Dr.Manju Kumari **14.06.21**

Sem IV, Paper Ic, Unit II……

Alkaloids

General methods of structural elucidation of Alkaloids. Structural Elucidation and synthesis of Papaverine, Quinine and Morphine. Stereoselective synthesis of Reserpine. Biosynthesis of Alkaloids.

NATURAL PRODUCTS CHEMISTRY

Definition :

"That branch of chemistry which deals with the isolation, identification, structure elucidation, and study of the chemical characteristics of chemical substances produced by living organisms"

Problems with Synthetic Drugs

- Potency
- Cost
- Side effects
- Requires close supervision of clinician
- Resistance
- Unavailability (Sometimes)
- Stability….

Source of Natural Products

- **Plants**
- Microorganisms
  - Bacteria, fungus
- Marine organisms
- Animal products

Plant research is at the forefront to find an effective, safe pharmacological treatment of diseases.

WHO estimates 65-80% of world population use traditional medicine & 80 % of these involves plant extracts**.**

Metabolites

Primary metabolites
(needful for the cell survival and present in all living system, plants and animals)

- Carbohydrates
- Lipids
- Proteins
- Organic acids
- Vitamins
- Chlorophylls

Secondary metabolites
(synthesized from primary metabolites; they are not needful for the cell survival, but contribute to the survival of the whole organism)

- Glycosides
- Phenolic compounds
- Terpenoids
- Alkaloids

ALKALOIDS

Alkaloids are naturally-occurring organic compounds containing nitrogen moiety, and are usually heterocyclic in nature. They are nitrogen based organic compounds, with nitrogen enclosed in an heterocyclic ring.

The alkyl amines are referred to as proalkaloids.

Characteristics of alkaloids

(1) They are basic in nature due to the presence of nitrogen in their ring.

(2) They have complex structures.

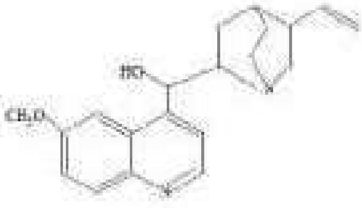
(3) They have bitter principles.

(4) They are mostly obtained from plant materials.

(5) They have high pharmacological and physiological activities.

Examples of alkaloids are:

(1)Quinine — an antimalarial drug isolated from a plant called *Cinchonia officialis*

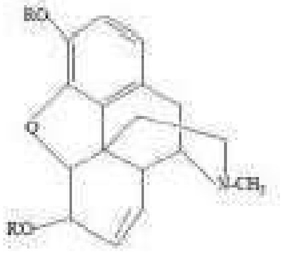


Quinine

Quinine is an antipyretic alkaloid. Its molecular formular is $C_{20}H_{24}N_2O_2$.

Functional groups present in quinine are: methoxyl –OCH_3, hydroxyl –OH, tertiary amine group, etc.

Other examples of alkaloids are: morphine, cocaine, heroine, etc. Most are highly narcotic in nature.

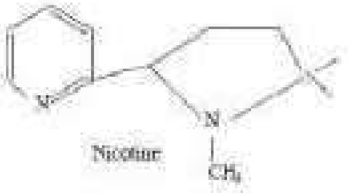


R = R' = H Morphine alkaloid
R =H, R' = CH_3 Codeine
R = R' = $COCH_3$ Heroine

Morphine is highly narcotic, analgesic and is isolated from the plant *Papavera omniferous*

☐ Morphine is an opium alkaloid.

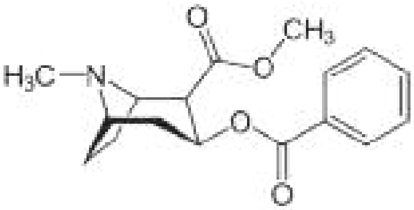
Nicotine is another example of alkaloid



Nicotine

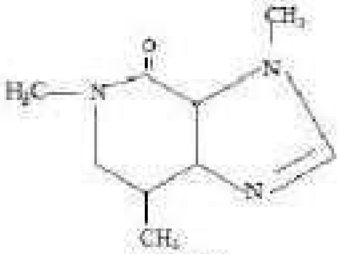
Cocaine -

- Cocaine is obtained from coca leaves,
- Cocaine is the first local anaesthetic ever discovered by man,
- Cocaine is highly narcotic and stimulates the central nervous system i.e. CNS depressant,
- Cocaine can lead to psychiatric problem when taken in high dose or when addicted to it.



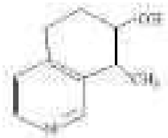
Cocaine

Caffeine is an alkaloid obtained from coffee, tea. It is also a strong stimulant which can increase alertness, thereby causing insomnia when the body gets addicted.

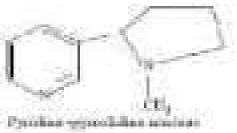


Caffeine

Structures of the various classification based on chemical structures are illustrated below



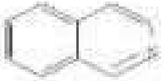
Pyridine nucleus



Pyridine-pyrrolidine nucleus

Pyridine-piperidine nucleus

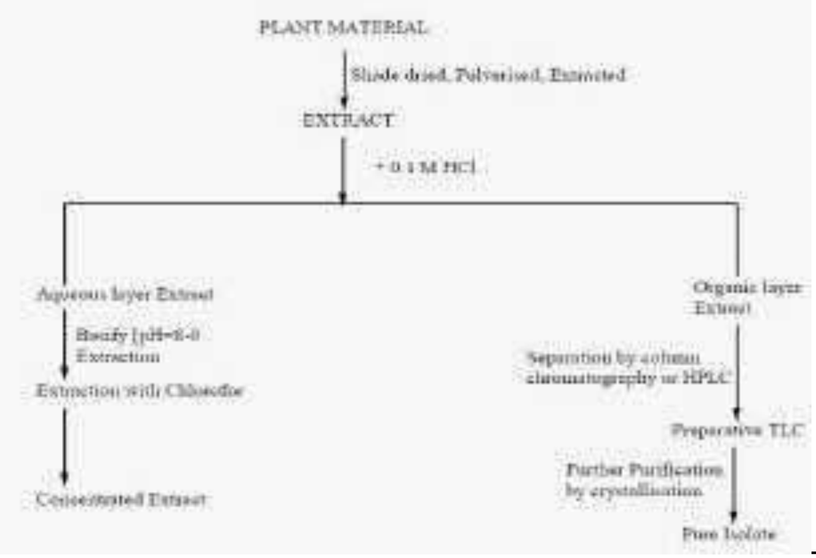
Quinoline nucleus



Isoquinoline nucleus

Extraction method for Alkaloids

The extraction procedure often used in the isolation of alkaloid is summarized in the table below.



Alkaloid as Natural Products

- Largest class of secondary metabolites, >6500 compounds known
- Contains N, most compounds are basic (alkaline)
- Often highly toxic
- Found in certain higher plants
- Little is known regarding why alkaloids are produced
- Biosynthesis from amino acids

Many of these substances have marked physiological effects, a fact discovered by many ancient people long before organic chemistry developed.

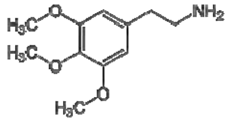
Like, alkaloid quinine, a chief constituent of bark of Cinchona, has been used as effective antimalarial since 1639.

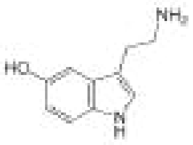
Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants and animals and are part of the group of natural products (also called secondary metabolites).

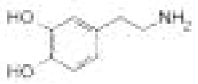
The boundary between alkaloids and other nitrogen-containing natural compounds is unclear.

Compounds like amino acid, peptides, proteins, nucleotides, nucleic acid, amines and antibiotics are usually not called alkaloids.

Natural compounds containing nitrogen in the exocyclic position (mescaline, serotonin, dopamine, etc.) are usually attributed to amines rather than alkaloids.







Some authors, however, consider alkaloids a special case of amines.

Effects of alkaloids on humans

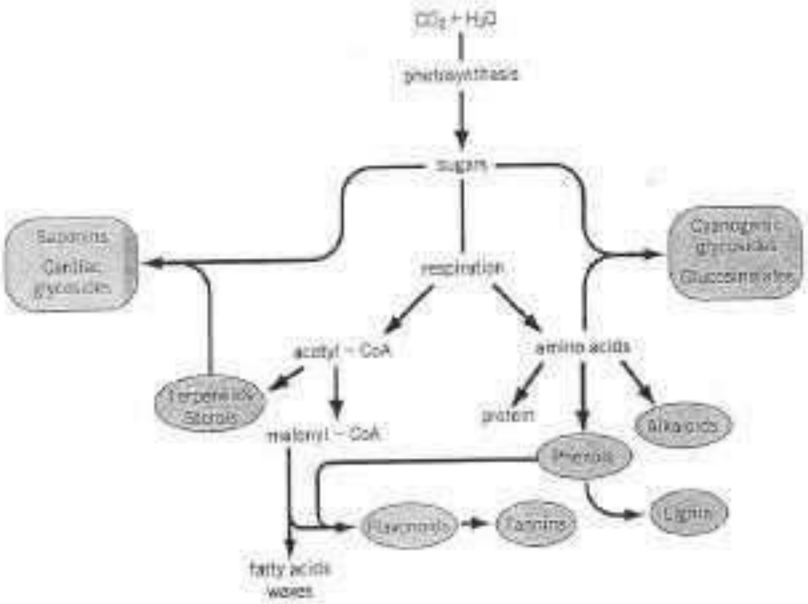
- High biological activity
- Produce varying degrees of physiological and psychological responses - largely by interfering with neurotransmitters
  - others interfere with membrane transport, protein synthesis or other processes
- In large doses - highly toxic - fatal
- In small doses, many have therapeutic value
  - muscle relaxants, tranquilizers, pain killers, mind altering drugs, chemotherapy

Psychoactive alkaloids (affecting mental process)

- Although only a small percent are psychoactive, these get much focus
- Affect the central nervous system - often by influencing neurotransmitters
- Categories of psychoactive compounds
  - Stimulants
  - Hallucinogens
  - Depressants
- May also be narcotic (*addictive*)

Psychoactive alkaloids

Stimulants	Hallucinogens	Depressants
Cocaine	Tropane alkaloids	Morphine
Ephedrine	Mescaline	Codeine
Caffeine	Psilocybin	Heroin
	Ergot alkaloids (LSD)	



Tests for Alkaloids

- Most alkaloids are precipitated from neutral or slightly acidic solution by
- Mayer's reagent (potassiomercuric iodide solution) ☐ Cream coloured precipitate.
- Dragendorff's reagent (solution of potassium bismuth iodide)☐ orange coloured precipitate.
- Wagner’s reagent (iodine in potassium iodide) ☐ red-brown precipitate
- Hagers reagent (picric acid) ☐ yellow precipitate

Physical & Chemical Properties of Alkaloids

MW: 100 – 900

Most bases which do not contain Oxygen are liquid at room temperature (nicotine), while those that do are solids.

In rare cases they are coloured.

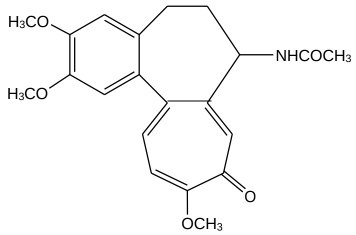
Most solid bases rotate the plane of polarized light, have high melting points.

Normally are not soluble in water (occasionally slightly soluble).

Soluble in non polar or slightly polar organic solvents.

The basicity of alkaloids depends on the availability of the lone pair of electrons on the N atoms: Electron donating groups enhance basicity, while e-withdrawing groups decrease it.

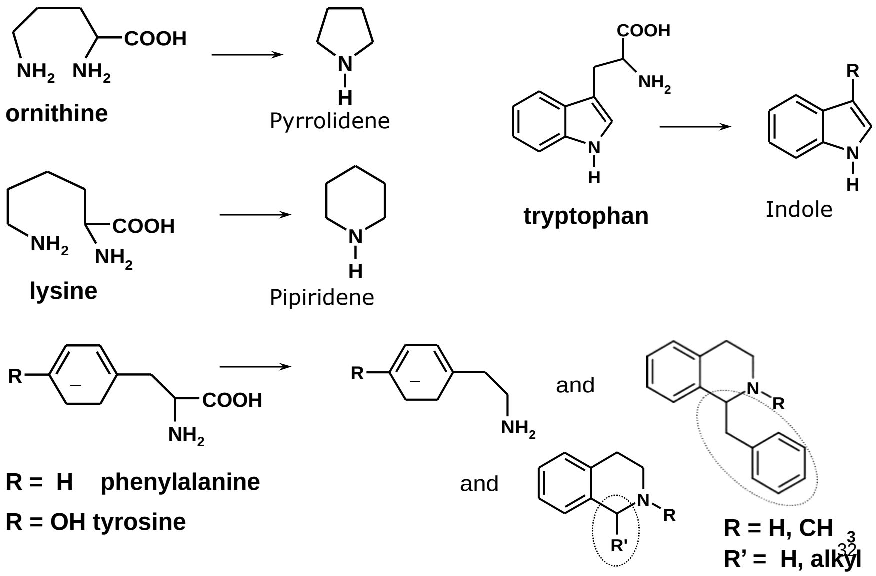
Because some alkaloids have a carbonyl group on the amide, they can also be neutral (colchicine & piperine).



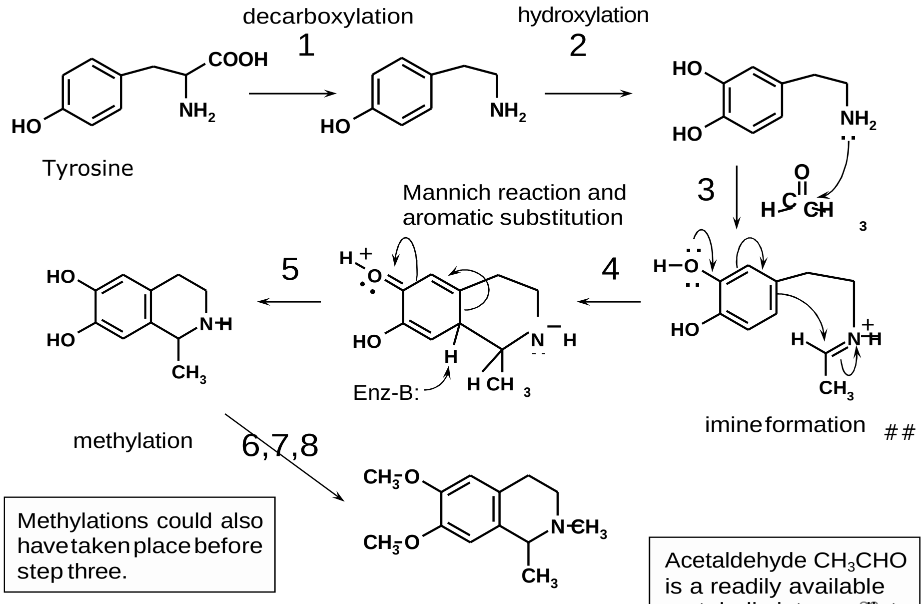
Colchicine

MOST ALKALOIDS ARE DERIVED FROM α-AMINO ACIDS

SOME OF THE MAJOR RELATIONSHIPS ARE SHOWN BELOW



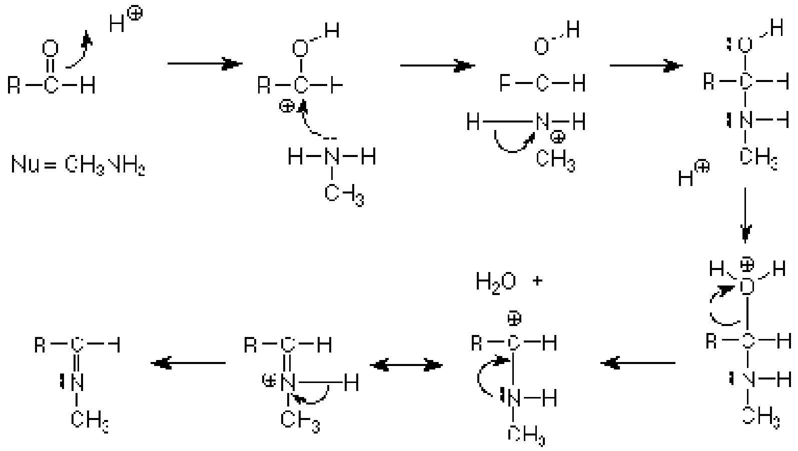
Ex: FORMATION OF ISOQUINOLINE ALKALOIDS



Methylations could also have taken place before step three.

Acetaldehyde CH_3CHO is a readily available metabolic intermediate

Mechanism – Imine formation



Biogenesis of Alkaloids

- Alkaloids are produced in plants by basic substances and reactions well-known in organic chemistry.
- Biosynthetic origin cannot be discussed in general terms for all alkaloids, instead it has to be covered separately for each of the major groups of alkaloids.
- True alkaloids are based on an amino acid (pre-cursor).
- Only a few amino acids form the pre-cursors for all alkaloids: ornithine, lysine, phenylalanine, tyrosine, tryptophan, histidine and anthranilic acid.

☐ Alkaloid formation may require the involvement of only one molecule of amino acid, or 2 molecules of the same AA, or less commonly, 2 molecules of different AA or else several molecules of the same AA.

☐ The formation starts with the creation of a Schiff base or a Mannich reaction.

☐ When the alkaloid has additional C-atoms, these play important roles in other metabolic pathways.

Alkaloids are often divided into the following major groups:

"**True alkaloids**", which contain Nitrogen in the heterocycle and originate from amino acids.

Their characteristic examples are atropine, nicotine and morphine.

This group also includes some alkaloids which beside nitrogen heterocycle contain terpene (e.g. evonine) or peptide fragments (e.g. ergotamine) as well as it also includes piperidine alkaloids coniine and coniceine although they do not originate from amino acids.

"**Protoalkaloids**", which contain nitrogen and also originate from amino acids but does not have heterocyclic ring. Examples include mescaline, adrenaline and ephedrine.

Polyamine alkaloids – derivatives of putrescine, spermidine and spermine.

Peptide and cyclopeptide alkaloids.

Pseudalkaloids – alkaloid-like compounds which do not originate from amino acids.

This group includes, terpene-like and steroid-like alkaloids, as well as purine-like alkaloids such as caffeine, theobromine and theophylline.

Some authors classify ephedrine and cathinone as pseudoalkaloids. Those originate from the amino acid phenylalanine, but acquire their nitrogen atom not from the amino acid but through transamination.

Some alkaloids do not have the carbon skeleton characteristic of their group. So, galantamine and homoaporphines do not contain isoquimoline fragment, but are generally attributed to isoquinoline alkaloids.

ERGOT POISONING..............

Ergotism is the effect of long-term ergot poisoning, traditionally due to the ingestion of the alkaloids produced by the *Claviceps purpurea* fungus which infects rye and other cereals, and more recently by the action of a number of ergoline-based drugs. It is also known as **ergotoxicosis**, **ergot poisoning** and **Saint Anthony's Fire**.

Causes

The toxic ergoline derivatives are found in ergot-based drugs (such as methylergometrine, ergotamine or, previously, ergotoxine).
Historically, eating grain products contaminated with the fungus *Clavicep purpurea* also caused ergotism.
Finally, the alkaloids can also pass through lactation from mother to child, causing ergotism in infants.

ERGOT POISONING..............

Q: How and when did the Salem witchcraft epidemic begin?
A: The epidemic that led to the Salem Witch Trials began in a town called Danvers, at the time known as Salem Village in colonial America. Sometime early in 1692, several children in the Samuel Parris household had convulsions and hallucinations. At first they accused Tituba, a Caribbean serving woman, of being a witch. Soon more cases of convulsions and accused witches spread throughout the county, and an epidemic began.

Q: What are the connections between ergot and Salem witch-hunting?
A: Ergot is a toxic fungus that affects rye; the toxin causes tingling in the fingers, hallucinations and convulsions—all symptoms that appeared in those who accused others of being witches. Ergot thrives in wet summers followed by cold summers, conditions that were present in Salem during January and February of 1692.

ERGOT POISONING..............

Fungal Pathogens on Food

- Ergot poisoning
  - Fungus (*Claviceps spp.)* growing on Rye or Wheat or other grasses; humans eat the flour
  - Ascomycete fungus; makes a hard black elongated structure
  - Grain containing more than 0.3% ergot is prohibited from sale
  - Over 40 alkaloids present; related to lysergic acid
  - Symptoms include irritable digestive tract, loss of balance, convulsions, drowsiness

GENERAL METHODS OF STRUCTURE DETERMINATION OF ALKALOIDS

- In structure determination of alkaloids, a variety of general chemical methods and more recently physical methods are employed.
- In general, elemental composition is obtained from combustion analysis and after determination of molecular weight, molecular formula is calculated. The measurement of optical rotation indicates the presence of optical activity.

- METHODS:
  - A. Chemical Methods
  - B. Degradation of Alkaloids
  - C. Physical Methods

CHEMICAL METHODS

- The alkaloids mostly contains one or more oxygen atoms, which may be present as hydroxyl, methoxy, methylenedioxy, carbonyl, carbonyl ester, lactone, amide, lactam, epoxide groups or ether linkage.
- ***i) Hydroxyl group***

  Molecule contains hydroxyl group or -NH group then the number of these groups can be estimated by acetylation or Zerewitinoff's method.
- **Acetylation's method**

$$\text{R-OH} + \text{CH}_3\text{-CO-Cl} \rightarrow \text{R-OCO-CH}_3$$

$$\text{R-NH-R}_1 + \text{CH}_3\text{-CO-Cl} \rightarrow \text{R-N(COCH}_3\text{)-R}_1$$

- **Zerewitinoff's method**

$$\text{R-OH} + \text{MeMgI} \rightarrow \text{R-OMgI} + \text{CH}_4$$

$$\text{R-NH-R'} + \text{MeMgI} \rightarrow \text{R-N(MgI)-R'} + \text{CH}_4$$

- If hydroxyl group is present it may be Alcoholic or Phenolic.

  Phenolic compounds are soluble in sodium hydroxide and are reprecipitated by carbon dioxide and give colouration with ferric chloride while alcoholic does not respond to these tests .

CHEMICAL METHODS Contd……

- ***ii) Carbonyl group***

  Ascertained by usual reactions with hydroxylamine, semicarbazide or 2,4-dinitrophenyldrazine. The carbonyl group may be present as an aldehyde or a ketone. This distinction can be made from Tollen's reagent and silver mirror.
- ***iii) Carboxyl group***

  Dissolved in bicarbonate or ammonia and reprecipitation with carbon dioxide indicates the presence of carboxyl group.

  The formation of ester on treatment with alcohol in the presence of dehydrating agent.
- ***iv) Methoxy group***

  Use Zeisel's method, which is similar to the Herzig-Meyer method

$$\text{R-OMe} + \text{HI} \xrightarrow[\text{AgNO3}]{} \text{R-OH} + \text{MeI} \longrightarrow \text{AgI}$$

CHEMICAL METHODS Contd……..

- ***v) Methylenedioxy group (-O-CH$_2$-O-)***

  On heating with hydrochloric or sulfuric acid yields formaldehyde.
- ***vi) Amide, lactam, ester, lactone groups***

  Be detected and estimated through acid or alkaline hydrolysis.
- ***vii) Epoxide and ether linkage***

  Be cleaved by the addition of hydrogen bromide or hydroiodic acid.
- ***viii) Tertiary methyl group***

  Estimated by Kuhn-Roth oxidation ($K_2Cr_2O_7/H_2SO_4$) to acetic acid, which is distilled off and titrated against standard base.

  $$\text{-C-Me} + K_2Cr_2O_7/H_2SO_4 \rightarrow CH_3COOH$$
- ***ix) Nature of nitrogen***

  The acetylation or benzoylation can distinguish tertiary amine from secondary amine, the former being inert whereas the latter gives acetate or benzoate derivative***.***

  This distinction can also be done by treatment with HNO_2 or methyl iodide or oxidation with 30% hydrogen peroxide.

CHEMICAL METHODS Contd………..

- ***ix) Nature of nitrogen***

  The presence of N-methyl group is often detected by distillation of amine with sodalime or estimated by the treatment with hydroiodic acid at 150-300 and conversion of methyl iodide produced to silver iodide as mentioned for estimation of methoxy groups.
- ***Secondary amine***
- $>N\text{-}H + HNO_2 \rightarrow >N\text{-}NO + H_2O$
- $>NH + CH_3I \rightarrow >N\text{-}Me + HI$
- ***Tertiary amine***
- $>N + CH_3I \rightarrow >N^+ \text{-}Me\ I^-$
- $>N + H_2O_2 \rightarrow >N^+\text{-}O^- + H_2O$
- ***N-Methyl group***
- $>N\text{-}Me + CaO \rightarrow CH_3NH_2$
- $>N\text{-}Me + HI \rightarrow N\text{-}H + MeI \xrightarrow{AgNO3} AgI$

DEGRADATION OF ALKALOIDS

The following methods are used to find out structural fragments of alkaloid molecules:

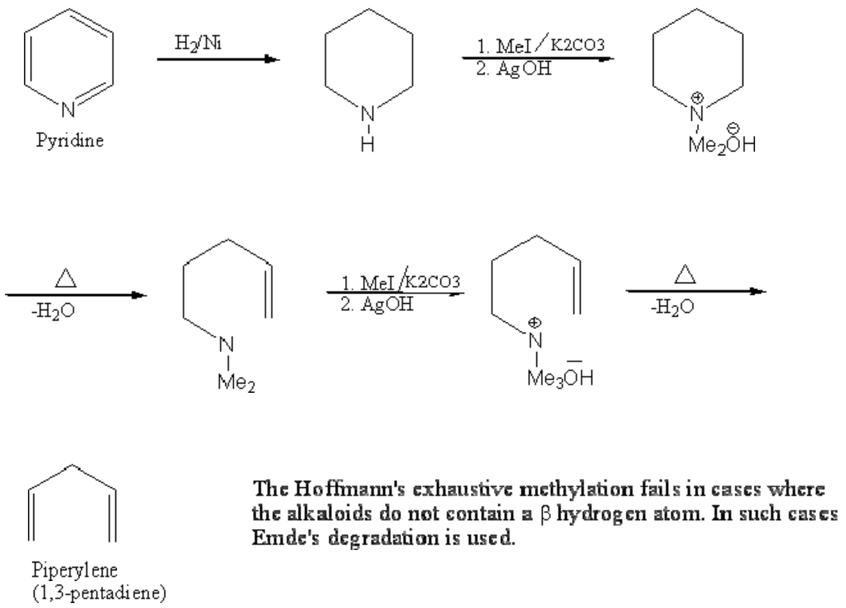
- ☐ i. **Hofmann exhaustive methylation**.
- ☐ **ii. Emde's degradation**.
- ☐ iii. von Braun's method.
- ☐ iv. Hydrolysis.
- ☐ v. Alkali fusion.
- ☐ vi. Dehydrogenation.

☐ DEGRADATION OF ALKALOIDS

Now we discuss the mainly used methods of Hofmann degradation and Emde's degradation.

i. Hofmann exhaustive methylation

- It consists in opening of the heterocyclic ring with elimination of ‘N’ to give a carbon fraction.
- In this method, the alkaloid is first hydrogenated (if it is unsaturated) and then converted into quaternary methyl ammonium hydroxide, which on heating loses a molecule of water.
- The hydroxyl group is eliminated from tetra methyl ammonium hydroxide and the hydrogen atom from the ⍰ position with respect to the ‘N’ atom resulting in ring opening at the “N’ atom on the same side from which the ⍰ hydrogen was eliminated.
- The process is repeated on the formed product till the ‘N’ is eliminated & an unsaturated hydrocarbon is left which isomerizes to a conjugated diene



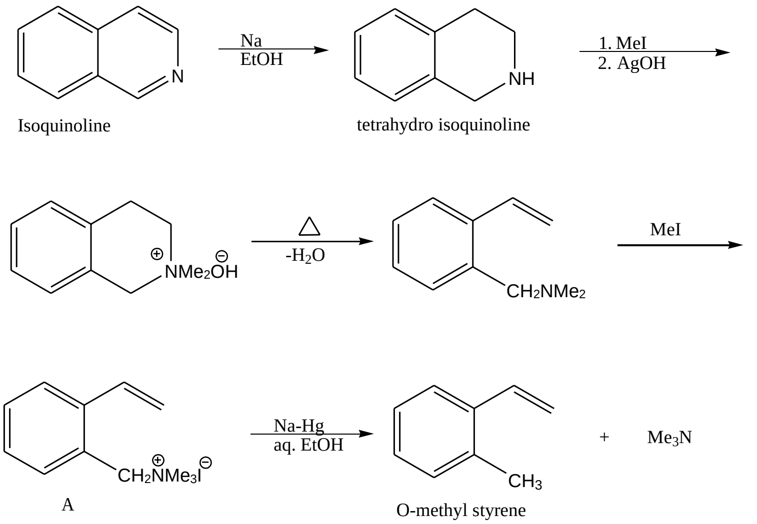
The Hoffmann's exhaustive methylation fails in cases where the alkaloids do not contain a β hydrogen atom. In such cases Emde's degradation is used.

☐ DEGRADATION OF ALKALOIDS

- ***ii. Emde's degradation***

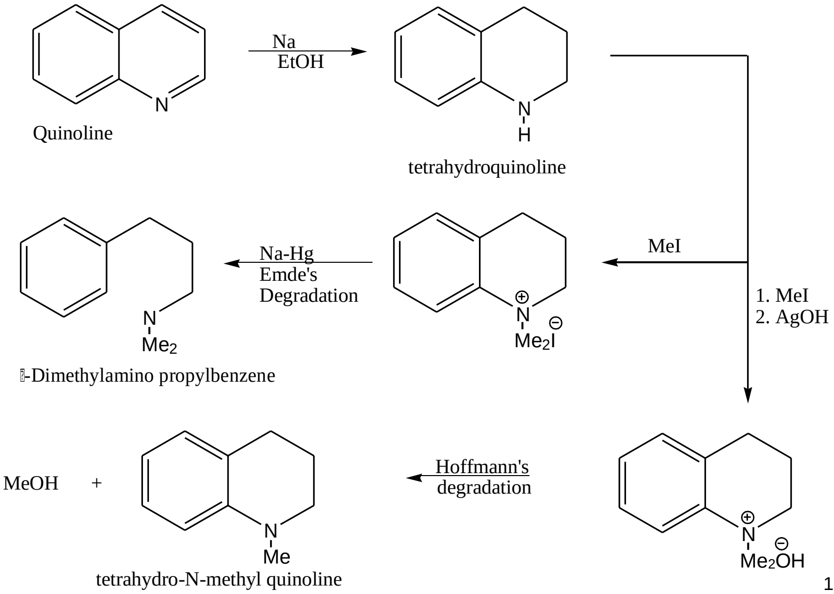
The alkaloid is converted to quaternary ammonium salt by refluxing with alkyl halide and the resulting salt is subjected to reductive cleavage by the treatment with sodium amalgam in alkanol or sodium in liquid ammonia or by catalytic hydrogenation.

Tetrahydroquinoline and tetrahydroisoquinoline quarternary salts undergo Emde's degradation.



The intermediate 'A' can not be degraded by Hoffmann's method as it has no hydrogen but it can be degraded by Emde's method.

In case of tetrahydroquinoline, though it contains a hydrogen, the Hoffmann's degradation fails. The ring may however be opened by Emde's degradation-

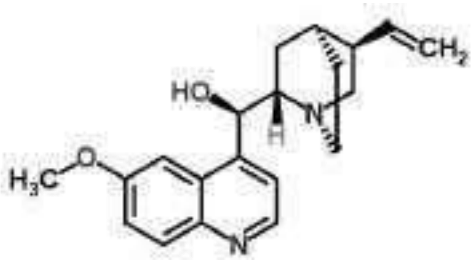


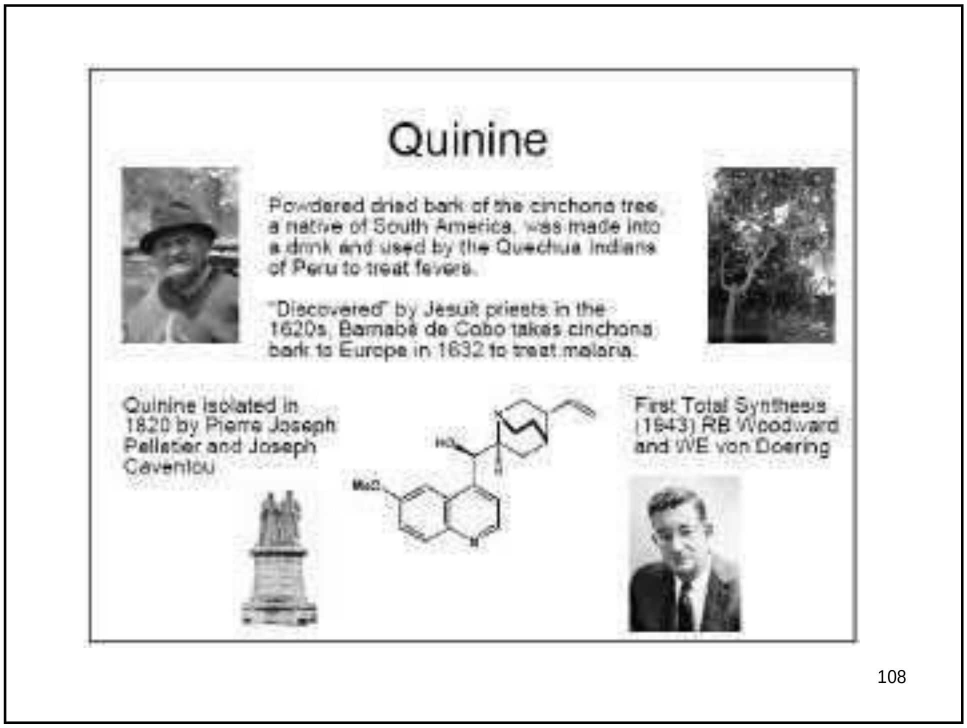
☐PHYSICAL METHODS

Recently physical methods are used, in conjunction with chemical reactions to elucidate structure of alkaloids and it is possible to determine a structure in a matter of days given a few milligrams(or less) of a pure compound.

- Infrared spectrum ： Gives information about many functional groups
- Ultraviolet spectra ： Used to indicate the nature of unsaturation or aromatic rings
- NMR spectroscopy ： More versatile for detecting many function groups, the nature of protons, carbons, heterocyclic rings etc
- Mass spectra ： The fragmentation gives the information about molecular weight and degradation of the skeleton.
- Single crystal X-ray analysis :Offers means for determining or confirming stereochemistry as well as distinguishing between alternate structures that appear to fit well for a particular alkaloid.
- optical rotatory dispersion or circular dichroism: Further support

QUININE





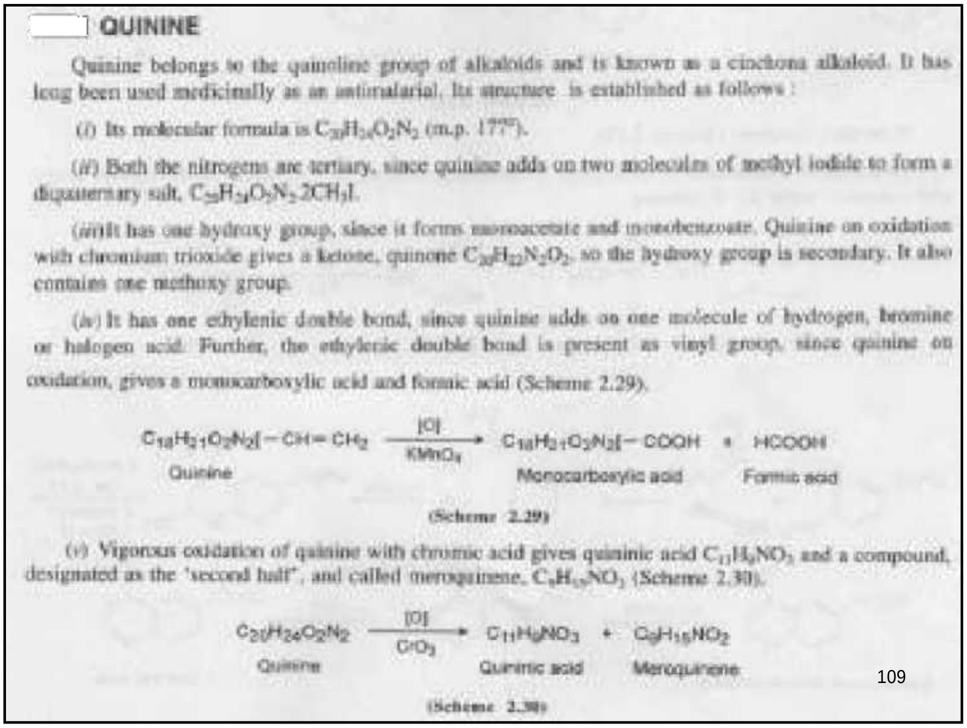
Quinine

Powdered dried bark of the cinchona tree, a native of South America, was made into a drink and used by the Quechua Indians of Peru to treat fevers.

"Discovered" by Jesuit priests in the 1620s, Barnabé de Cobo takes cinchona bark to Europe in 1632 to treat malaria.

Quinine isolated in 1820 by Pierre Joseph Pelletier and Joseph Caventou

First Total Synthesis (1943) RB Woodward and WE von Doering



QUININE

Quinine belongs to the quinoline group of alkaloids and is known as a cinchona alkaloid. It has long been used medicinally as an antimalarial. Its structure is established as follows :

(*i*) Its molecular formula is $C_{20}H_{24}O_2N_2$ (m.p. 177°).

(*ii*) Both the nitrogens are tertiary, since quinine adds on two molecules of methyl iodide to form a diquaternary salt, $C_{20}H_{24}O_2N_2.2CH_3I$.

(*iii*) It has one hydroxy group, since it forms monoacetate and monobenzoate. Quinine on oxidation with chromium trioxide gives a ketone, quinone $C_{20}H_{22}N_2O_2$, so the hydroxy group is secondary. It also contains one methoxy group.

(*iv*) It has one ethylenic double bond, since quinine adds on one molecule of hydrogen, bromine or halogen acid. Further, the ethylenic double bond is present as vinyl group, since quinine on oxidation, gives a monocarboxylic acid and formic acid (Scheme 2.29).

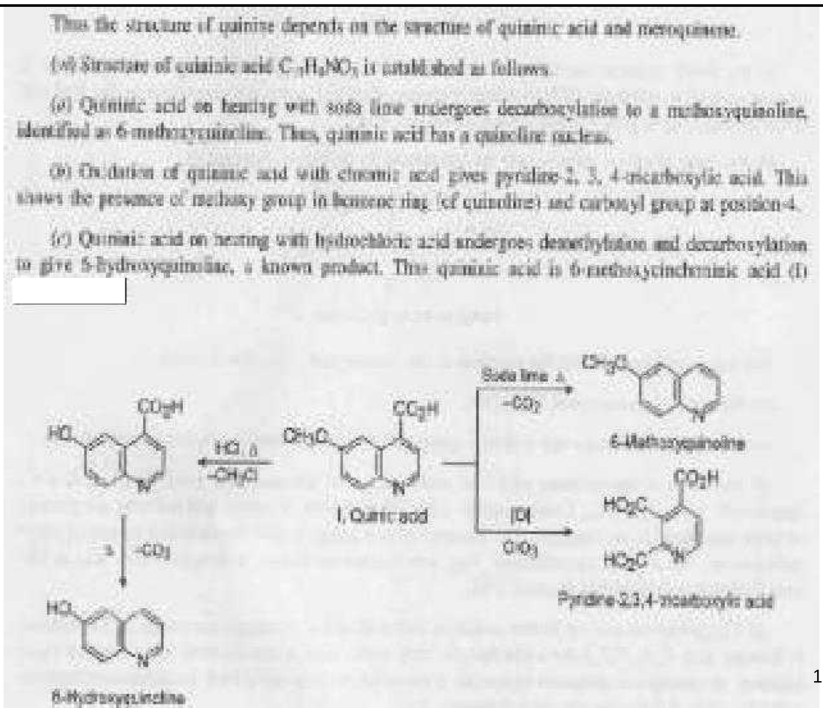
$$\underset{\text{Quinine}}{C_{18}H_{21}O_2N_2[-CH=CH_2} \xrightarrow[KMnO_4]{[O]} \underset{\text{Monocarboxylic acid}}{C_{18}H_{21}O_2N_2[-COOH} + \underset{\text{Formic acid}}{HCOOH}$$

(Scheme 2.29)

(*v*) Vigorous oxidation of quinine with chromic acid gives quininic acid $C_{11}H_9NO_3$ and a compound, designated as the 'second half', and called meroquinene, $C_9H_{15}NO_2$ (Scheme 2.30).

$$\underset{\text{Quinine}}{C_{20}H_{24}O_2N_2} \xrightarrow[CrO_3]{[O]} \underset{\text{Quininic acid}}{C_{11}H_9NO_3} + \underset{\text{Meroquinene}}{C_9H_{15}NO_2}$$

(Scheme 2.30)



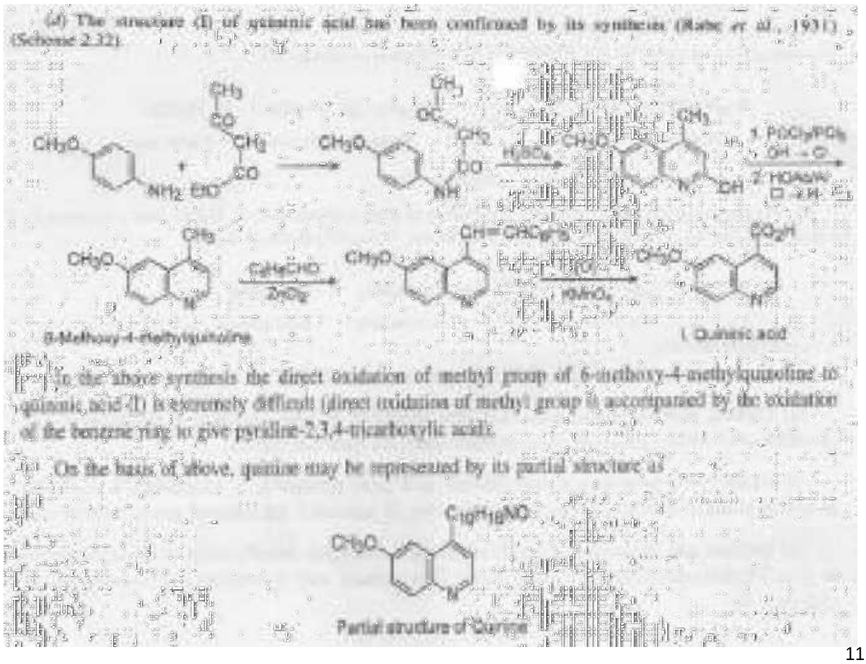
Thus the structure of quinine depends on the structure of quininic acid and meroquinene.

(vi) Structure of quininic acid $C_{11}H_9NO_3$ is established as follows.

(a) Quininic acid on heating with soda lime undergoes decarboxylation to a methoxyquinoline, identified as 6-methoxyquinoline. Thus, quininic acid has a quinoline nucleus.

(b) Oxidation of quininic acid with chromic acid gives pyridine-2, 3, 4-tricarboxylic acid. This shows the presence of methoxy group in benzene ring (of quinoline) and carboxyl group at position-4.

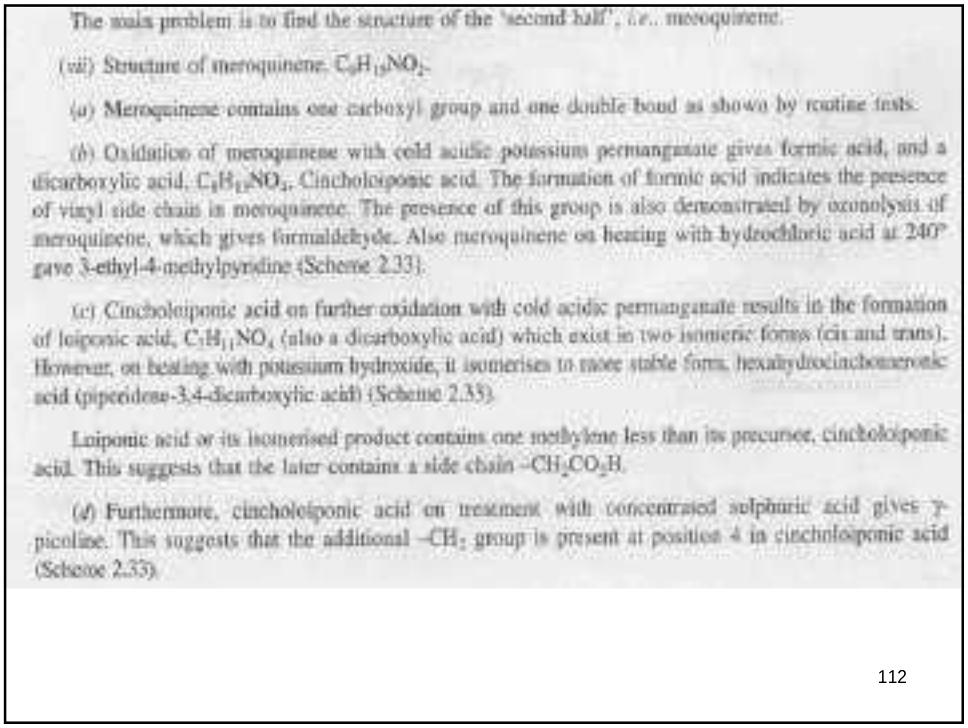
(c) Quininic acid on heating with hydrochloric acid undergoes demethylation and decarboxylation to give 6-hydroxyquinoline, a known product. Thus quininic acid is 6-methoxycinchoninic acid (I)



(d) The structure (I) of quininic acid has been confirmed by its synthesis (Rabe et al., 1931) (Scheme 2.32).

In the above synthesis the direct oxidation of methyl group of 6-methoxy-4-methylquinoline to quininic acid (I) is extremely difficult (direct oxidation of methyl group is accompanied by the oxidation of the benzene ring to give pyridine-2,3,4-tricarboxylic acid).

On the basis of above, quinine may be represented by its partial structure as



The main problem is to find the structure of the 'second half', *i.e.*, meroquinene.

(*vii*) Structure of meroquinene, $C_9H_{15}NO_2$.

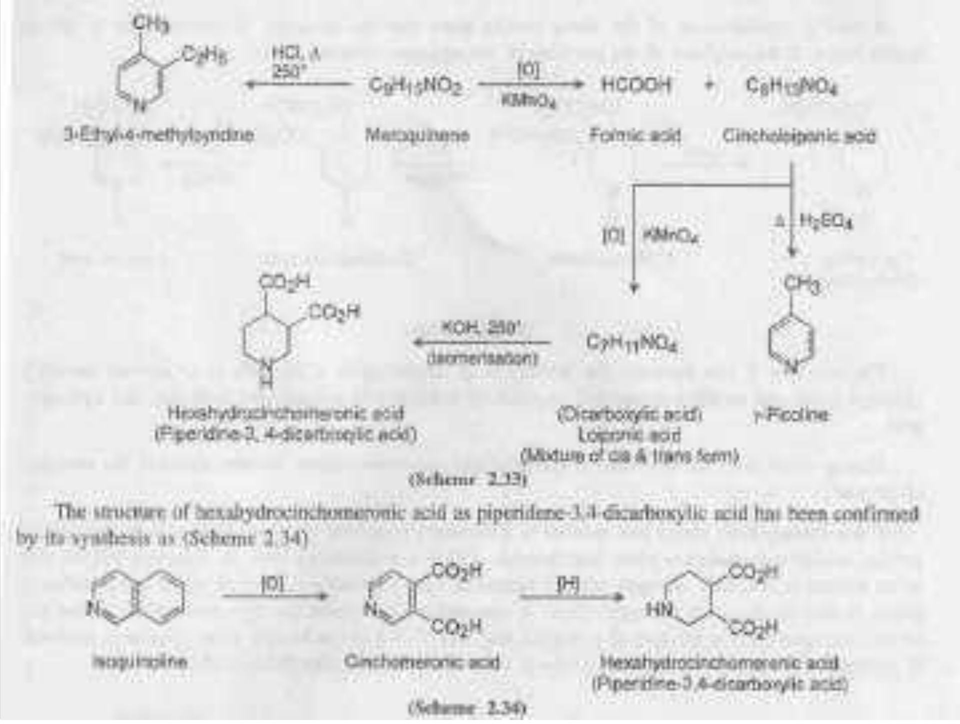
(*a*) Meroquinene contains one carboxyl group and one double bond as shown by routine tests.

(*b*) Oxidation of meroquinene with cold acidic potassium permanganate gives formic acid, and a dicarboxylic acid, $C_8H_{13}NO_4$, Cincholoiponic acid. The formation of formic acid indicates the presence of vinyl side chain in meroquinene. The presence of this group is also demonstrated by ozonolysis of meroquinene, which gives formaldehyde. Also meroquinene on heating with hydrochloric acid at 240° gave 3-ethyl-4-methylpyridine (Scheme 2.33).

(*c*) Cincholoiponic acid on further oxidation with cold acidic permanganate results in the formation of loiponic acid, $C_7H_{11}NO_4$ (also a dicarboxylic acid) which exist in two isomeric forms (cis and trans). However, on heating with potassium hydroxide, it isomerises to more stable form, hexahydrocinchomeronic acid (piperidene-3,4-dicarboxylic acid) (Scheme 2.33).

Loiponic acid or its isomerised product contains one methylene less than its precursor, cincholoiponic acid. This suggests that the later contains a side chain $-CH_2CO_2H$.

(*d*) Furthermore, cincholoiponic acid on treatment with concentrated sulphuric acid gives γ-picoline. This suggests that the additional $-CH_2$ group is present at position 4 in cinchloiponic acid (Scheme 2.33).

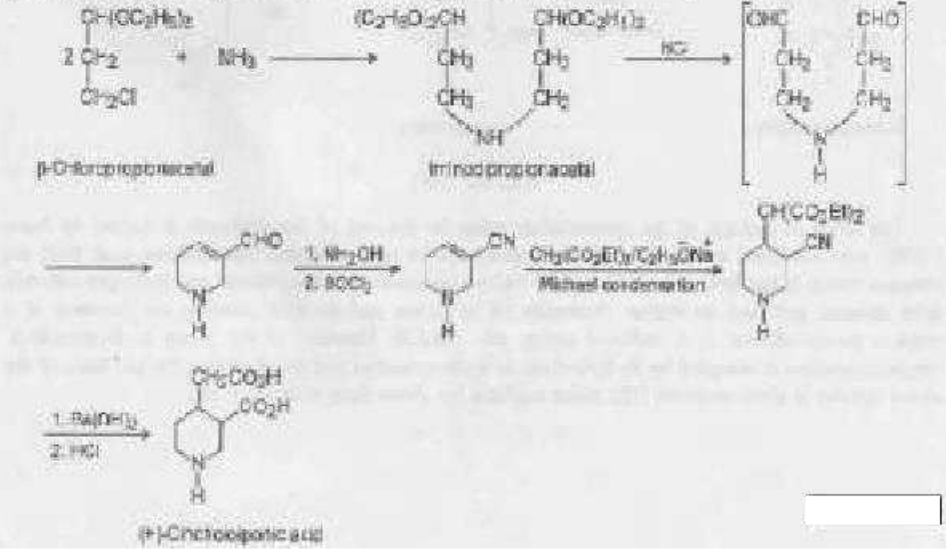


(Scheme 2.33)

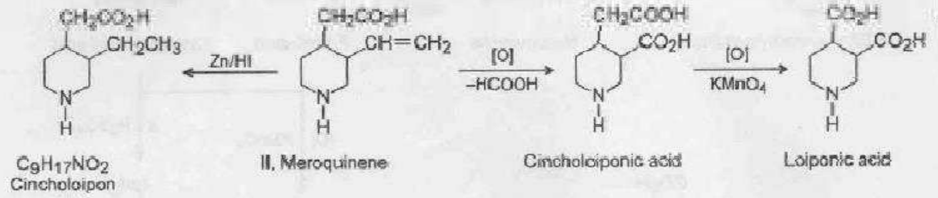
The structure of hexahydrocinchomeronic acid as piperidene-3,4-dicarboxylic acid has been confirmed by its synthesis as (Scheme 2.34)

(Scheme 2.34)

On the basis of the above cincholoiponic acid is represented as shown below. This structure has been confirmed by its synthesis (Wohl and Losanitsch; 1970)



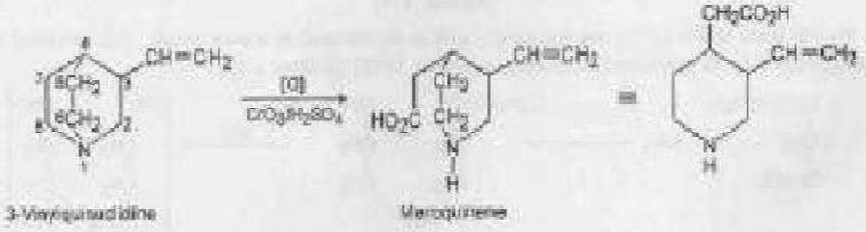
A careful consideration of the above results show that the structure of meroquinene is (II) as shown below. It also explains all the reactions of meroquinene



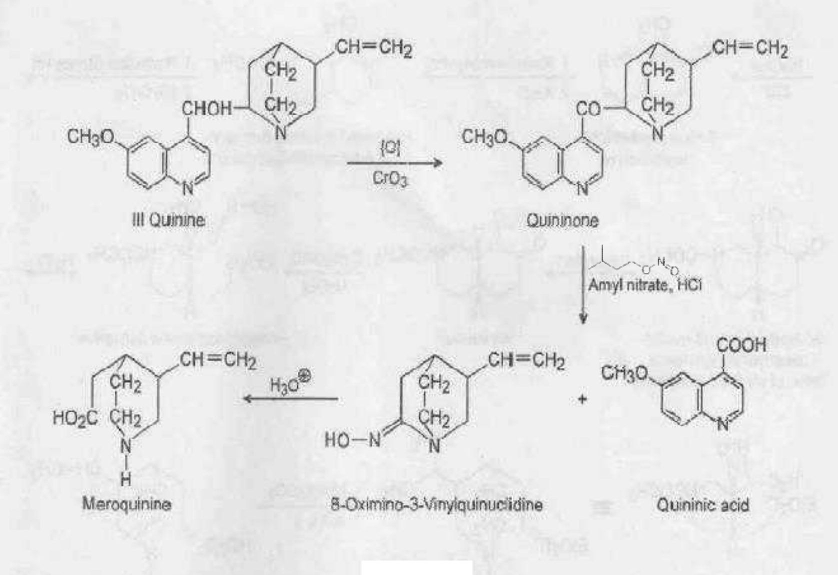
The structure II also explains the formation of cincholoipon, $C_9H_{17}NO_2$ (a compound having a carboxyl group and an ethyl group) and obtained by reduction of meroquinene with zinc and hydriodic acid.

Having established the structures of quininic acid and meroquinene, we now establish the structure of quinine.

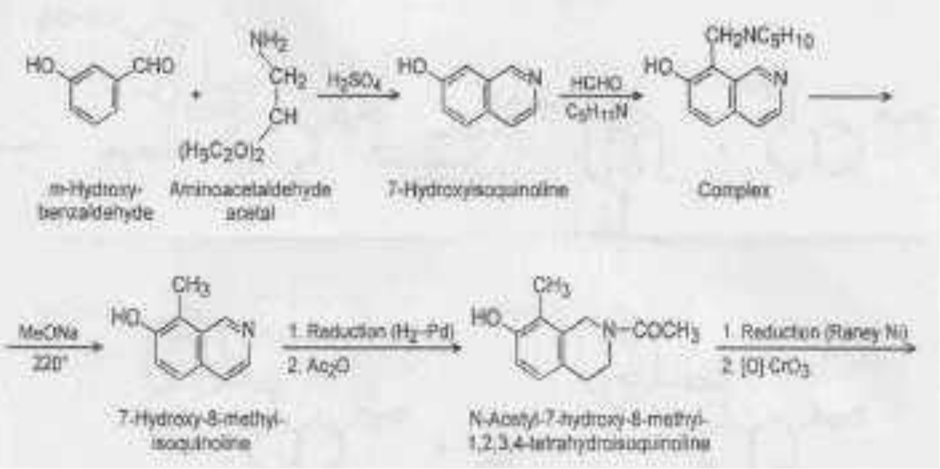
It has already been stated that quinine is a ditertiary base (and does not have a N-methyl group) and on oxidative degradation gives meroquinene, which is a secondary base. It, therefore follows that in its formation a tertiary nitrogen atom is converted into a secondary nitrogen atom, and a carboxyl group is also produced at the same time. A reasonable explanation for this observation is that the tertiary nitrogen atom is the part of a bridged ring, one C–N bond is broken when quinine is oxidised. A junction of this type is shown in a synthetic compound, 3-vinylquinuclidine

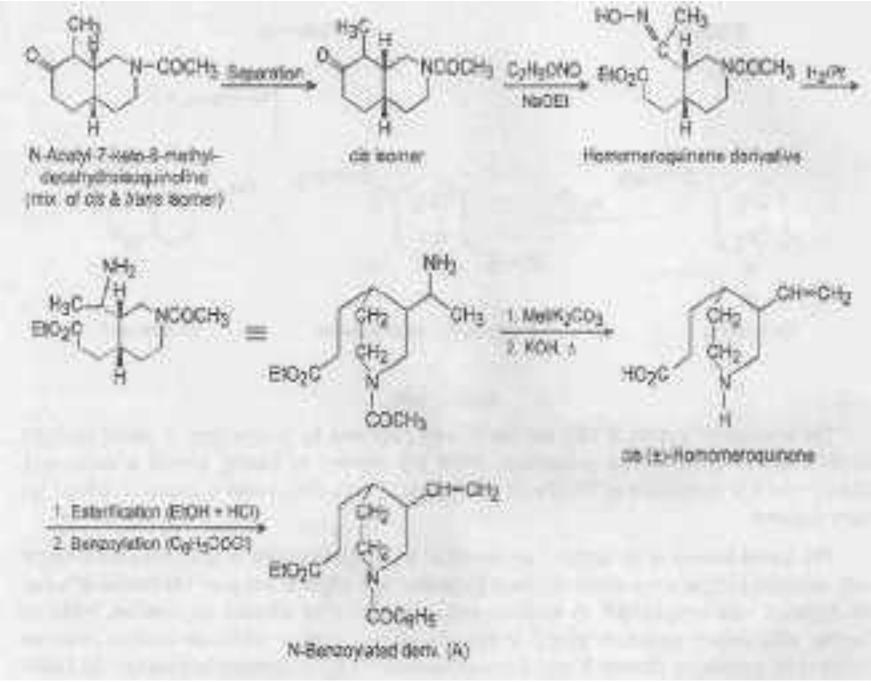


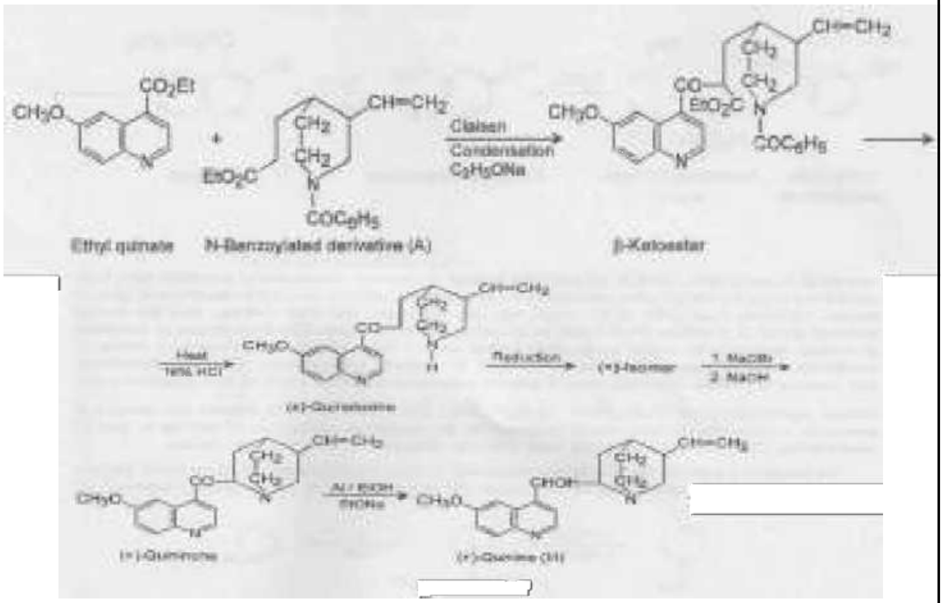
The point of linkage of the quinuclidine group to the rest of the molecule is settled by Rabe (1908), who converted quinine into a ketone, quininone by mild oxidation with chromic acid. Both the nitrogen atoms in this ketone are still tertiary and on treatment with amyl nitrite and hydrogen chloride gave quininic acid and an oxime. Formation of an oxime and an acid indicates the presence of a methine group adjacent to a carbonyl group, viz. –COCH. Structure of the oxime as 8-oximino-3-vinylquinuclidine is assigned by its hydrolysis to hydroxylamine and meroquinene. On the basis of the above quinine is given structure (III) which explains the above facts

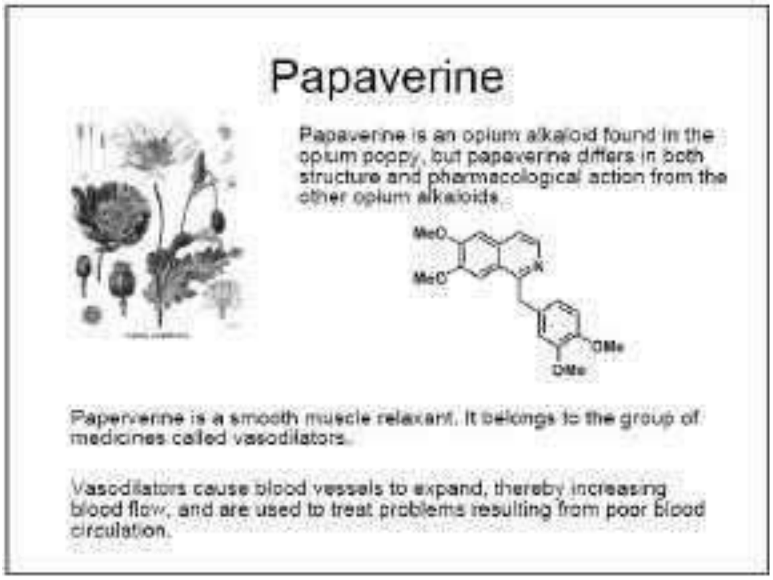


The structure of quinine as (III) has finally been confirmed by its synthesis. A partial synthesis (Rabe *et al.*, 1918) starts from quinotoxine, which was obtained by heating quinine in acetic acid. Quinotoxine was synthesised by Woodward and Doering (1944). Thus a total synthesis of quinine has been achieved.


m-Hydroxy-benzaldehyde
Aminoacetaldehyde acetal
H_2SO_4
7-Hydroxyisoquinoline
HCHO
$C_5H_{11}N$
Complex
MeONa
220°
7-Hydroxy-8-methyl-isoquinoline
1. Reduction (H_2-Pd)
2. Ac_2O
N-Acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline
1. Reduction (Raney Ni)
2. [O] CrO_3


N-Acetyl-7-keto-8-methyl-decahydroisoquinoline (mix. of cis & trans isomer)
Separation
cis isomer
C_2H_5ONO
NaOEt
Homomeroquinene derivative
H_2/Pt
1. MeI/K_2CO_3
2. KOH, Δ
cis (±)-Homomeroquinene
1. Esterification (EtOH + HCl)
2. Benzoylation (C_6H_5COCl)
N-Benzoylated deriv. (A)





Papaverine

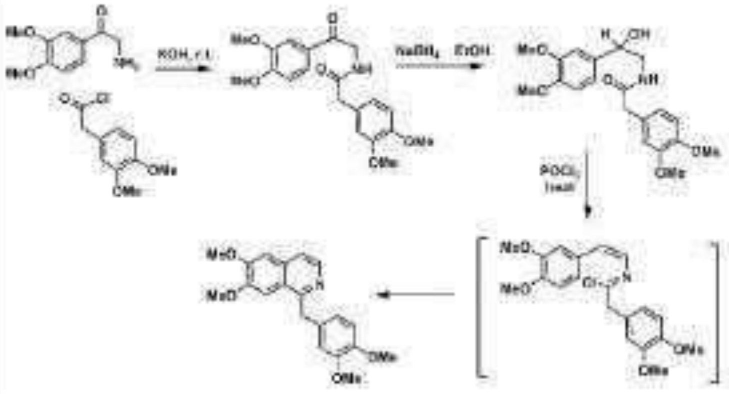
Papaverine is an opium alkaloid found in the opium poppy, but papaverine differs in both structure and pharmacological action from the other opium alkaloids.

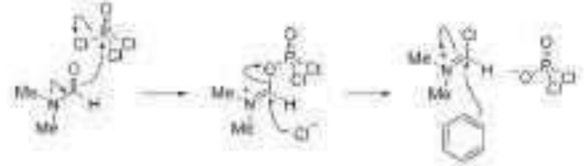
Paperverine is a smooth muscle relaxant. It belongs to the group of medicines called vasodilators.

Vasodilators cause blood vessels to expand, thereby increasing blood flow, and are used to treat problems resulting from poor blood circulation.

Synthesis of Papaverine

using the Pictet Gams modification of the Bischler-Napieralski method





Vilsmeir Haack Formylation

MORPHINE

Synthesis of Morphine Alkaloids and Derivatives

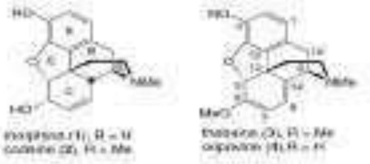


Fig. 1 Morphine and congeners

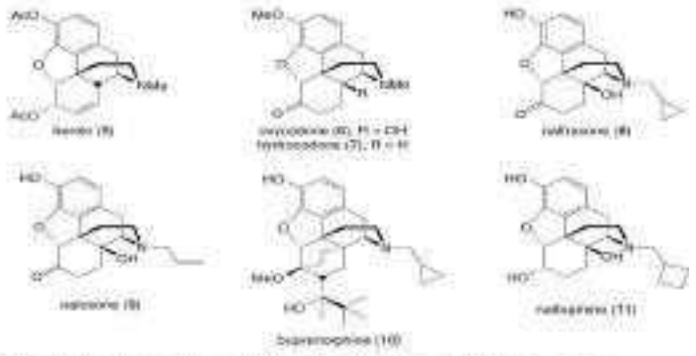
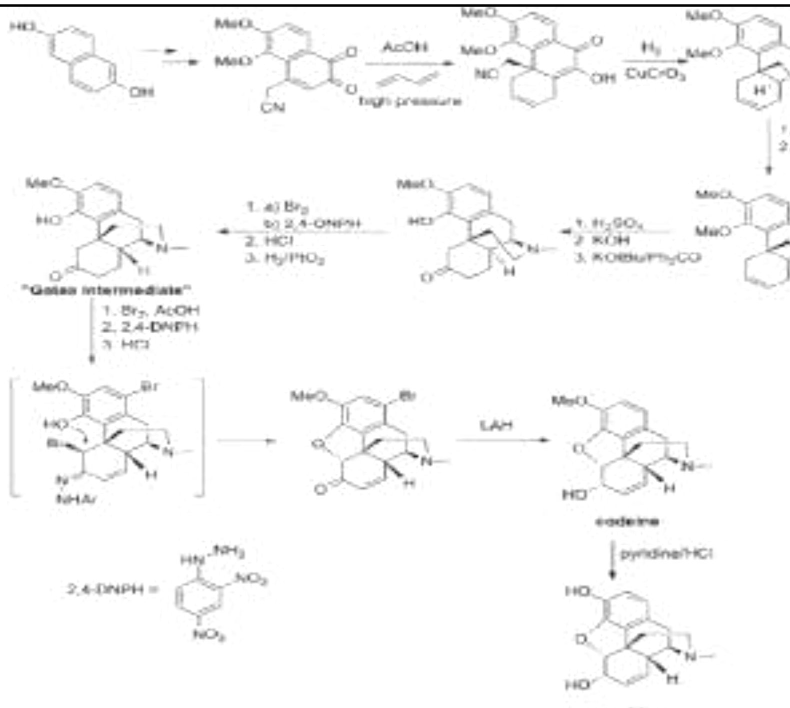
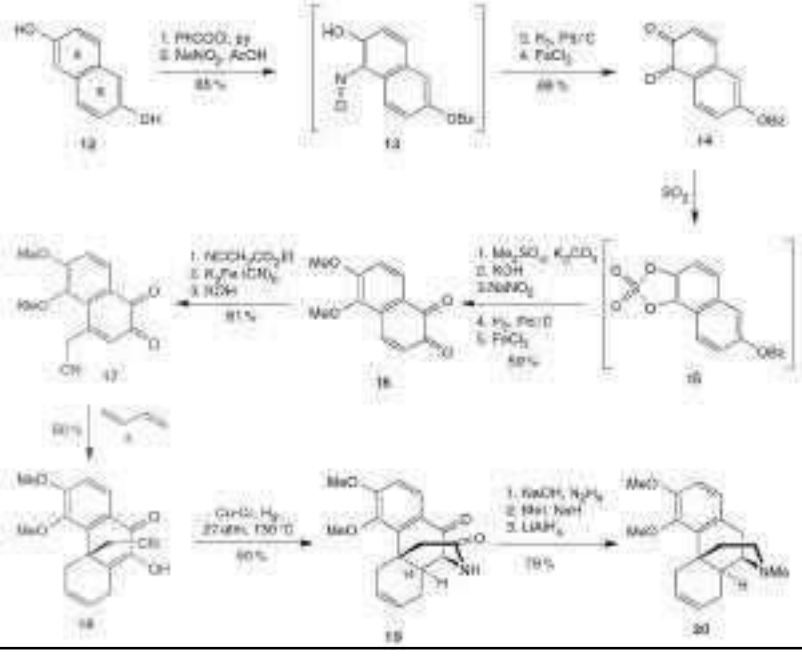


Fig. 2 Opiate-derived agonists and antagonists for legal and illicit (i.e., heroin) use



OR

Gates Synthesis (1952)



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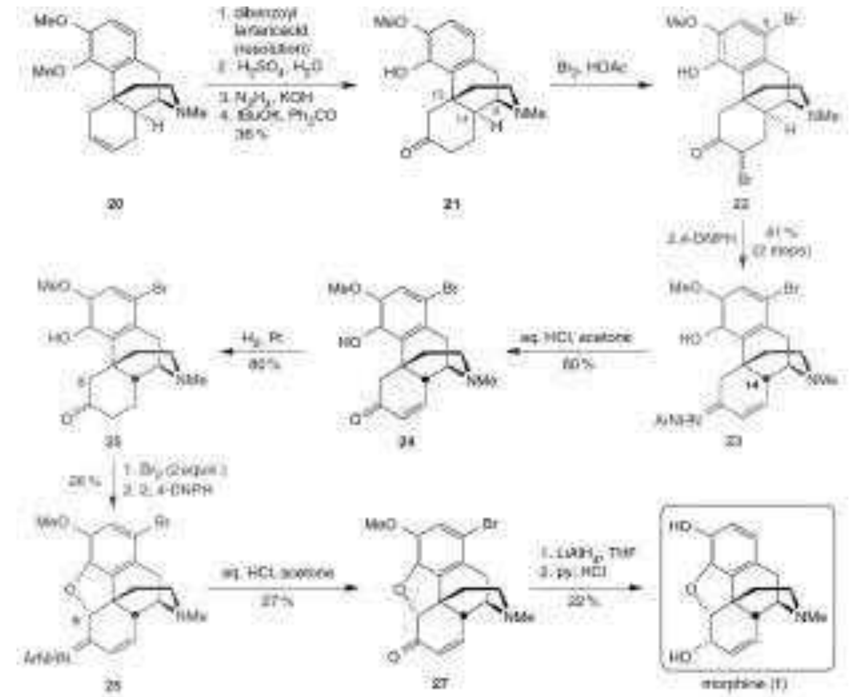
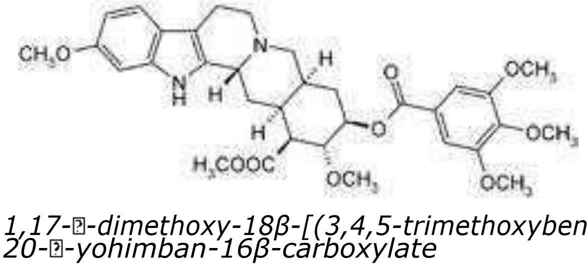


SYNTHESIS OF RESERPINE (1958)

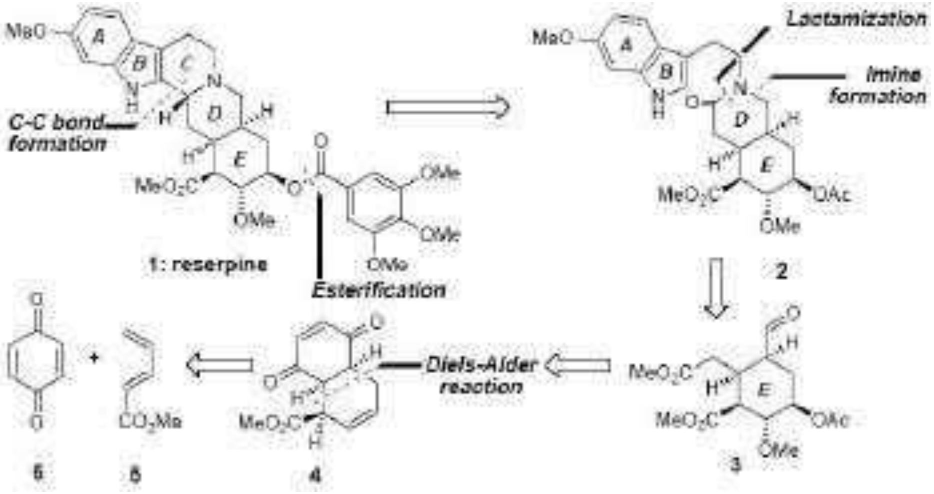
☐Reserpine, a constituent of the Indian snakeroot *Rauwolfia serpentina (Sarpgandha)*, is an alkaloid with curative properties for the treatment of hypertension, as well as nervous and mental disorders.

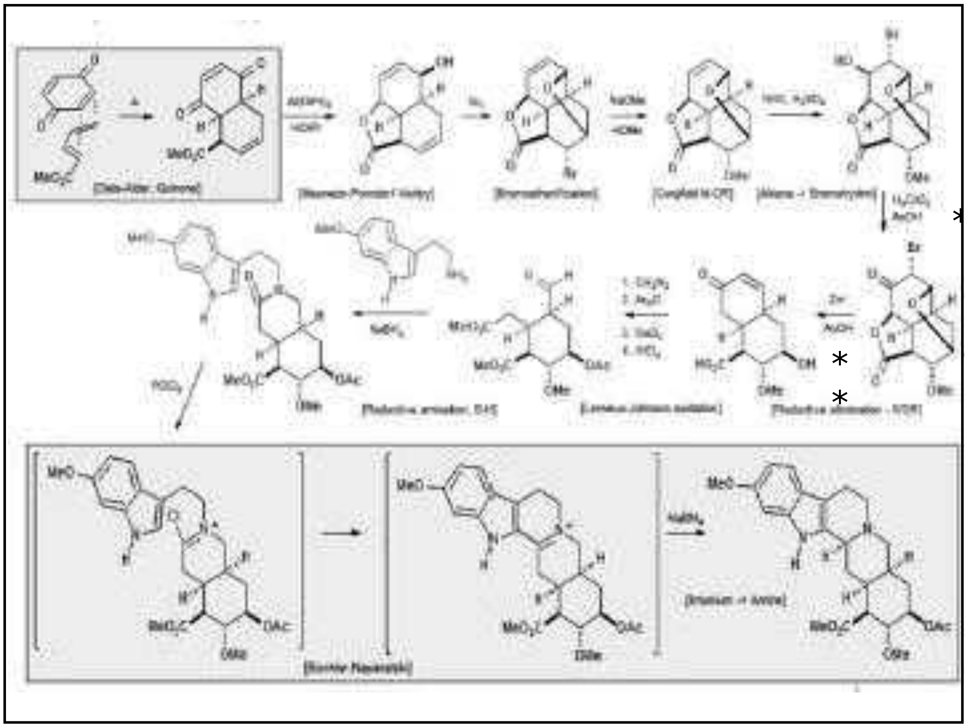
☐Reserpine was isolated in 1952 and yielded to structural elucidation in 1955 (Schlittler and co-workers) and to total synthesis in 1958 (Woodward et al.).

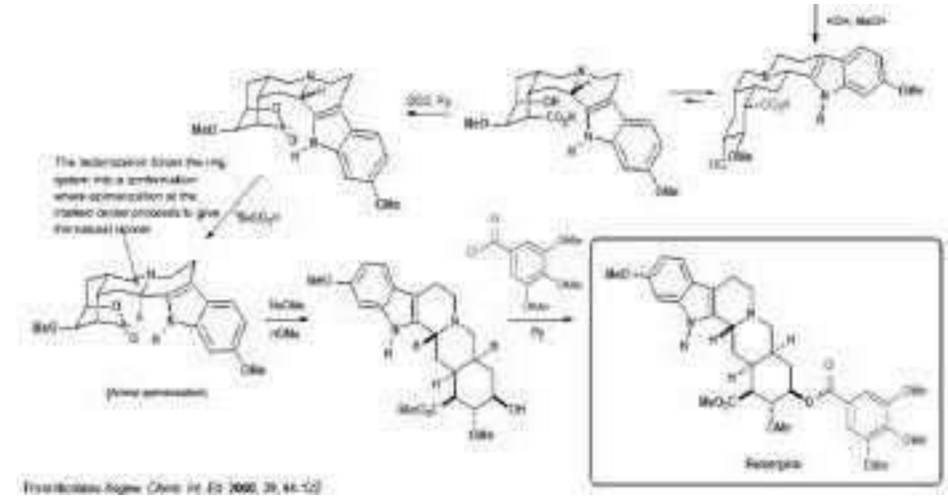


methyl-11,17-⍰-dimethoxy-18β-[(3,4,5-trimethoxybenzoyl) oxy]-3β,20-⍰-yohimban-16β-carboxylate

- Reserpine consisted of three parts: the indole (the AB unit), the trimethoxybenzene system, and the highly substituted E-ring cyclohexane.







The lactonization forces the ring system into a conformation where epimerization at the indicated center proceeds to give the natural isomer

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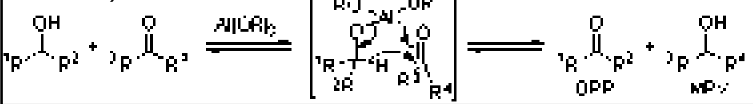
MPV (Meerwein Pondorff Valery Reduction) vs OPP (Oppenauer oxidation)



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