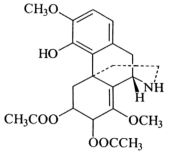

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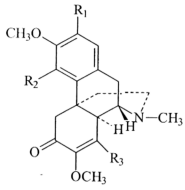
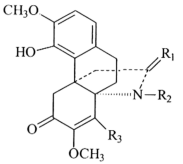


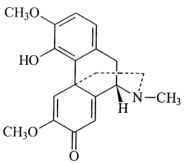
78 : R_1= R_3= H, R_2 = OH
79 : R_1= R_3= OCH_3, R_2=H



82: R_1=H_2, R_2=CH_3, R_3=H
83: R_1=H_2, R_2=CH_3, R_3=OCH_3

84: R_1=H_2, R_2=H, R_3=OCH_3

85: R_1=O, R_2=CH_3, R_3=OCH_3



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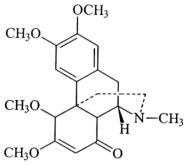

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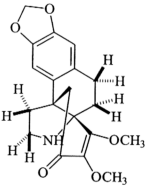

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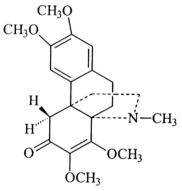

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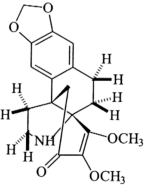

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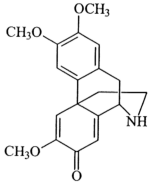

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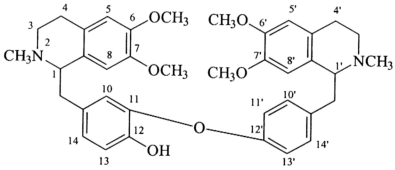
2.2.8 Bisbenzylisoquinoline alkaloids (BBIQ)

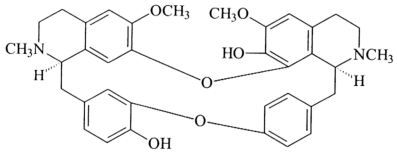
This group of bisbenbenzylisoquinoline alkaloids is composed of two benzylisoquinoline units attached to each other by one, two or three bonds. In most cases, the units are joined *via* ether linkages. The alkaloids may be subdivided into the following five major groups[77].

a. Alkaloids containing one diaryl ether linkage. Example: Dauricine **91**, the ether linkage between C-11 and C-12'.



91

b. Alkaloids containing two diaryl ether lingkages. Examples: Aromoline **92** repandine series) and atherospermoline **93** (berbamine type) All these types contain ether linkages between the aromatic rings of tetrahydroisoquinoline component and the benzyl rings.



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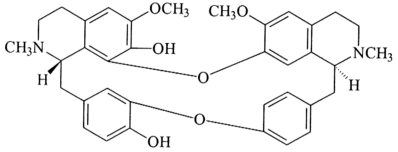

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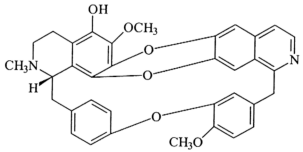
c. Alkaloids with three ether linkages. Example: Siddiquamine **94**[78]



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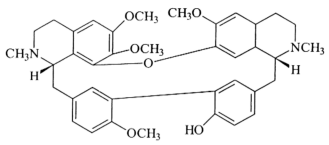
d. Alkaloids containing a diphenyl bond and one or two ether lingkages. Example: Rodiasine **95**.



95

e. Some alkaloids consist of a benzylisoquinoline unit attached to an aporphine unit, *via* a single ether linkage. Of these, fauridine **61**, faurithaline **62** and 3-methoxylfaurithaline **63** are typical.

^{1}H NMR of of type II (two ether linkages) bisbenbenzylisoquinoline alkaloids

Type II BBIQ alkaloids have several subtypes such as repandine type and berbamine type. This text shall discuss briefly on the spectral data of the repandine series since the author has isolated bases of such series.

Resonances of OMe and NMe groups[79]

A methoxyl group attached to a benzene ring has a normal chemical shift at δ 3.8. This chemical shift is an average value taken over the various orientations of the methoxyl group with respect to the benzene ring reached by rotation about the aromatic C-O bond. A methoxyl group lying in the plane of the ring will have lower chemical shift than those of a methoxyl group above or below the ring due to the anisotropic effect generated by π-electron system in benzene ring[80]. The presence of bulky substituents near a methoxyl group will tend to force it out of the aromatic plane[81]. Therefore, its chemical shift will be more shielded as in the position 7' of the

repandine-oxyacantine series (~δ 3.12)[78], whereas the same group at position 11 has a chemical shift at around δ 3.87-3.95 that is slightly lower field than the normal value of δ ~3.8. The *N*-methyl group resonances also exhibit a range of values δ 2.25-2.65[78].

UV-VIS spectroscopy

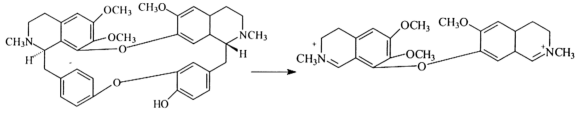
The bisbenzylisoquinolines typically exhibit two UV max at approximately 283 and 261 nm. For example, oxyacanthine **96**[82] shows two UV maxima at 285 (3.85) and 260 (3.31).

Mass spectrometry

Structural classification of bisbenzylisoquinoline alkaloids according to the number and the mode of the diphenyl ether linkages are well correlated with their mass spectrometric fragmentations. The mass spectra of type II with two biphenyl ether linkages head to head bisbenzylisoquinoline are described and interpreted here[83-84].

Molecular ion of this type is 40 to 60% of the base peak, and its always accompanied by $[M-1]^+$ and $[M-2]^+$ peaks. The most characteristic feature of the mass spectra of this type is the fragmentation through the loss of ring C from the molecular ion. The intensity of an $[M-106]^+$ peak is usually about 4% of the base peak. Oxyacanthine **96** represents this type of compound, reveals the most intense peak at m/z 198 with an isotope peak at m/z 198.5. This fragment is formed by two cleavages

similar to the formation of m/z 206 for dauricine, with two charges retained on the tetrahydroisoquinoline groups.

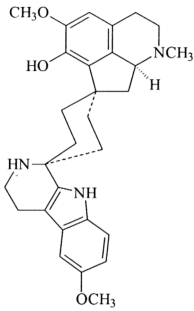


96

A fragment at m/z 501, loss of 107 mass unit corresponds to loss of benzylic group plus a hydrogen atom.

2.3 Alkaloids from genus *Phoebe* and *Dehaasia*

Although investigation on the alkaloids of the family Lauraceae is quite extensive but studies on the alkaloids of *Phoebe* and *Dehaasia* species are still rare[85-86]. The author reported two proaporphine-tryptamine dimers from the leaves of *Phoebe grandis* in 1997 as the first predicted in the genus *Phoebe*[40]. *Phoebe grandis* (Lauraceae) widely distributed throughout Peninsular Malaysia, which leaves and bark were found to be rich in alkaloids. It was collected from Northern part of Peninsula Malaysia and was investigated for bark and leaves alkaloids and had resulted in the isolation of phoebegrandine A **28** and phoebegrandine B **29**.



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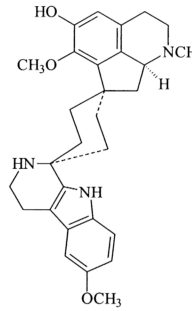

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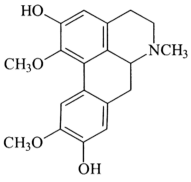
Phoebegrandine B **28** is isomeric to phoebegrandine A **29**, methoxyl is attached to C-1 instead of C-2 as in phoebegrandine A, while hydroxyl group is at C-2. *Phoebe grandis* (Lauraceae) and *Roemeria hybrida* (Papaveraceae) are the only two plants containing proaporphine-tryptamine dimers. The substitution pattern of the aromatic rings of all those alkaloids is very similar. However, two methoxyl groups were found in the aromatic ring of the tryptamine part of some *Roemeria* alkaloids. The main difference between the dimers of these two species is that the absence of aliphatic methoxyl group in Phoebegrandines A and B, which is present in ring D of all *Roemeria* alkaloids[39].

In New Guinea, a rain forest tree, *Phoebe clemensii* Allen (Lauraceae)[87], was found to give high yield of aporphines in the bark and leaves, but there are marked differences in the substitution patterns of the component alkaloids. The only alkaloid isolated was isocorydine, which has previously been obtained from other families

such as Menispermaceae, Papaveraceae and Annonaceae. Similar aporphine alkaloids also produced by bark of *Phoebe grandis*[42] such as boldine **97**, norboldine **98**, laurotetanine **99** and lindcarpine **100**.



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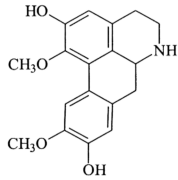

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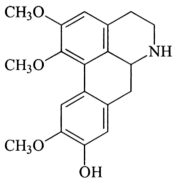

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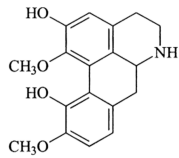

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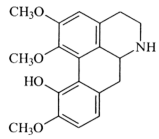
Among *Dehaasia* species, *Dehaasia kurzii*, *D. incrasata*, *D. triandra* are extensively studied on their alkaloids. *Dehaasia incrassata*[88] is found in the jungle throughout the Peninsular Malaysia. Fractionation of the crude alkaloid mixture from the leaves gave two aporphines, isocorydine **46** and norisocorydine **101**[88]. The Formosan Lauraceous Plants, *Dehaasia triandra*[89] is found growing on Orchid Island

and in the Philipines. Previous studies showed that *Dehaasia triandra* contained isocorydine and bisbenzylisoquinoline.

Studies on chemical constituents of *Dehaasia triandra* Merr (Lauraceae)[90] by Sheng The Lu and co-workers resulted in the isolation of several alkaloids, isocorydine **46**, atheroline **102**, and a quartenary aporphine alkaloid, xanthoplanine **103**. Reinvestigation of *D. triandra* by Shoei-Sheng Lee and co-workers[91] have resulted in the isolation of three novel alkaloids and those are isocorydione **104**, norisocorydione **105**, dehatripine **106**; besides the most abundant aporphine, isocorydine from leaves. Dehatripine **106**, the first ether-linked bisaporphine, was elucidated as 9-*O*-(8'-isocorydinyl)-N-methyllaurotetanine.

A continuing study by Shoei-Sheng Lee and co-workers[92], on the chloroform soluble fraction of *D. triandra* yielded five additional novel alkaloids besides the four known aporphines; isoboldine **107**, norisocorydine **101**, *N*-methyllindcarpine **108**, and *N*-methyllaurotetanine **109**. The five novel alkaloids are secoxanthoplanine **110**, dehydroisocorydione **111**, (8,8'-*R*)- bisisocorydine **112** and (8,8'-*S*)-bisisocorydine **113**, and 11,8'-O-bisisocorydine **114**. Both of (8,8'-*R*)- and (8,8'-*S*)-bisisocorydine are the first C-C linked aporphines at C-8, while 11,8'-O-bisisocorydine is the first bisaporphine with a diphenyl ether-linkage at C-8 and C-11.



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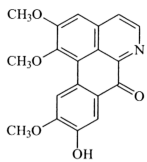

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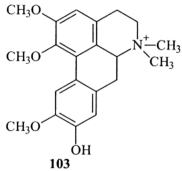

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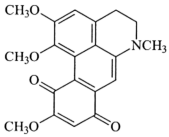

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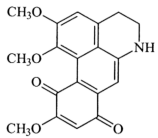

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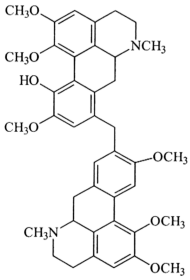

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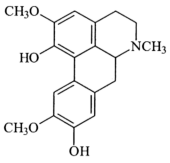

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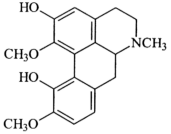

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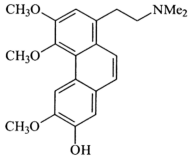

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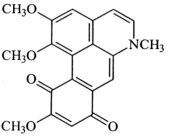

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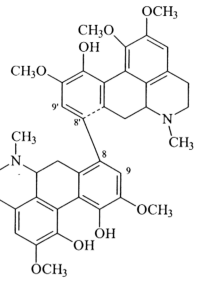

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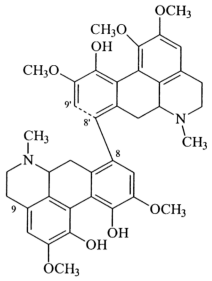

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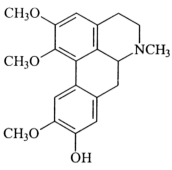

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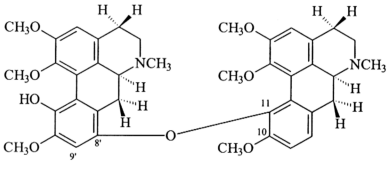


114

The alkaloids and other compounds found in these two genera are summarized in Table 2.6 below.

Table 2.6: Chemical constituents isolated from the species of *Phoebe* and *Dehaasia*

Plant	Part of plant	Alkaloids Isolated	References
P. clemensii	Bark	Mecambroline **115** *N*-methyllindcarpine **108**	93
P. farmosana	Bark	Lauformine **116** *N*-methyllauformine **117** Laurotetanine **99** Asimilobine **57** Norjuziphine **118** Juziphine **119** Laurodionine **120** Vitexin **121** Isovitexin **122** Quercetin-3-O-galactoside **123** Quercetin-3-O-α-L-arabinopyranoside **124** Kaemferol-3-O-α-L-rabinofuranoside **125** Kaemferol-3-O-α-L-rhamnoside **126** Kaemferol-3-O-β-D-xylopyranoside **127** Dihydroquercetin **128** Adenosine **129** Adenine **130**	94-100

Table 2.6 [continued]

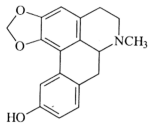
Plant	Part of plant	Alkaloids Isolated	References
P. molicella	Bark	Norpreocoteine **131** Norpurpureine **132** Preocoteine **133** Thalicsimidine **134** Isocorydine **46** 10-hydroxy-1,2-metylenedioxyaporphine **105** *N*-methyllindcarpine **108** Laurolitsine **98** Roemerine **47** Ushinsunine **37** Liriodenine **135**	101-102
P. pittieri	Bark	Norlirioferine **136** 1,2,3-Trimethoxy-9,10-methylenedioxy-noraporphine **137**	103
P. valeriana	Bark	1,2-dimethoxy-3-hydorxy-9,10-methylenedioxy Noraporphine **138** Nordelporphine **139** Phoebine **140** Dehydrophoebine **141** Norphoebine **142** Oxophoebine **143**	104

Table 2.6 [continued]

Plant	Part of plant	Alkaloids Isolated	References
P. elliptica	Bark	Boldine **97**	105
		Norpredicentrine **144**	
		Laurolitsine **98**	
		Actinodaphnine **145**	
		Glaziovine **12**	
		Amuronine **1**	
		Linearsine **146**	
		Dihydroamuronine **147**	
		Magnocurarine **148**	
P. grandis	Bark	Boldine **97**	42
		Norboldine **98**	
		Laurolitsine **99**	
		Lindcarpine **100**	
	Leaves	Phoebegrandine A **28**	
		Phoebegrandine B **29**	
P. minutiflora	Bark	Armepavine **149**	106
		Norarmepavine **150**	
		N-methylisococlaurine **151**	
		Coclaurine **152**	
		Laudanidine **153**	
		Reticuline **154**	
		Norjuziphine **118**	
		Juziphine **119**	
		Norisocorydine **101**	
		Isoboldine **107**	
		Corytuberine **155**	
		Laurolitsine **98**	
		N-methylsecoglaucine **156**	
		O-methylcorypalline **157**	

Table 2.6 [continued]

Plant	Part of plant	Alkaloids Isolated	References
P. cinnamomifolia	Bark	Oxoglaucine **158**, Oxopurpureine **159**	107
P. chekiangensis	Bark	5-Hydroxyindoline **160** Tyramine **161**, *N*-norarmepavine **150**	108
D. triandra	Leaves	Isocorydine **46** Corytuberine **155** Atheroline **102** Xanthoplanine **103** Dehatridine **162** Dehatrine **163** Obaberine **164** Isocorydione **104** Norisocorydione **105** Dehatripine **106** Secoxanthoplanine **110** Dehyroisocorydione **111** (8,8'-R)-Bisisocorydine **112** (8,8'-S)-Bisisocorydine **113** 11,8'-O-Bisisocorydine **114** Isoboldine **107** *N*-Methyllindcarpine **108** *N*-Methyllaurotetanine **109**	89-91
D. incrassata	Leaves	Isocorydine **45** Norisocorydine **101**	88
D. kurzii	Leaves	Boldine **97**	109
D. longipedicellata	Bark	11-Methoxylcassythicine **165** Boldine **97** Norboldine **98** Litsericine **166**	110



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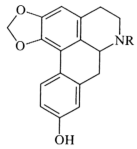
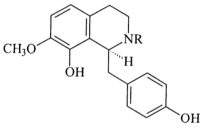
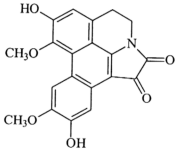


116: R=H
117: R=CH_3



118: R=H
119: R= CH_3



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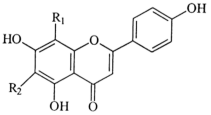
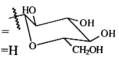
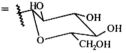
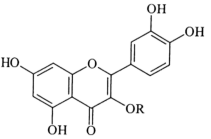


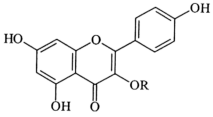
121: R_1 =
R_2 =H



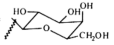
122: R_1 = H,
R_2 =



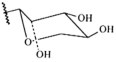




123: R =

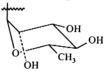


124: R =

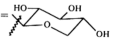


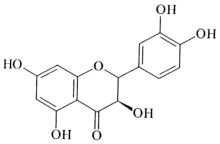
125: R =

126: R =



127: R =





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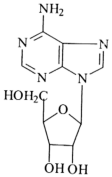

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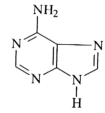
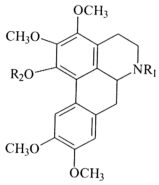
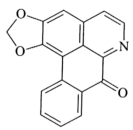


130



131: R_1= R_2 = H
132: R_1= H, R_2= CH_3
133: R_1= CH_3, R_2= H
134: R_1= R_2 = CH_3



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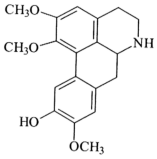
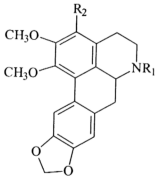
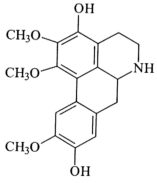


136



137: R_1 = H, R_2= OCH_3
138: R_1 = H, R_2= OH
140: R_1 = R_2 = CH_3
142: R_1 = H, R_2 = CH_3



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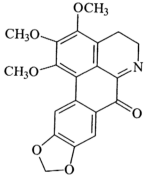

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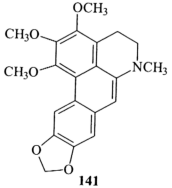
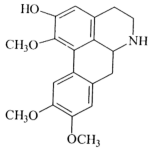


141



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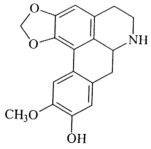
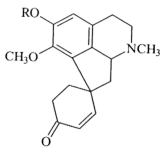
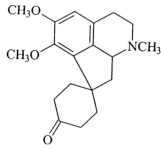


145



146: R = H



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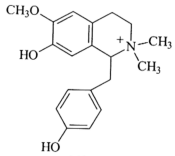

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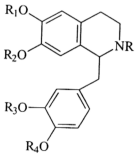
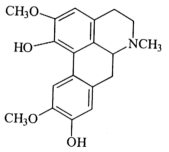
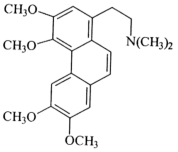


	R	R_1	R_2	R_3	R_4
149:	CH_3	CH_3	CH_3	H	H
150:	H	CH_3	CH_3	H	H
151:	CH_3	H	CH_3	H	H
152:	H	CH_3	H	H	H
153:	CH_3	CH_3	CH_3	OH	CH_3
154:	CH_3	CH_3	H	OH	CH_3



155



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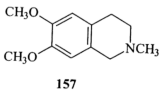
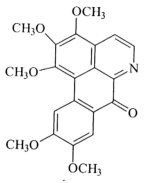


157



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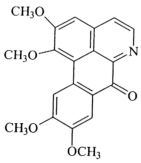

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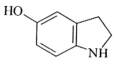
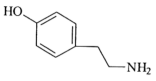


160



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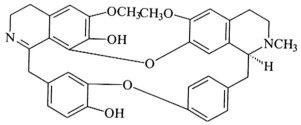

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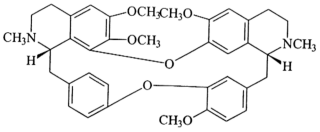
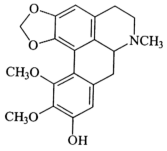
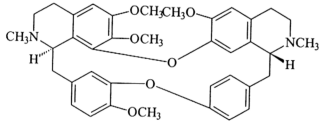


164



165



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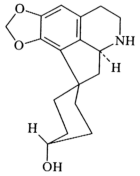


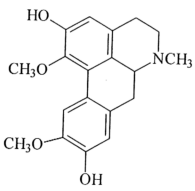
166

2.4 Isoquinolines used in modern medicines[19,111]

Some useful medicinal properties of plants have been documented by Colegate (1993)[17] and Roberts (1998)[111]. The first observation was made on chimpanzees in wild, which selectively pick plants rich in antimicrobial thiophenes when suffering from diarrhea. Many birds decorate their nests with oak leaves rich in tannins because tannins might help to control the development of bacteria and fungi. In addition, the early humans used alkaloid and other plants as painkillers, stimulants, or hallucinogens. The treatments of disease or illness, with medicinal plants were documented for the last 3000 to 5000 years ago.

In this section the author will describe those alkaloids that are used in modern medicine with a short summary of their occurrence in plants and their therapeutic as well as traditional use in medicine[111].

***Boldine* 97**



97

Source: *Peumus boldo* (Monimiaceae); leaves contain 0.4 - 0.5% alkaloids. Boldine is the major component (20-25%) of the alkaloidal fraction.

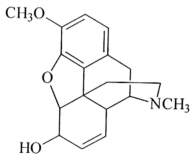
Pharmaceuticals (examples): Boldina Houde, Boldoflorine, Boldosal, Digedryl, Ibsesal, Menabil Complex, Oxyboldine, and Sambil.

Therapeutic use: Treatment of cholelithiasis, stomachic disorders, vomiting, constipation, and dyspepsia.

Use in traditional medicine: In Chile boldine is used as an anthelmintic drug; it has diuretic properties and stimulates liver metabolism.

Mechanism: Boldine exhibits morphinelike antinociceptive properties. Besides opioid receptors, alpha receptors might also be involved in this action.

***Codeine* 167**



167

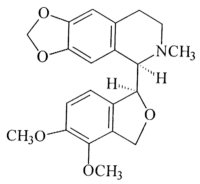
Source: *Papaver somniferum* (Papaveraceae). It is obtained from the dried latex by incision of the unripe capsules. Codein is a component of opium (0.2-3.0%). Because of its low content in the plant, codeine is obtained through methylation of morphine. It is also preparable from thebaine, which is the major component of roots, aerial parts (1%) and the capsules (3.5%) of *Papaver bracteatum* (Papaveraceae).

Pharmaceuticals (examples): Antituss, Bisolvon-Gribletten, Bronchicum Tropfenmit Codein, Codicaps, Codipront, Contrapect, Contrapect Infant N, Dolodens, Dolorol Forte, Spasmo-Cibalgin com., Tussipax.

Therapeutic use: as antitussive in the treatment of cough, and as an analgesic and mild sedative.

Mechanism: Codeine binds to opiate receptors, diminishes brochial secretion, and acts as a supressent on the cough center of the modulla oblongata.

***Hydrastine* 168**



168

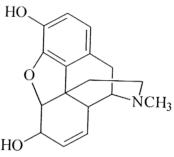
Source: Dried rhizome and roots of cultivated *Hydrastis Canadensis* (Berberidaceae), indigenous to Canada and the eastern United States, containing 1.5-4.0% hydrastine.

Pharmaceuticals (examples): Gine Sedans, Kollyr.

Therapeutic use: treatment of gastrointestinal disorders.

Mechanism: Hydrastine acts as a sympatholytic and thus causes a slowdown of heart action. It is paralyzing to the CNS and causes limp paralysis of all muscles.

***Morphine* 169**



169

Source: *Papaver somniferum* (Papaveraceae); morphine is a component of opium, which is obtained from the dried or partially dried latex after incision of the unripe capsules. The incision is done 8-10 days after the corolla leaves have fallen.

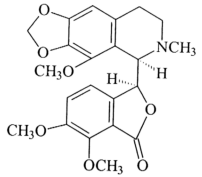
Pharmaceuticals (examples): Collis Brown's, Diastat, Diocalm, Duromorp, Enterosen, Morphalgin, Nephenthe, Oramorph, Roxanol, Spasmofen.

Therapeutic use: Morphine is used in the control of the moderate and severe pain, e,g., in cancer patients. It is also used in the treatment of diarrhea.

Use in traditional medicine: Morphine has been used for its emphorizing properties. For this purpose it is smoked in cigarettes and water pipe. It is also long known analgesic.

Mechanism: It has agonistic activity at u-opiate receptors and also the lesser extent, at k-receptors. Morphine also acts directly on smooth muscles as in the intestine.

Noscapine **170**



170

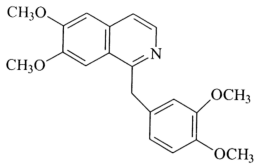
Source: *Papaver somniferum* (Papaveraceae): opium contains about 2-10% noscapine.

Pharmaceuticals (examples): Bequitusin, Capval, Degoran, Difmetus, Finipect, Lyobex retard, Nipaxon, Nitepax, Noscalin, Rea Tos, Rectolmin Bronquial, Ribelfan, Tossamine, Tussisedal, Tussoretard.

Therapeutic use: it is used as a central cough suppressant.

Mechanism: Noscapine affects the cough center directly, increase respiration, and acts as a weak bronchodilator.

Papaverine **171**



171

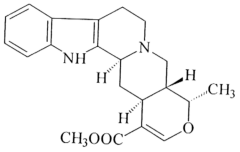
Source: *Papaver somniferum* (Papaveraceae). Papaverine is a component of opium (1%) and also of *Chelidonium majus* (Papaveraceae); the aerial parts contain about 0.1-1.0% alkaloids.

Pharmaceuticals (examples): Acticarbine, Opdensit, Optenil, Pameion, Panergon, Pavabid, Pavasule, Paveron, Riddobron,Vasocalm.

Therapeutic use: It is used as vasodilator, because of its smooth muscle relaxant properties. Papverine is also used in the treatment of impotence by intracavernosal injection. It has be given to patients with cerebral, peripheral,and vascular disorders. In the treatment of gastrointestinal disorders it is employed as an antipasmodic.

Mechanism: Papaverine is a direct relaxant on all smoothmuscles. It inhibits the activity of phosphodiesterase and thus causes an increase in CAMP level. In turn Ca^{2+} concentrations are reduced, which are an important trigger in muscle contraction.

***Raubasine* 172**



172

Source: *Rauwolfia serpentina* (Apocynaceae); roots contain about 0.8-2% alkaloids. Raubasine is also isolated from *R. vomitoria*.

Pharmaceuticals (examples): Card-Lamuran, Circolene, Cristanyl, Duxil, Duxor, Hydrosarpon, Iskedyl, Isosarpan, Isqubral, Lamuran, Melanex, saltusin Co., salvalion, Sarpan.

Therapeutic use: Treatments of peripheral and cerebral vascular disorders.

Mechanism: Raubasine acts as a selective alpha symphatholytic drug. It depletes peripheral noradrenalin stores, resulting in decrease of peripheral resistance and blood pressure. It is also causes depletion of catecholamine and serotonine storesin the brain, heart and many other organs.

2.5 Conclusion

Many alkaloids as described above are used in modern medicine. This is an indicator that the exploitation of alkaloids and alkaloidal plants is economically interesting and important. It has been estimated that approximately 20% of all plants produce alkaloids and only 10 to 15% of all plants have been studied phytochemically and even less pharmacologically. It seems to be important that new alkaloids should be screened using modern pharmacological assays to fully understand their target, potential action and application.

In conclusion, the significance of alkaloids in various branches of biology and chemistry hardly needs emphasizing especially in pharmacology and medicinal chemistry because they present a continuing challenge in terms of structure determination, synthesis and biosynthesis.