CHAPTER 2

GENERAL CHEMICAL ASPECTS

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2.1 Introduction

The exploration of the Lauraceous plants for alkaloids of medicinal value has been going on since last decade. Indeed, herbalism and folk medicine, ancient and modern, have been the source of much useful theraphy, pharmacology and taxonomy. These chemical compounds also important to economic and nutrition field. Besides alkaloids, they produced a wide range of non-alkaloidal compounds including carbohydrate, proteins, lipid, amino acids, terpenes, essential oils, acetogenins, polyphenols and aromatic compounds.

The alkaloids are one of the most diverst groups of secondary metabolites found in living organisms and have an array of structure types, biosynthethic pathways, and pharmacological activities and are of limited distribution in the plant kingdom. Their amine character produce and alkaline solution in water and hence the origin of their name-alkaloid[27].

It is generally accepted that secondary metabolites have a role in the survival of the organism. In plants, these compounds are involved as attractants to ensure pollination and are found to play an important role in plant interactions with animals and higher and lower plants. Alkaloids are now generally considered to be part of an elaborate system of chemical defense in plants and indeed the same seems to be true in vertebrates, invertebrates and microorganisms[28].

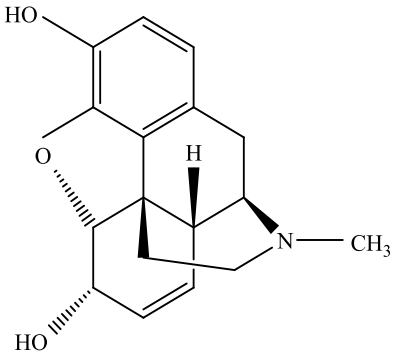
2.2 Alkaloids

From ancient times man has utilized alkaloids as medicines, poisons, and magical potions. Only recently has he gained precise knowledge about the chemical structures of many of these interesting compounds. The term alkaloid, or ‘’alkali-like’’ was first proposed by the pharmacist, W. Meissner, in 1819. It is usually applied to basic, nitrogen-containing compounds of plant origin. Two further qualifications are usually added to this definition, alkaloids have complex molecular structure, and they manifest significant pharmacological activity. Such compounds occur only in certain genera and families, rarely being universally distributed in large groups of plants. Chemical, pharmacological, and botanical properties must all be considered when classifying a compound as an alkaloid. Examples of well-known alkaloids are morphine **27** (opium poppy), nicotine **28** (tobacco), quinine **29** (cinchona bark), reserpine **30** (rauwolfia) and strychnine **31**(strychnos nuxvomica).

It should be emphasized that many widely distributed bases of plant origin, such as methyl, trimethyl, and other open chain simple alkylamines, the cholines, and the betaines are not classed as alkaloids. These are designated by some authorities as ‘’biological amines’’ or ‘’protoakaloids’’. Certain authorities also class the phenylalkylamines among the ‘’biological amines’’. In certain cases, the distinction drawn between the ‘’biological amines’’ and alkaloids is rather arbitrary. Alkaloids usually have a rather complex structure with the nitrogen atom involved in a heterocyclic ring. Interestingly, colchicine **32** is classed as an alkaloid even though it is not basic, and its nitrogen atom is not incorporated in a heterocyclic ring, because of its particular pharmacological activity and limited distribution in the plant world[29].

Nearly 300 alkaloids had been isolated by 1939 and about 200 of these had at least reasonable well defined structure. In the first publishing in 1950, more than 1000 alkaloids are noted.

With the development of chromatographic techniques and sophisticated spectroscopic instrumentations, the number of known alkaloids has risen dramatically. In 1978 review, nearly 4000, structurally defined alkaloids were reported[30].



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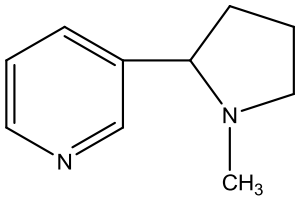

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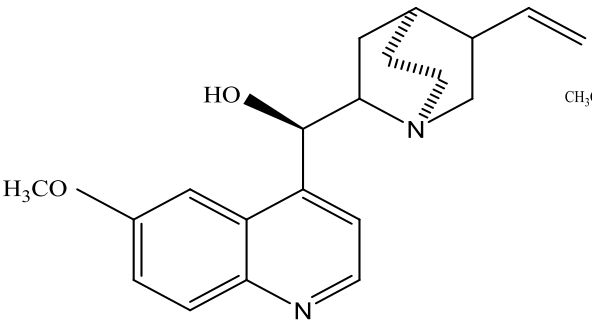

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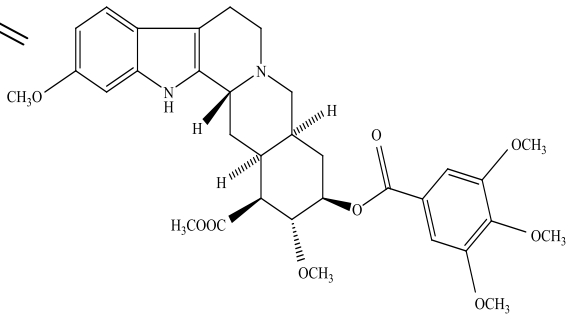

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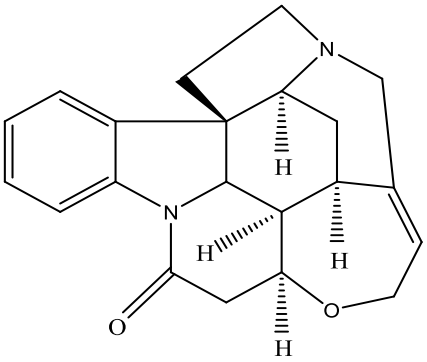
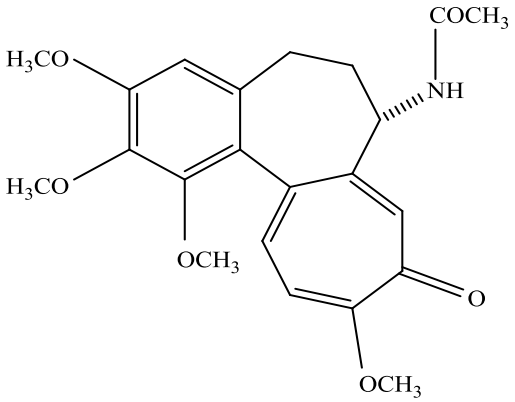




31 **32**

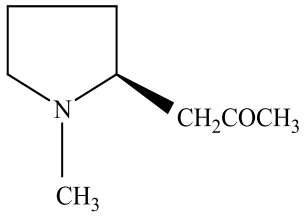
2.3 Classification of the Alkaloids

Alkaloids are the largest group of natural nitrogen-containing heterocyclic compounds. When a nitrogen atom is part of a ring, the molecule is refered to as a heterocyclic compound, meaning that a hetero atom (an atom other than carbon) exists in the ring[31]. Alkaloid can be categorised into three groups based on their biogenetic pathways, chemical structure, pharmacological action, botanical and biochemical origin[32]. Several examples of common alkaloid ring skeletons are shown in Scheme 2.1

a. The **true alkaloids** mainly contain nitrogen in their heterocyclic system, derived from a biogenetic amine and formed by decarboxylation of an amino acid. It can be found in the plant as salt E.g.: morphine **27** and hygrine **33.**

b. The **pseudoalkaloids** mainly contain characteristic of all true basic alkaloids, but they are not derived from amino acid. It also known as heterocyclic containing nitrogen and derived from terpenoids. E g.: actinidine **34** and coniine **35**.

c. The **protoalkaloids** mainly contain nitrogen but that not as part of the heterocyclic system, also basic and like true alkaloids, they are derived from amino acid. E. g.: serotonine **36** and cathinone **37**.



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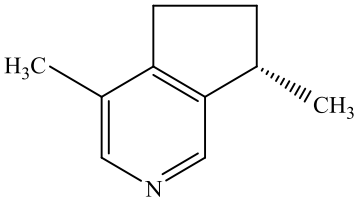

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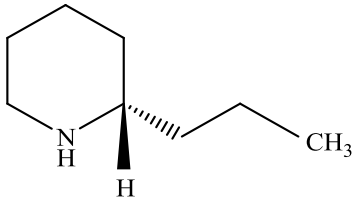

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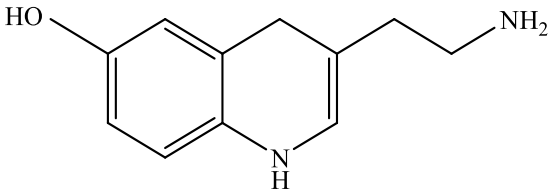

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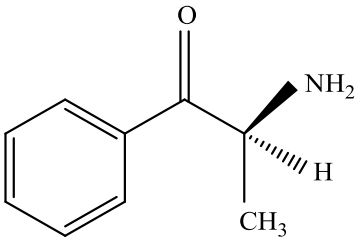

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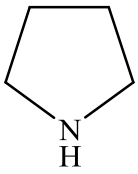
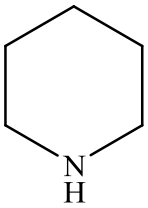
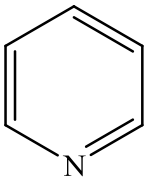


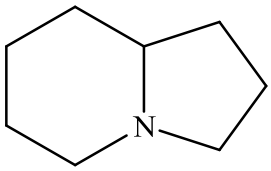
Pyrolidine



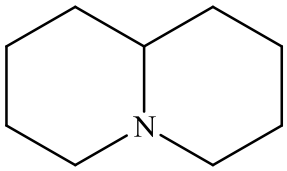
piperidine



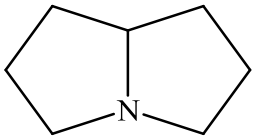
pyridine



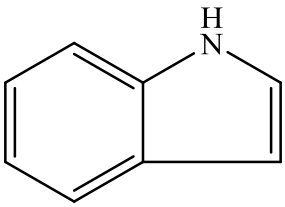
indolizidine



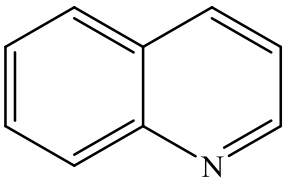
quinolizidine



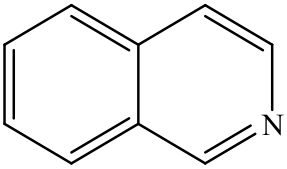
pyrrolizidine



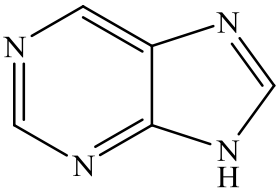
Indole



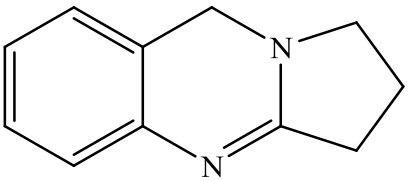
quinoline



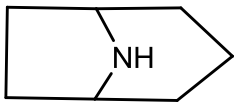
isoquinoline



Purine



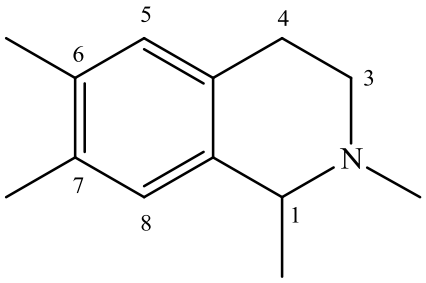
quinazoline



tropane

Scheme 2.1: Examples of Alkaloid Ring Skeletons.

2.4 Classification of Isoquinoline Alkaloids

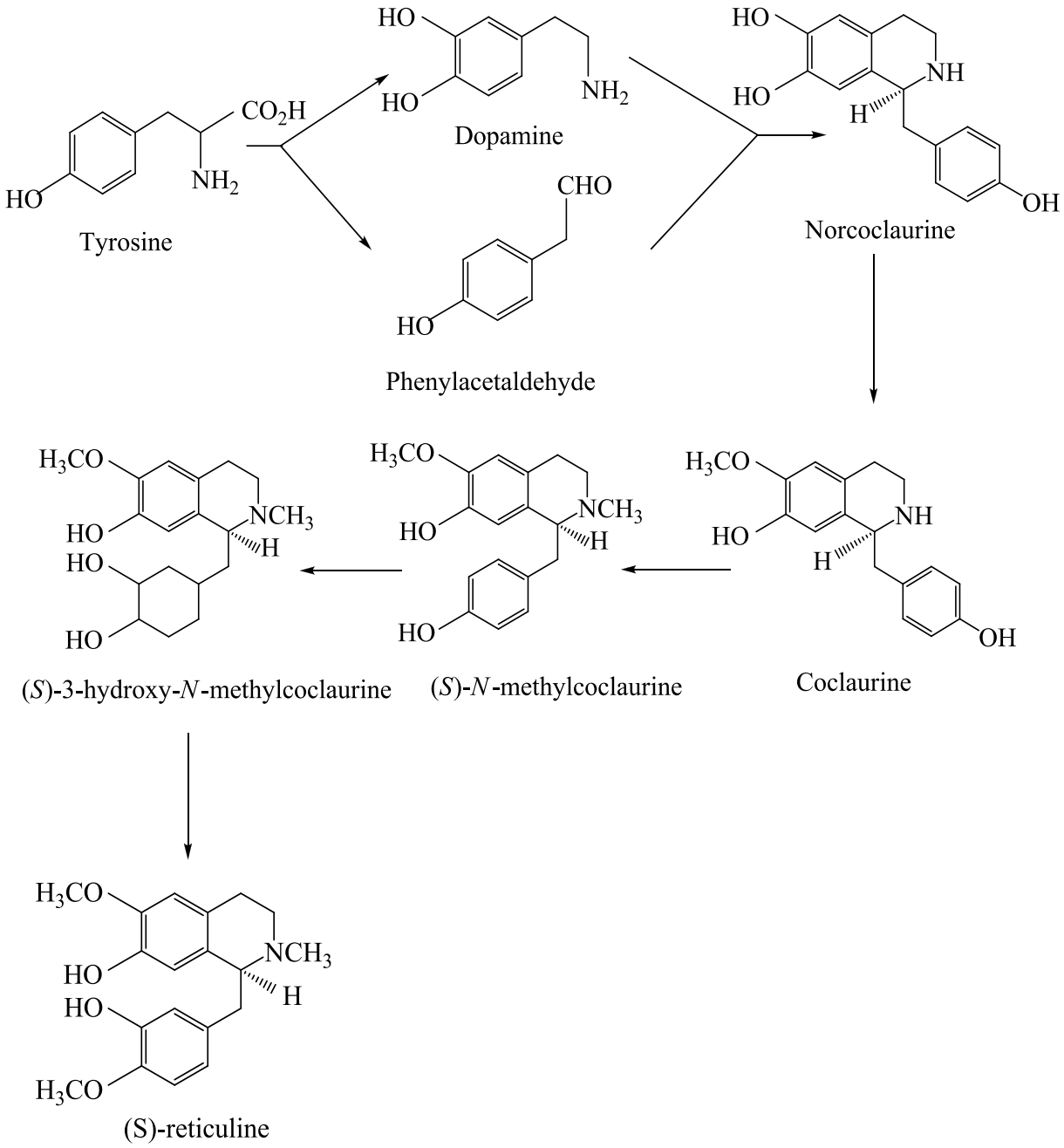


Benzyltetrahydroisoquinolines are intermediate in the metabolism of isoquinoline alkaloids. They are found by a Manich-type condensation between two metabolites of phenylalanine. The experiments with labeled precursors and cell culture showed that the true precursors are dopamine on one hand and 4-hydroxyphenylacetaldehyde on the other hand. The condensation of these two molecules leads to (*S*)-6-demethylcoclaurine, which is subsequently methylated (on the 6-position of the phenol and on the nitrogen atom) before being hydroxylated at C-12 and finally methylated to (*S*)-reticuline **14**[33] (Scheme 2.2).

Isoquinoline can be categorised into several classes base on the skeletal of the structure (Table 2.1).

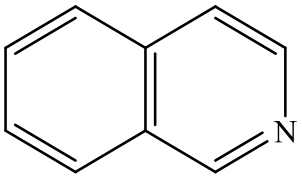
Table 2.1: Categorises of Isoquinoline Alkaloids

Simple isoquinoline	Dibenzazonines
Benzylisoquinoline	Protoberberines and retroprotoberberines
Isoquinolones	Secoberberines
Pavines and isopavines	Benzophenantridhines
Bisbenzylisoquinolines	Arylisoquinolines
Baluchistanamines	Protopines
Cularines	Phthlideisoquinolines
Dibenzopyrrocolines	Rhoeadines
Proaporphines	Emetines
Aporphines	Phenethylisoquinolines
Proaporphine-benzylisoquinoline	Homoaporphines and homoproaporphines
Dimers	1-Phenylisoquinolines
Aporphine-pavine dimmers	*N*-Benzyltetrahydroisoquinolines
Oxoaporphines	4-Arylisoquinolines
Aristolochic acid and aristolactams	Azafluoranthenes and tropolosoquinolines
	1, 6-Diazafluoanthenes



Scheme 2.2: Biosynthetic origin of the benzyltetrahydroisoquinoline.

2.4.1 Simple Isoquinoline

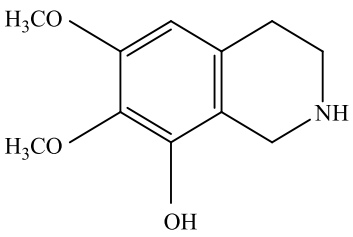


The simple isoquinoline are structurally the simplest of the isoquinoline type and usually bicyclic. These alkaloids are derived from tetrahydroisoquinoline and they may be found in the fully aromatic form or in partially reduced form[34]. They also may be defined as those containing only one aromatic nucleus and no other cyclic structure except a methylenedioxy substituent and most of it has a carbon chain attached to C-1, often a carbon substituent[35]. Simple isoquinoline derivatives can be further sub-divided into:

a) those not bearing a carbon substituent at C-1 and which are basic, eg. anhalamine **38**

b) those with an amide carbonyl group at C-1 and therefore non-basic, eg. corydaldine **39** and

c) those with a methyl group at C-1 eg. salsoline **40**.



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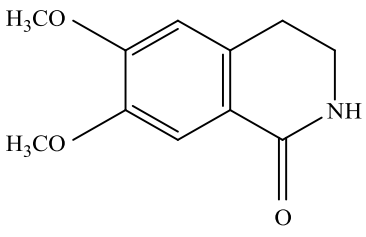

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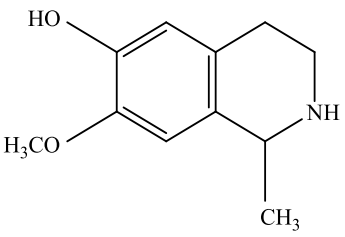

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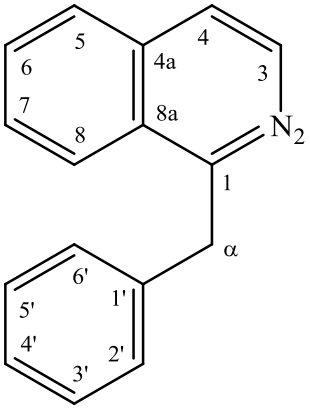
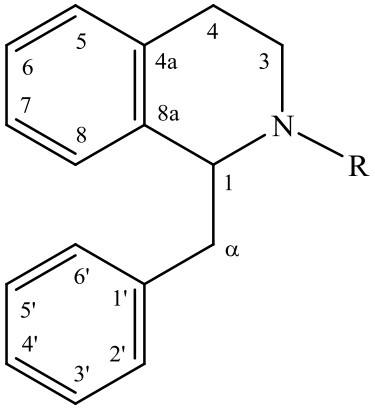
2.4.2 Benzylisoquinoline



A



B

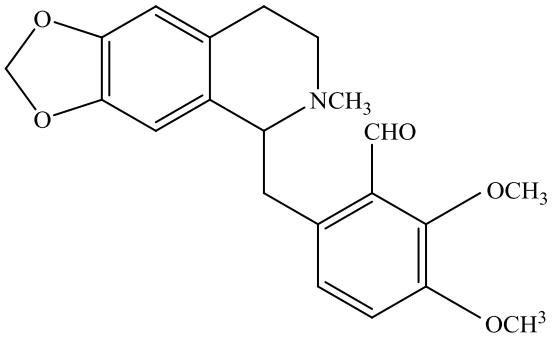
The benzylisoquinoline types of alkaloids were derived from phenylalanine or tyrosine and are the parent skeleton of a wide variety of alkaloids belonging to numerous different ring systems. The benzylisoquinoline alkaloids include both the benzylisoquinoline bases of type **A** and the benzyltetrahydroisoqunolines of type **B**. The alkaloids with the unmodified benzlisoquinoline skeleton may be divided into two subgroups:

a) 1,2,3,4-tetrahydrobenzylisoquinolines, e.g. reticuline **14** – of central importance in the elaboration of other alkaloids; and
b) alkaloids with a carbon substituent at C-2; such as canadaline **41**. These may be regarded as ring – opened berberines.

It was proposed that reticuline **14** acts as a precursor for the C-9, C-10 or the C-10, C-11 substituted aporphine (scheme 2.3) while *N*-methylcoclaurine **44** is the precursor for most of the mono-oxygenated C-10 or non oxygenated ring D (scheme 2.4) and orientaline **1** precursor for the C-9 or C-11 mono-oxygenated ring D aporphine

(scheme 2.5). All the reactions occurred involved radicals and in the cases of the latter two the corresponding alkaloids were formed via proaporphine which is another type of isoquinoline alkaloid that occur in the nature.

Benzylisoquinoline alkaloids are widely distributed in the family Anonaceae[36-43], Lauraceae[13,20,43-44], Menispermaceae[45-48], Papaveraceae[49-51], Fumariaceae[52-53], Ranuculaceae[54-55] and Berberidaceae[56-57].



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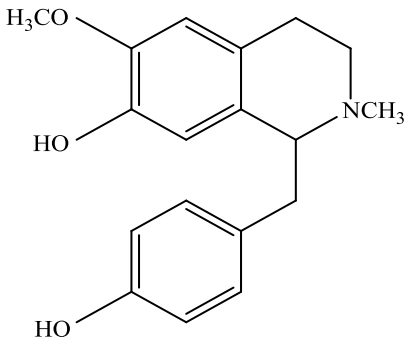

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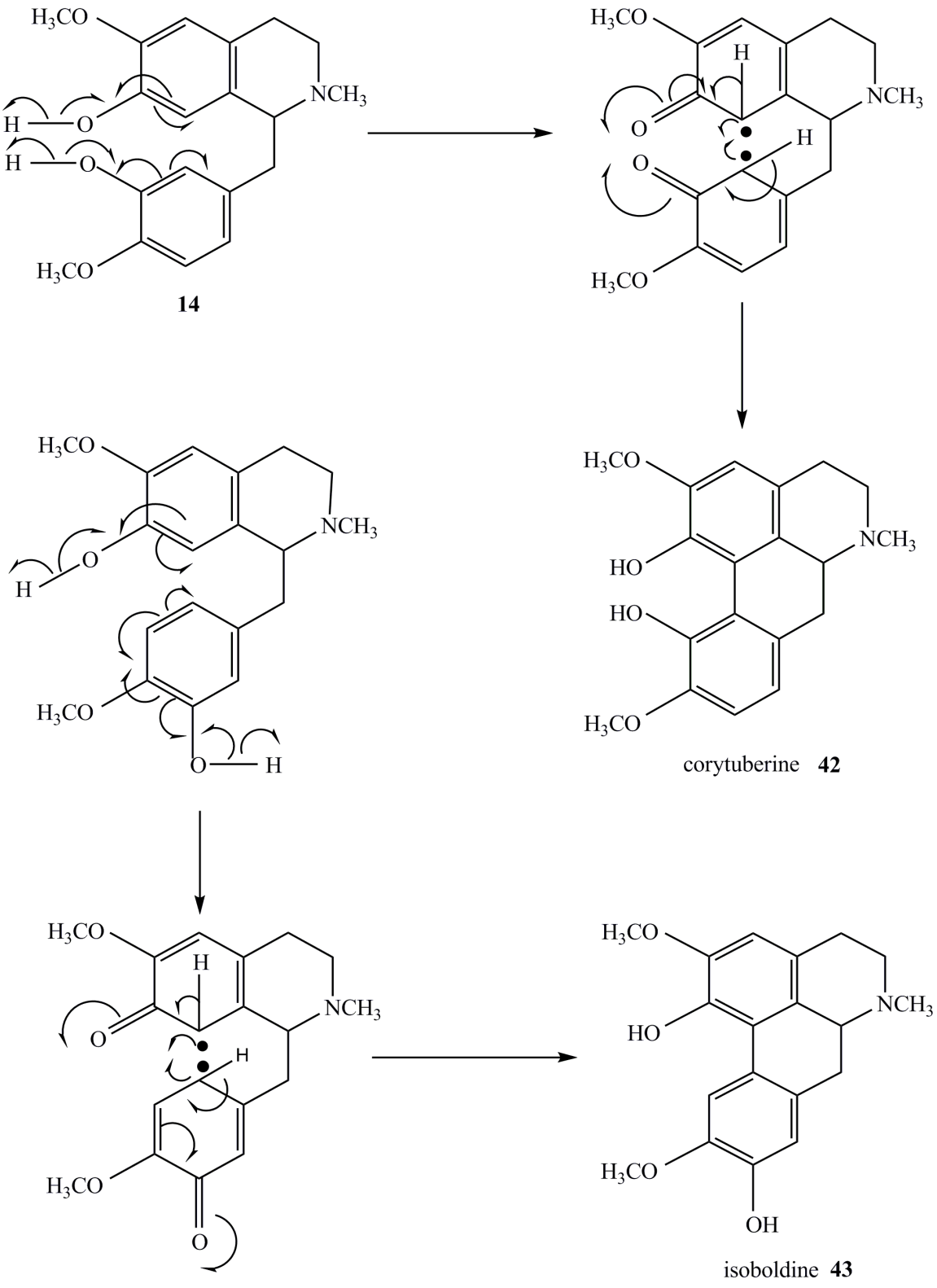
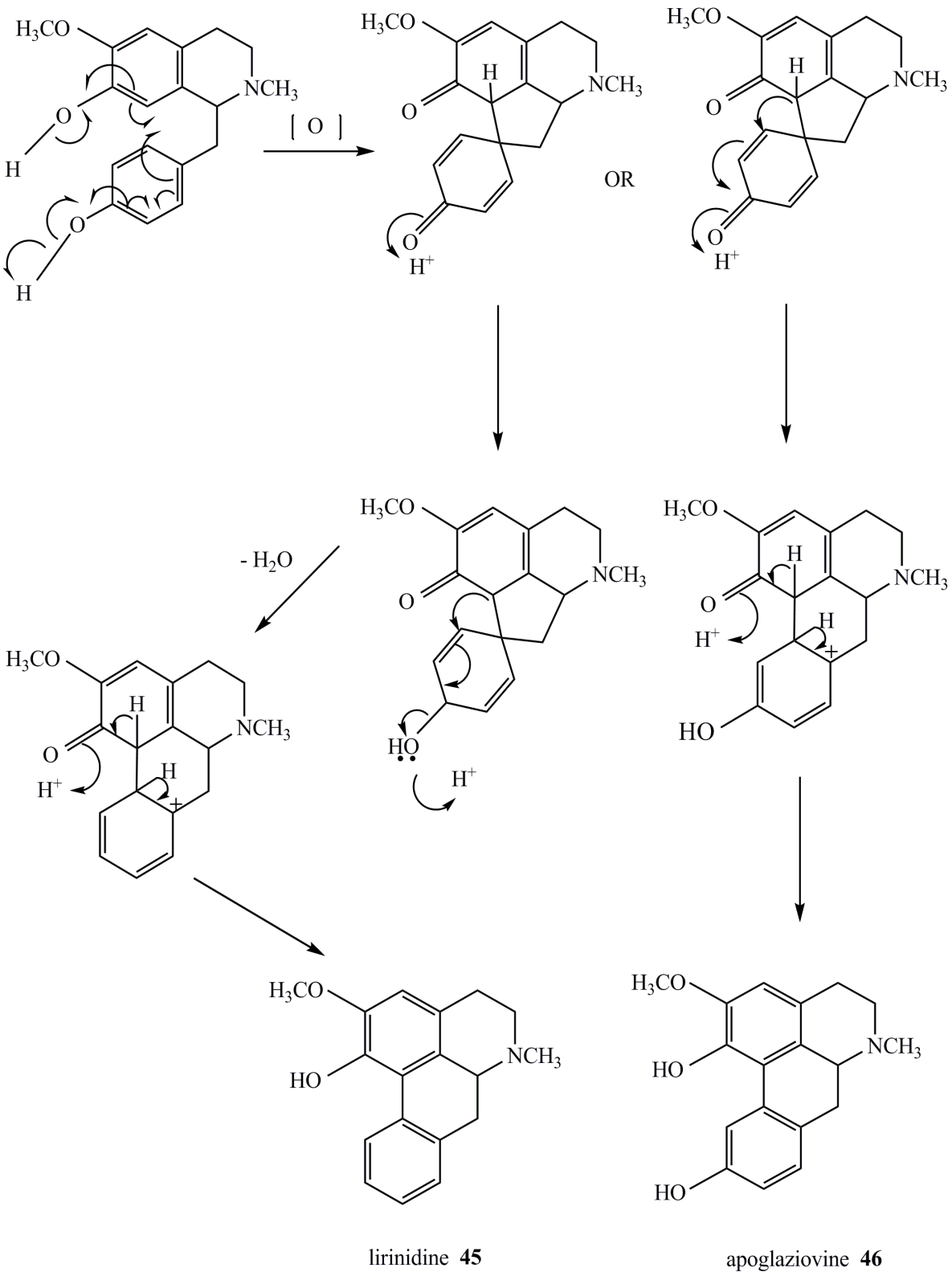
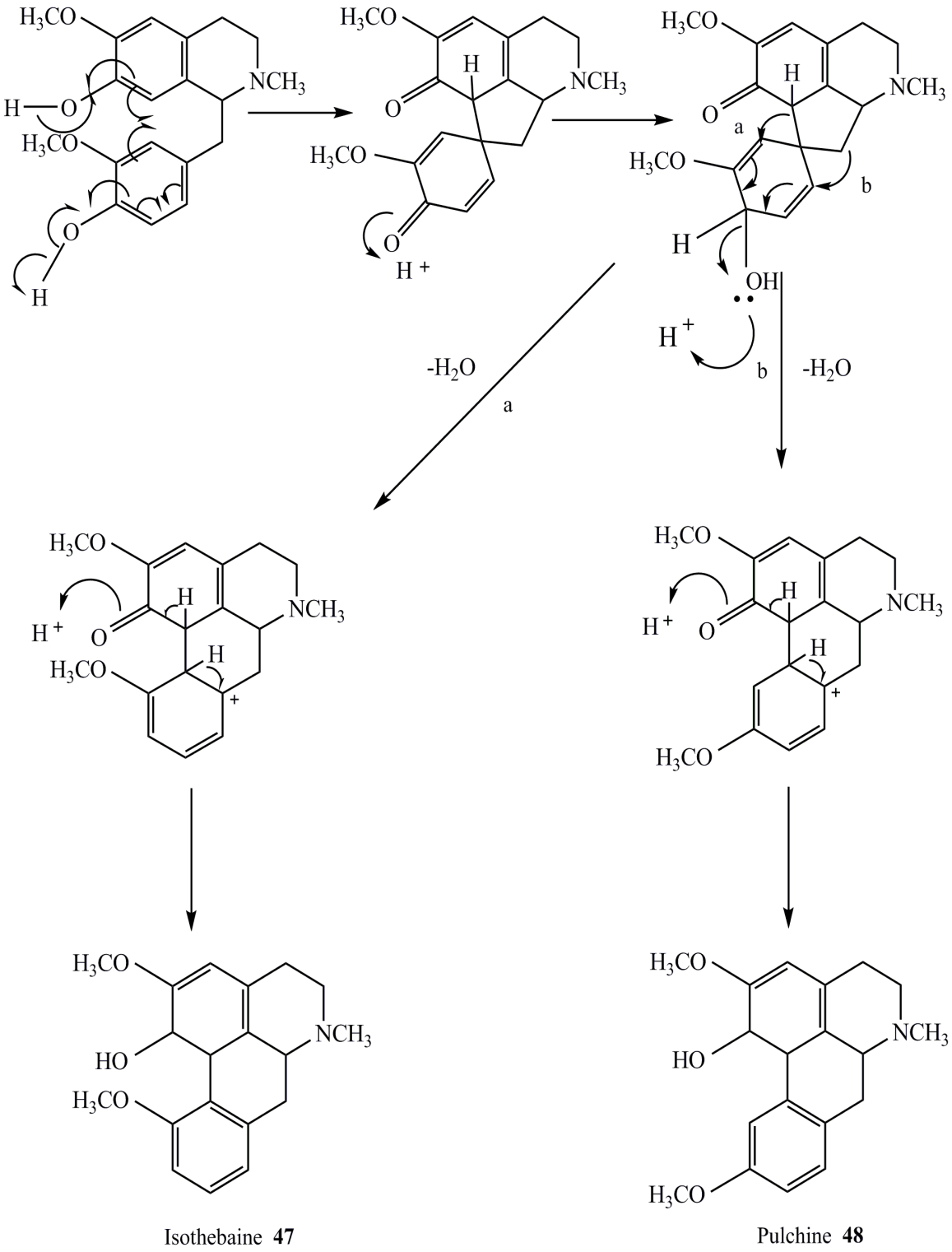


Scheme 2.3: The biogenetic pathway to C-9,10 and C-10,11-disubstituted aporphine.



Scheme 2.4: The biogenetic pathway to C-10 monosubstituted and unsubstituted ring D aporphine.



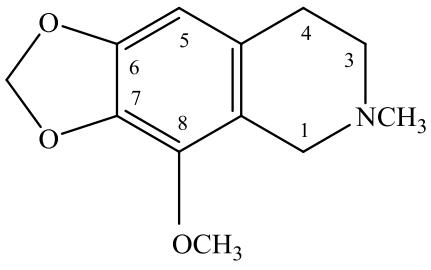
Scheme 2.5: The biogenetic pathway to C-11 and C-9 monosubstituted aporphine.

^{1}H NMR

The ^{1}H NMR data of benzylisoquinoline (Table 2.2) shows a number of interesting features due to the one asymmetric center. The H-1 showed a triplet or doublet-doublet (J_1 = 8-9, J_2 = 1.5-3 Hz) with chemical shift (in $CDCl_3$) between δ 3.6-3.7 while the aliphatic proton signals for H-3, H-4 and H-α, normally appeared as multiplet at δ 2.5-3.5.

The methylenedioxy resonated at δ 5.6-6.0. Base on the study of benzylisoquinoline, this group can be attached to C-6,7 and C-3',4'. When the position of methylenedioxy attached to C-6 and C-7, the signal showed as a doublet or singlet.

The methoxyl groups of the benzylisoquinoline, generally resonated at δ 3.50-4.00. Normally, *N*-methyl groups resonated in the region of δ 2.4-2.6. Table 2.3 showed the examples chemical shift of ^{1}H NMR for some benzylisoquinolines, i.e. hydrocotarnine **49**, laudanosine **50**, laudanine **51**,



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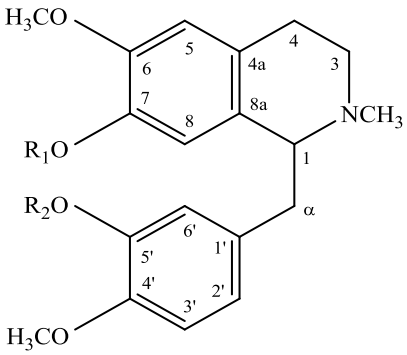


50 $R_1 = OCH_3$, $R_2 = OCH_3$

51 $R_1 = OCH_3$, $R_2 = H$

Table 2.2: ^{1}H NMR (in $CDCl_3$, ppm) for some benzylisoquinoline.

Position of H	**49**	**50**	**51**
H-1	3.44	3.64	3.64
H-3	2.60	2.73 and 3.12	2.74 and 3.09
H-4	2.80	2.55 and 2.78	2.57 and 2.74
H-5	6.31	6.50	6.45
H-6	-	-	-
H-7	-	-	-
H-8	-	6.02	5.81
H-α	-	2.17 and 3.10	2.54 and 3.03
H-2’	-	6.55	6.58
H-3’	-	-	-
H-4’	-	-	-
H-5’	-	6.71	6.60
H-6’	-	6.58	6.36
6-OCH_3	-	3.77	3.68
7-OCH_3	-	3.53	3.37
8-OCH_3	3.98	-	-
3’-OCH_3	-	3.73	-
4’-OCH_3	-	3.78	3.68
N-CH_3	2.45	2.49	2.40
OCH_2O	5.85	-	-

^{13}C NMR

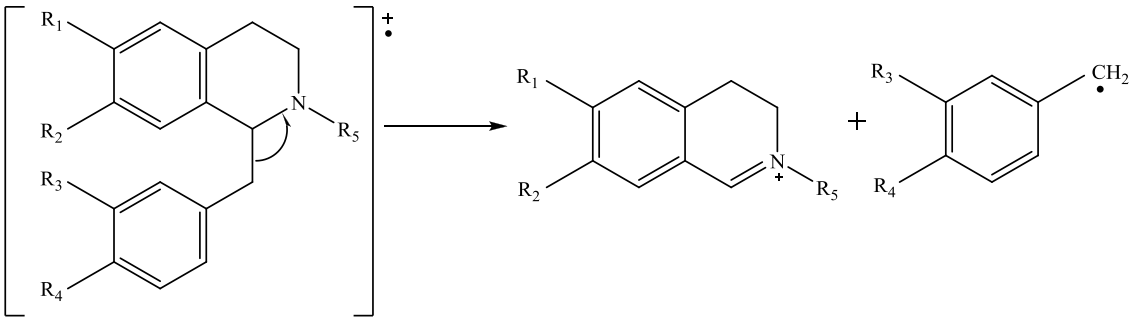
In the ^{13}C NMR spectra, C-1 normally resonated at δ 52-58, but it resonated at lower field i.e. δ 60-67 in the presence of *N*-methyl group. Substituted carbons *N*-methyl, methoxyl and methylenedioxy appeared at δ 40-45, δ 54-63 and δ 100-103, respectively. The quaternary carbon at the position 4a, 8a and 1’ resonated at δ 115-132. The quaternary carbons with methoxyl and hydroxyl groups appeared at δ 140-152. Unsubstituted sp^2 carbons usually appeared at δ 100-130 and the sp^3 carbons at the

position C-α and C-3 resonated at δ 38-40 and δ 45-46, respectively. The chemical shift of C-4 with *N*-methyl group in the structure appeared at δ 23-24, but it will appear at δ 28-29 without *N*-methyl group.

Mass spectrometry

In the mass spectra of benzylisoquinoline, the main cleavage occurs between C-1 and C-α to form an imine ion. The fragmentation at m/z 192 appeared as a base peak indicated that the carbons C-6 and C-7 was substituted with methoxyl and hydroxyl groups, respectively and in the structure beared *N*-methyl group. If both C-6 and C-7 was substituted with methoxyl groups peak at m/z 206 appeared as a base peak. The fragmentation at m/z 176 which appeared as a base peak indicated the carbons C-6 and C-7 attached to methylenedioxy without *N*-methyl in the structure.

The compounds having a methoxyl and hydroxyl groups in the ring C displayed peak at m/z 137. Two methoxyl groups attached to C-3' and C-4' showed the fragmentation peak at m/z 151 and a hydroxyl group in the ring C showed peak at m/z 107[58]. The illustration of mass fragmentation pattern of benzylisoquinoline is shown in Scheme 2.6.



m/z = 192 $R_1 = OCH_3$, $R_2 = OH$, $R_5 = CH_3$ m/z = 107 $R_3 = H$, $R_4 = OH$

m/z = 176 $R_1 = R_2 = OCH_2O$, $R_5 = H$ m/z = 121, $R_3 = OCH_3$, $R_4 = H$

m/z = 206 $R_1 = R_2 = OCH_3$, $R_5 = CH_3$ m/z =137 $R_3 = O3\ H$, $R_4 = OCH_3$

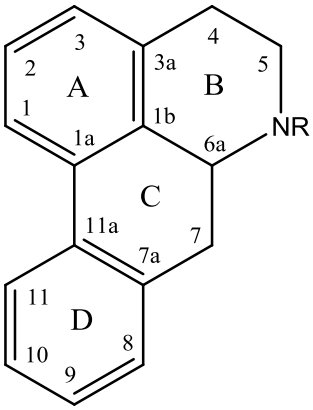
Scheme 2.6: The illustration of mass fragmentation pattern of benzylisoquinoline.

Ultraviolet spectrum

The ultraviolet spectra of benzylisoquinoline showed maxima between 280 and 296 nm which was little effect by additional aromatic substitution. Compounds having methylenedioxy and fully aromatic show increased and more intensity absorption maximum.

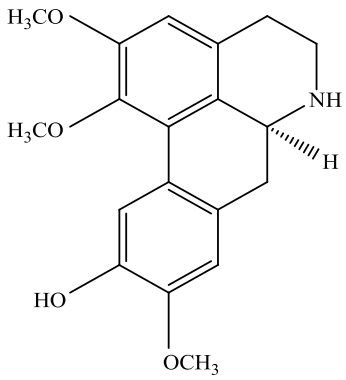
2.4.3 Aporphine

The aporphines represent a large and still expanding group of isoquinoline alkaloids. They are found only in plants belonging to the families of Annonaceae, Berberidaceae, Lauraceae, Magnoliacea, Menispermaceae, Monimiaceae, Ranunculaceae (order Ranales), Papaveraceae (order Rhoedales), and Rhamnaceae (order Rhamnales) and were represented by the general structure below.



The aporphine alkaloids contain a twisted biphenyl system. Its consists with four rings, A, B, C, D. The whole aporphines alkaloids are based on the 4H-diben[de,g]quinoline structure or its *N*-methyl derivative commonly known as the aporphine nucleus. It can be divided into three groups:

a) The noraporphine, which possess a secondary nitrogen atom, eg: norlirioferine **52**
b) The aporphines which contain *N*-methyl function, lirioferine **13**, *N*-methyllauroteanine **53**
c) The quaternary aporphines salts, for example *N, N*-dimethylhernovine **54**



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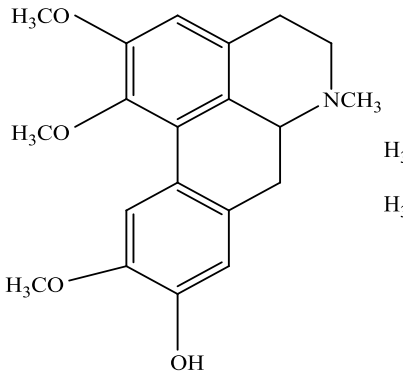

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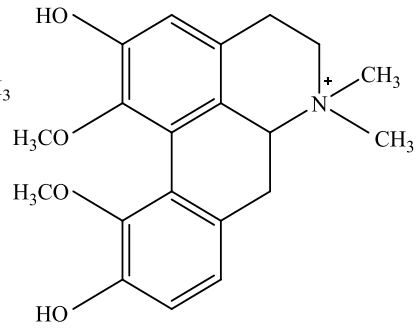

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^{1}H NMR

The ^{1}H NMR spectrum can yield important and valuable information leading to the structural elucidation of aporphines. The chemical shifts are very dependent on the position of the protons with respect to the aromatic rings. Several general features have been observed in the proton shifts of these alkaloids. The following chemical shifts have been observed.

Methoxyl group

From the ^{1}H NMR spectrum, the aromatic protons appeared at δ 6.3-8.2 and the methoxyl groups revealed at δ 3.3-3.9. The most deshielded methoxyl groups were attached at C-2, C-9 and C-10 and the most shielded was C-1, except if C-1 substituted with methylenedioxy. The methoxyl that attached to C-1 appeared at high field due the steric effect of ring D.

The most downfield aromatic proton (H-11) was observed between δ 7.5 and 8.2 depending on the adjacent group C-10. The substituted of C-10 will shield the H-11 proton. The C-3 proton was most shielded and typically appeared as a singlet in the range of δ 6.5-7.5. The presence of methoxyl group at C-11 causes the proton at H-8 and H-9 to had significantly different chemical shift. If a C-11 bears a hydroxyl group, the chemical shift of H-8 and H-9 were overlapped and no coupling was observed. The position of C-2 is also substituted when position of C-1 and C-11 are substituted. This affects 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 shielded area. In addition, ring A and ring D is facing each other. Hence the protons of the methoxyl

groups can arrange themselves on top of the adjacent ring, which happens to be a shielded zone giving a more upfield shift[59].

Methylenedioxy group

The methylenedioxy group shows resonances at range of δ 5.87-6.02. The five possible location for this group are C-1, 2; C-2, 3; C-9, 10; and C-10, 11. The presence of C-1, 2 methylenedioxy group is proved by an up field shift of the C-11 proton which appeared in the range δ 7.47-7.86, and caused the twisted biphenyl system induce magnetic nonequivalent between the methylene proton, which then appeared as doublets at δ 5.9 and 6.1.

At position C-9 and C-10, the two protons appear as a singlet whereas at position C-1 and C-2; C-2 and C-3; C-10 and C-11, they appear as two doublets with coupling constant of about 1.5 Hz. This inequivalence arises from the torsion caused by the twisted biphenyl system of ring A and D[60]. The appearance of the torsional effect on the methylenedioxy depends on their positions and at position C-9, 10 the effect appears to be negligible[61].

Aromatic proton

The hydrogens at C-3, C-8 and C-9 of aporphine are located upfield between δ 6.38-7.00 and cannot be easily differentiated from one another while hydrogen at C-11 is found relatively downfield between δ 7.57-8.05. Nevertheless, H-3 normally resonates at a higher field compared to the other aromatic protons (δ 6.50-6.70) when it is ortho to a hydroxyl or a methoxyl. This is due to induction effect. On the other hand,

H-11 is usually resonates at a lower field with respect to the other protons due to the deshielding effect imposed by the facing aromatic ring A and hydrogen bonding with the C-1 substituent in ring A.

_N_-methyl group and aliphatic protons

The *N*-methyl group was typically observed at δ 2.4-2.8. The aliphatic protons of C-4, C-5 and C-7 displayed a complex resonance pattern with absorption in the region of δ 2.40-4.40 whereas the methyl group resonated in the region of δ 2.50-2.60. Summary of the ^{1}H NMR data of aporphine given in the table 2.3 below

Table 2.3: ^{1}H NMR data (δ/ppm) of aporphine alkaloids in $CDCl_3$

Position of substituted	Methoxyl group	Methylenedioxy	Aromatic proton	*N*-methyl group	Aliphatic group
C-1	3.70-3.55				
C-2	4.12-3.75				
C-3					
C-8			7.00-6.38		
C-9	4.12-3.75		7.00-6.38		
C-10	4.12-3.75				
C-11	3.75-3.65		8.74-8.68		
C-1, 2		5.87-6.02			
C-2,3		5.87-6.02			
C-8, 9		5.87-6.02			
C-9, 10		5.87-6.02			
C-10, 11		5.87-6.02			
N-Me				2.50-4.44	
C-4					2.40-4.00
C-5					2.40-4.00

^{13}C NMR

The general characteristic of the different type of carbons are mentioned below.

a) Sp^2 carbon bearing hydrogen: δ 105-112.
b) Sp^2 carbons at position 1a, 1b, 3a, 7a and 11a: δ 119-130.
c) Sp3 carbons at position 4(δ 28-30), 7(δ 35) and 5 and 6a (about δ 42 and 53 for noraporphine) and (about δ 53 and 62 for aporphine).
d) Carbon of the substituents: *N*-methyl (about δ 43), methoxyl (δ 56-62) and methylenedioxy (δ 100).

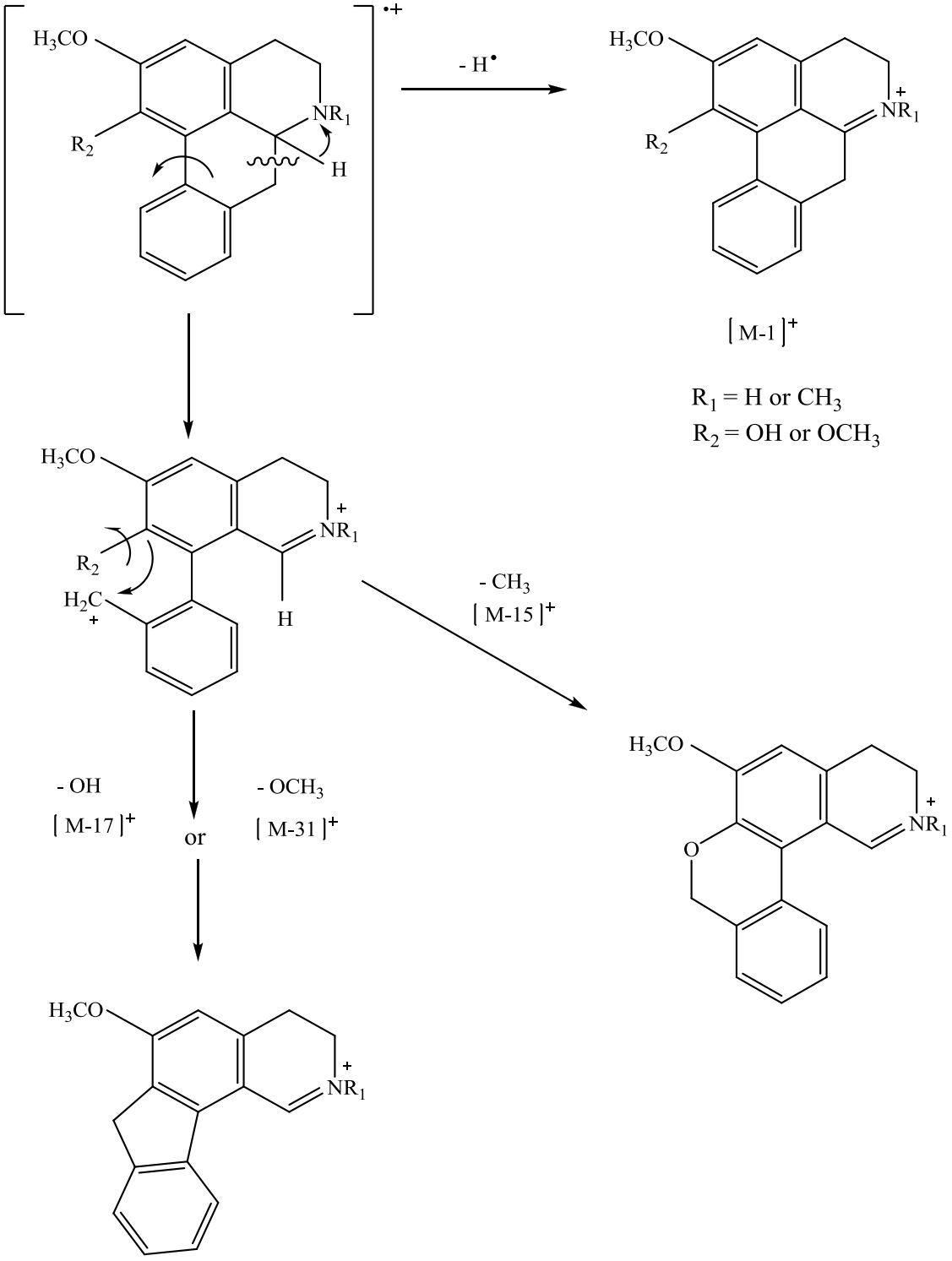
The quaternization of the *N*-atom causes deshielding of C-5 and C-6a and shielding of C-1b, C-3a, C-7 and C-7a.

Mass spectrometry

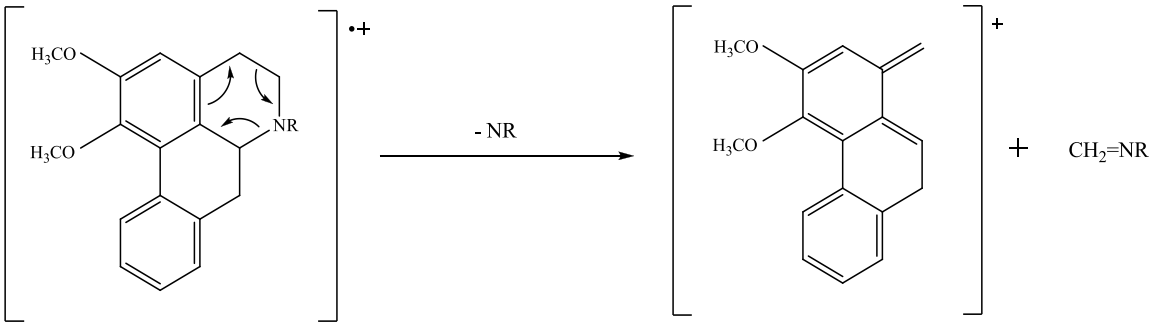
In mass spectrum, the principle fragmentation of the aporphine is the loss of the hydrogen atom on C-6a. The $[M-1]^+$ peak always serves as the base peak of the molecule. If the molecule was substituted; $[M-15]^+$ and $[M-31]^+$ peak will also be observed due to the expulsion of a methyl, hydroxyl or methoxyl group respectively (Scheme 2.7). Also if it is a hydroxyl group substituted at the ring D, a $[M-17]^+$ peak will be observed.

Aporphine compound having the *N*H or *N*-CH_3 groups will display peaks at $[M-29]^+$ and $[M-43]^+$ respectively. The fragment lost is methylene imine group (-CH_2=NR) which is expelled via a retro Diels-Alder mechanism (scheme 2.8) (or by the cyclic

process in ring B.) The ion formed can further loose another methyl or methoxyl to produce peaks at $[M-74]^+$, $[M-58]^+$, $[M-60]^+$, and $[M-44]$[62].



Scheme 2.7: The principle mass fragmentation of aporphines.



R = H or CH_3

If R = H, peak observed is $[M-29]^+$

If R = CH_3, peak observed is $[M-43]^+$

Scheme 2.8: The mass fragmentation of aporphine with *N*-methyl or *N*-H function group.

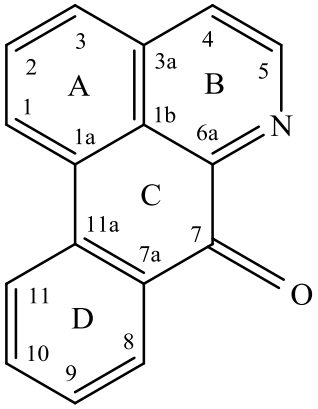
Ultraviolet spectrum

The positions of the maximum absorptions in the ultraviolet spectra of aporphines depend mainly upon the location 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 are listed as below.

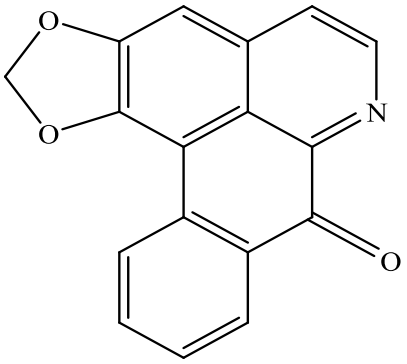
Position of substituents	Absorption maximums (nm)
1, 2	234, 273, 312
1, 2, 9	233, 280, 305
1, 2, 10	226, 266, 275, 305
1, 2, 11	220, 265, 272, 300
1, 2, 9, 10	220, 282, 305
1, 2, 10, 11	220, 270, 305

The shape of the curve and the density of the latter two maxima depend on the substitution in ring D. Furthermore, the monophenolic aporphine position at C-3 and C-9 display a bathochromic shift at 315 nm and 350 nm in the alkaline environment[63-64].

2.4.4 Oxoaporphine



The oxoaporphines consist of carbonyl group at C-7. They are usually colored such as red, orange and yellow because of their high degree of aromaticity. Oxoaporphines are widely distributed and the first reported oxoaporphine was liriodenine **55**, which was isolated from *Liriodendron tulipfera*[65-66]. From the species of Artabotrys unicinatus, a novel 11-oxoaporphine were isolated, namely artacinatine **56**[65].



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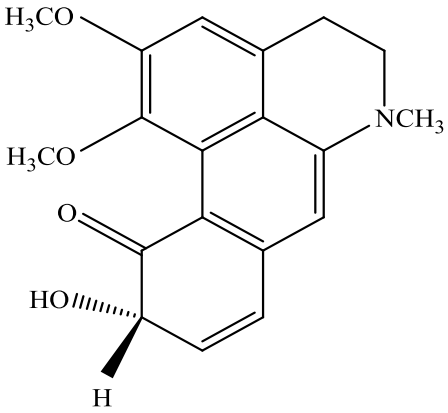


56

^{1}H NMR

The most characteristic features of oxoaporphine are the existence of highly deshielded chemical shift values of the aromatic protons and the absence of the aliphatic proton signals. 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 referred to a double bond between C-4 and C-5. The C-3 proton singlet appeared at higher field if C-1 and C-2 were substituted. On contrary, the C-11 proton is usually the most downfield as a result of the ring current effect of the facing ring A.

The methylenedioxy group observed a singlet with two protons at about δ 6.1 compared to the two doublets in the aporphine. This was due to the planarity of the oxoaporphine skeleton. Moreover, H-8 resonates at a lower field (δ 8.2-8.6) because of the neighouring C-7 carbonyl which exerts an inductive effect compared to the H-8 in aporphine.

The methoxyl group located at C-1 gave the average shifts of about δ 3.55 meanwhile methoxyl groups present at position C-2, C-9 and C-10 reveal peaks at δ 3.80. Nevertheless we found that in the position C-1 and C-11, the methoxyl gave chemical shift at δ 3.70. In the latter case, the more upfield shift may be due to the OCH_3 bond sticking out of the plane of the benzene rings which a deshielded effect is expected.

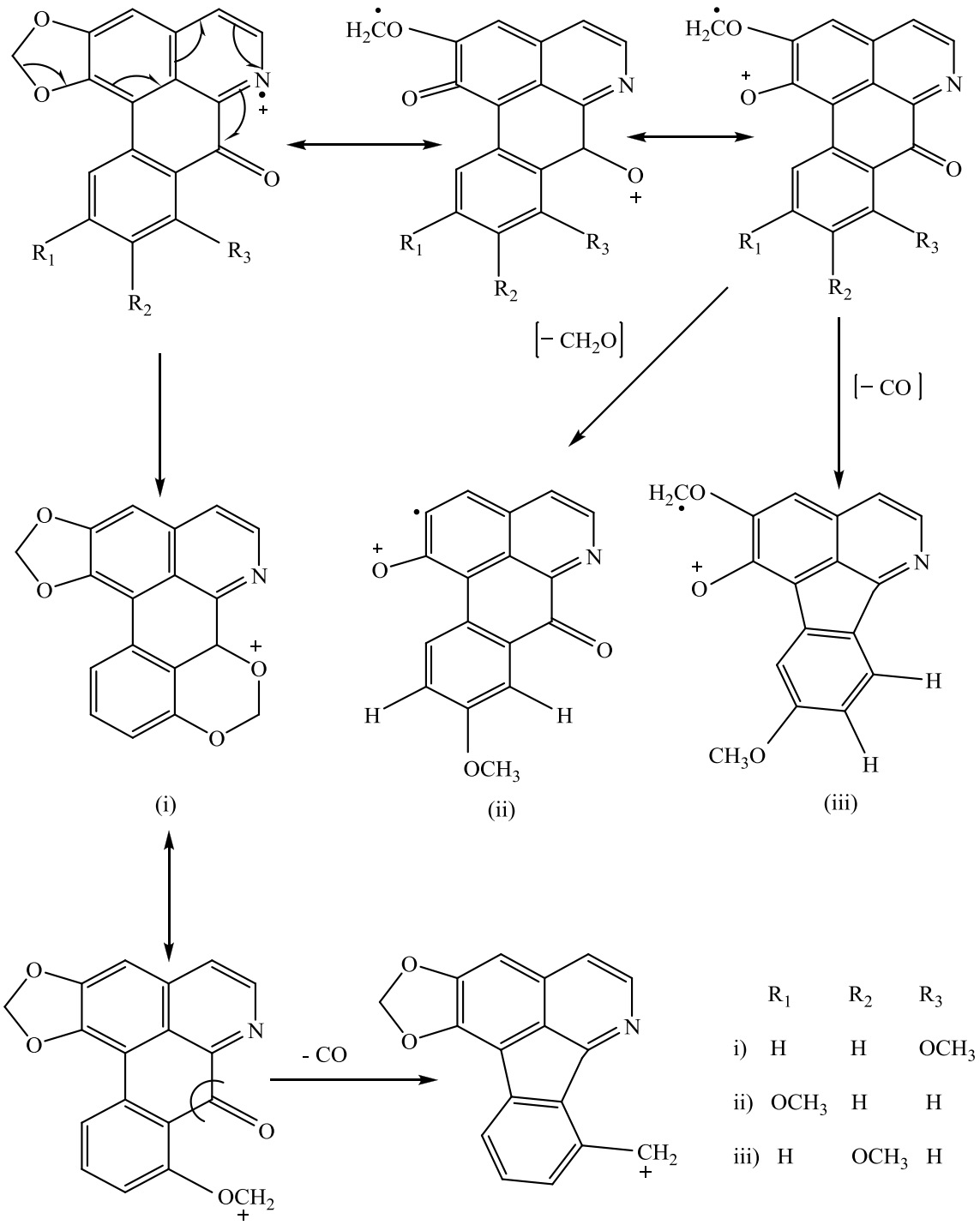
^{13}C NMR

The ^{13}C-NMR spectral data of oxoaporphines showed much closer to those observed in aporphines. The carbons are all sp^2, indicating that it was unsaturated and fully aromatic. The general characteristic of the dfferent type of carbons are mentioned below.

a) Sp^2 carbon bearing a hydrogen: 105-112 ppm
b) Sp^2 carbons at position 1a, 1b, 3a, 7a, and 11a: δ 119-130
c) Sp^3 carbons at positions 4(δ 28-30), 7(δ 35) and 5 and 6a (about δ 42 and 53 for noraporphine) and (about δ 53 and 62 for aporphine).
d) Carbon of the substituents: *N*-methyl (about δ 43), methoxyl (δ 56-62) and methylenedioxy (δ 100).

Mass spectrometry

The main fragment ions observed in the mass spectrum of oxoaporphine are given in scheme 2.9 The important fragmentations are the $[M-CO]^+$, $[M-CH_2O]^+$ and $[M-CHO]^+$



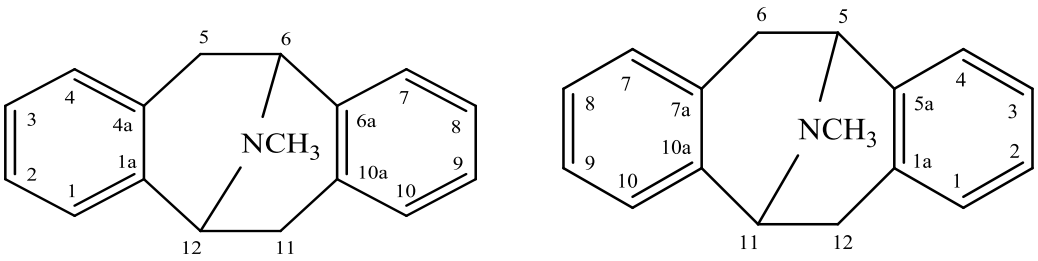
Scheme 2.9: The mass fragmentation of an oxoaporphine.

Ultraviolet spectrum

The UV spectral data for the oxoaprphines are quite characteristic for the skeletal type. These yellowish colored alkaloids posses a highly unsaturated chromophoric system with extended absorption in the ultraviolet and visible.

For example liriodenine **55** shows three main absorption bands at 245-270, 309 and 413 nm. On acidification, the oxoaporphine exhibit bathochromic shift or the spectrum is shifted to longer wavelengths with a series of undulating maxima between 325 and 460 nm[67].

2.4.5 Pavine Alkaloids



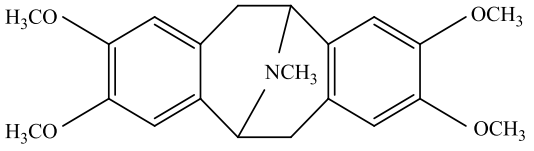
A **B**

The isoquinoline alkaloids with a pavine skeleton are very rare in plant kingdom. The alkaloids are found at least in four plant families, namely Papaveraceae, Berberidaceae, Lauraceae and Ranuculaceae. The structure of the first pavine alkaloid to be identified as having the pavine skeleton was argemonine **57**, isolated from *Argemone hispida*[68], *A.munita* and *Thalictrum dasycarpum*[69]. Furthermore, only the genus Cryptocarya in the family of Lauraceae is known to posses pavines. Several of

the pavines are probably derived biogenetically from the tetrahydrobenzylisoquinoline. Two numbering system have been used for the pavines, represented by expressions **A** and **B**. The characteristic of pavine is due to nitrogen atom must bridge the eight-membered ring in the *cis* configuration and only two stereoisomers of the alkaloids are possible.

^{1}H NMR

In the ^{1}H NMR, the chemical shifts of methoxyl group of the pavine alkaloids appeared at δ 3.7-3.9. The methylenedioxy group resonated at δ 5.8-5.9 while aromatic proton will appeared at δ 6.5-6.7. One peak attributed to methyl group attached to nitrogen was observed at δ 2.4-2.5. The determining factor has been stated to be the inductive effect of the bridgehead C-N bond, causing deshielding and consequently downfield shifting of H-1 and H-7[70]. Chemical shift of pavine alkaloids, (-) thalimonine-*N*- oxide **58** and (-) thalimonine **59** are shown in Table 2.4.



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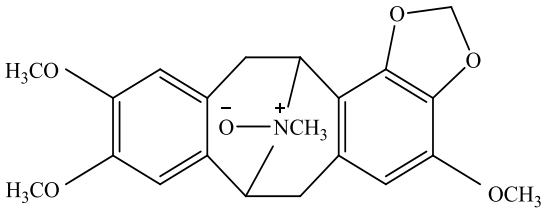

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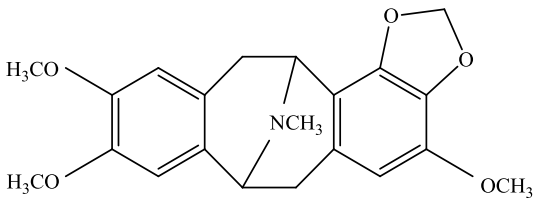

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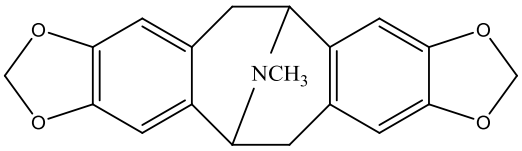


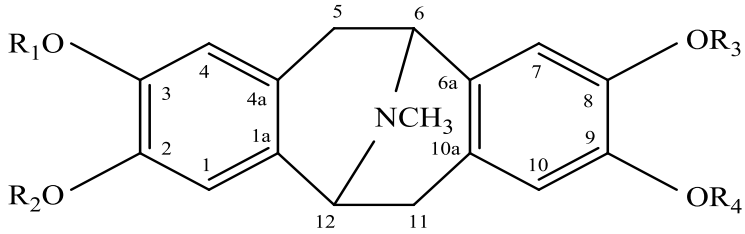
60

Table 2.4: ^{1}H NMR of some pavine alkaloids

Position of H	**58**	**59**
1	6.37, *s*	6.32, *s*
5a	3.33, *d* (17.2)	2.63, *s*
5b	3.10, *d* (5.9)	3.20, *dd* (5.9, 16.5)
6	4.65, *d* (5.7)	4.03, *t*
7	6.61, *s*	6.61, *s*
10	6.53, *s*	6.45, *s*
11a	2.73, *d* (16.0)	2.56, *s*
11b	4.24, *dd* (5.8, 16.00)	3.41, *dd* (5.9, 16.2)
12	4.54, *d* (5.7)	4.03, *t*
2-OMe	3.90, *s*	3.86, *s*
8-OMe	3.85, *s*	3.84, *s*
9-OMe	3.80, *s*	3.78, *s*
3, 4-OCH_2O	5.95, *dd* (1.4, 26.7)	5.88, *dd* (1.4, 23.2)
N-Me	3.39, *s*	2.53, *s*

^{13}C NMR

The ^{13}C chemical shifts of the symmetrical pavine alkaloids argemonine **57** and crychine **60** are presented in table 2.5.The different in chemical shifts between the two alkaloids in large measure reflect the different in substituents on the aromatic rings. A discrepancy is present between the two alkaloids in the chemical shift of C-6 but the reason for this is not apparent[71].



57 Argemonine $R_1 = R_2 = R_3 = R_4 = CH_3$

60 Crychine $R_1 + R_2 = R_2 + R_3 = CH_2$

Table 2.5: ^{13}C NMR of Argemonine and Crychine

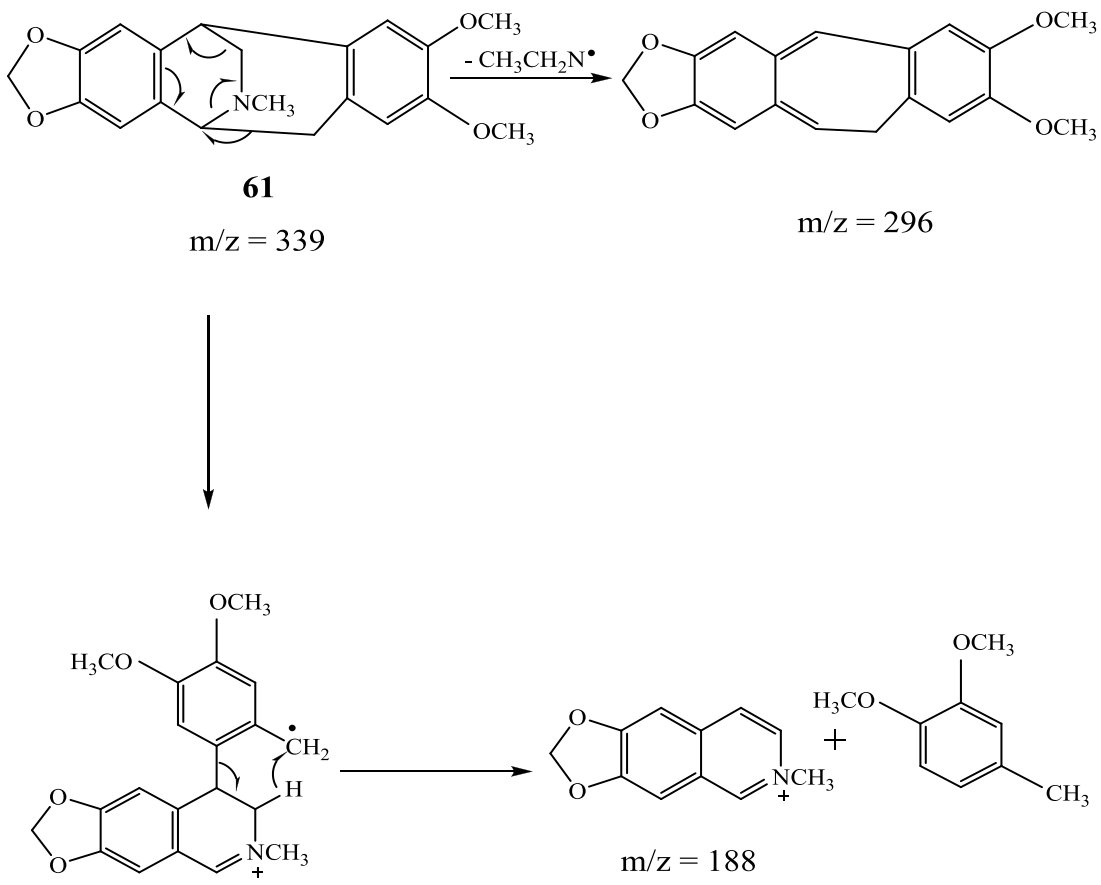
Position	**57**	**60**
1, 7	109.9	107.1
2, 8	147.3	146.1
3, 9	147.7	146.5
4, 10	111.4	108.7
4a, 10a	123.7	125.6
5, 11	33.3	34.1
6, 12	66.2	56.8
6a, 12a	129.7	131.1
2, 8-OCH_3	55.4	
3, 9-OCH_3	55.8	
2, 3-OCH_2		100.6
8, 9-OCH_2		100.6
N-CH_3	40.6	40.8

The general shift regions of the different type of the carbons in the ^{13}C NMR spectra are summarized as a follows:

a) Sp^2 carbon bearing hydrogen: δ 106-112
b) Sp^2 carbon at positions 4a, 6a, 10a and 12a: 120-135
c) Sp^3 carbon at positions 5 and 11: δ 27-32 and sp^3 at positions 11 and 12: δ 56-70
d) Carbon of the substituent *N*-methyl: δ 40-41 and δ 75-76 (*N*-oxide)
e) Carbon methoxyl: δ 55-57 and methylenedioxy: δ 100-101.

Mass spectrometry

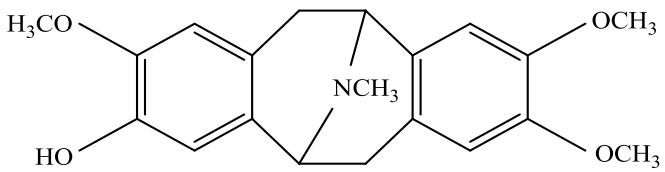
In mass spectra, the principle fragmentation of the pavine alkaloids occurred the molecule lost one phenyl ring to give a basic ion as a base peak. For example, the isopavine alkaloid amurensinine **61**, shows a molecular ion at m/z 339, a strong $[M-43]^+$ ion and a base peak at m/z 188[72]. These ions have been proposed as shown in Scheme 2.10.



Scheme 2.10: The mass fragmentation of pavine alkaloid.

Ultraviolet spectrum

A pavine skeleton may be regarded as two *N*-methyl-1,2,3,4-tetrahydroisoquinoline nuclei fused together. In accordance with this observation, the UV spectrum of a pavine alkaloid demonstrates close similarity to that of an analogous tetrahydroisoquinoline[73] 2,3,8,9-Tetrasubstituted *N*-methylpavines generally display a broad absorption band between 287 and 295 nm in polar solvents[73-76] however, a triplet absorption has also been reported in ethanolic solutions between 280 and 295 nm, where the lowest and highest wavelength absorptions may appear as shoulders[73, 77-78] Some generalizations have been made about the affect of various substituents on the absorption maxima and molar absorptivities[79] as expected the absorption band around 280 nm is displaced to lower wavelengths when two methoxyls are replaced by a methylenedioxy group. The UV spectra of pavine are slightly affected by protonation on nitrogen[73]. Similarly quaternary species furnish UV spectra which closely resemble those of their tertiary counterparts. In some pavine bases such as norargemonine **62**, the expected bathochromic shift on addition of alkali has not been discovered.



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