

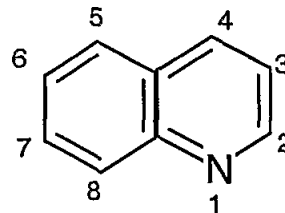


Pharmacognesy III

From textbooks: (*Pharmacognesy and Pharmacobiotechnology, 9th ed, Robbers JE, Speedie MK, Tyler VE.*)

Quinoline Alkaloids

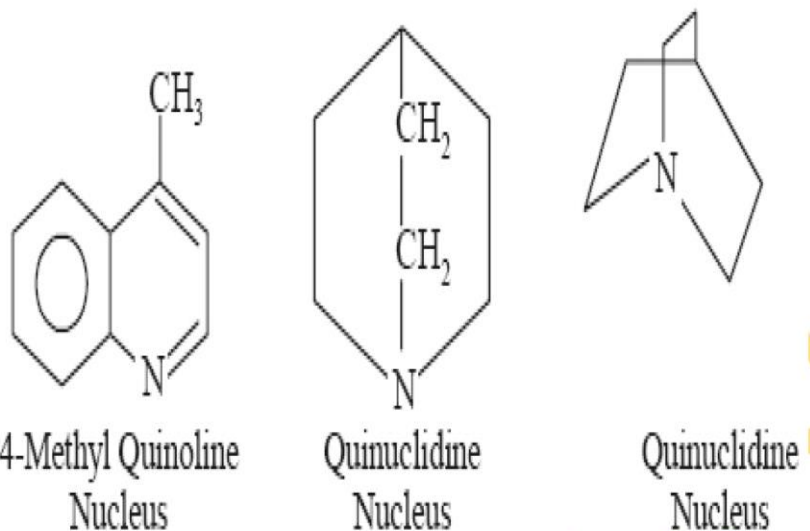
- In general, the alkaloids containing essentially the 'quinoline' nucleus include a series of alkaloids obtained exclusively from cinchona bark.
- The major members of this particular group are, namely:
 - quinine
 - quinidine
 - cinchonine
 - cinchonidine.



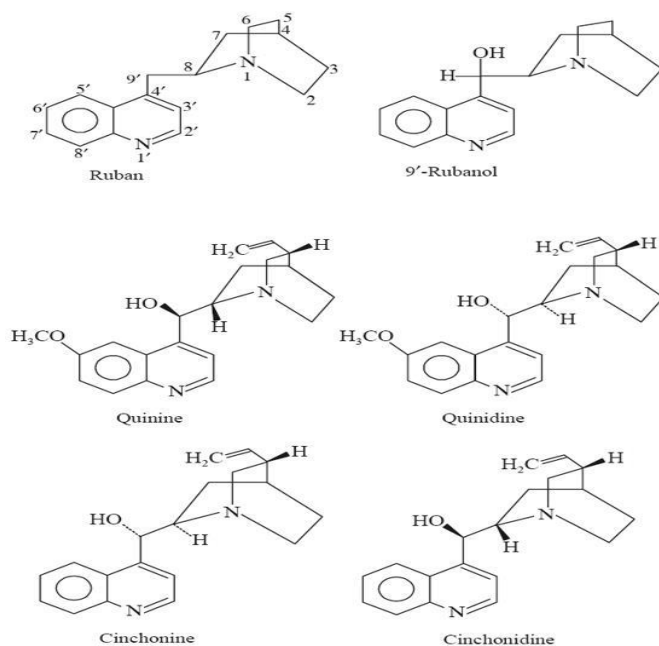
- More than twenty five alkaloids have been isolated and characterized either from the **Yellow Cinchona** i.e. *Cinchona calisaya* and *Cinchona ledgeriana*, or from the **Red Cinchona** i.e. *Cinchona succirubra* (F. *Rubiaceae*).

Basic Structures of Cinchona Alkaloids:

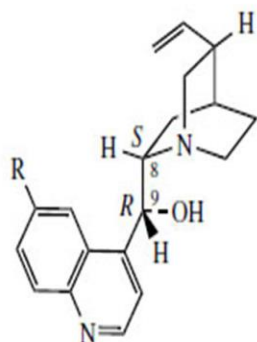
- Cinchona alkaloids usually possess two ring : quinolone (which consist from benzene ring + pyridine) and bicyclic quinuclidine.
- Cinchona possess the basic skeleton of 9'-rubanol that is derived from the parent compound known as ruban.
- Thus, ruban is obtained from the combination of two distinct heterocyclic nuclei, namely:
 - (a) 4-methyl quinoline nucleus.
 - (b) quinuclidine nucleus.



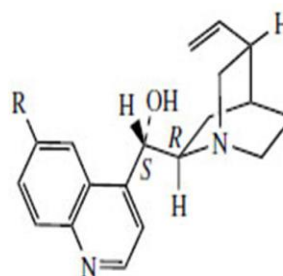
- However, this particular nomenclature was suggested by Rabe so as to simplify the naming of such compounds and also to signify its origin from the natural order *Rubiaceae*.



- Quinine & quinidine are stereoisomers
- Cinchonine & cinchonidine are stereoisomers
- For cinchonine & quinidine C8= R , C9 = S
- For cinchonidine & quinine C8 = S , C9 = R
- **Stereoisomers are isomeric molecules that have the same molecular formula and sequence of bonded atoms (constitution), but that differ *only* in the three-dimensional orientations of their atoms in space.**



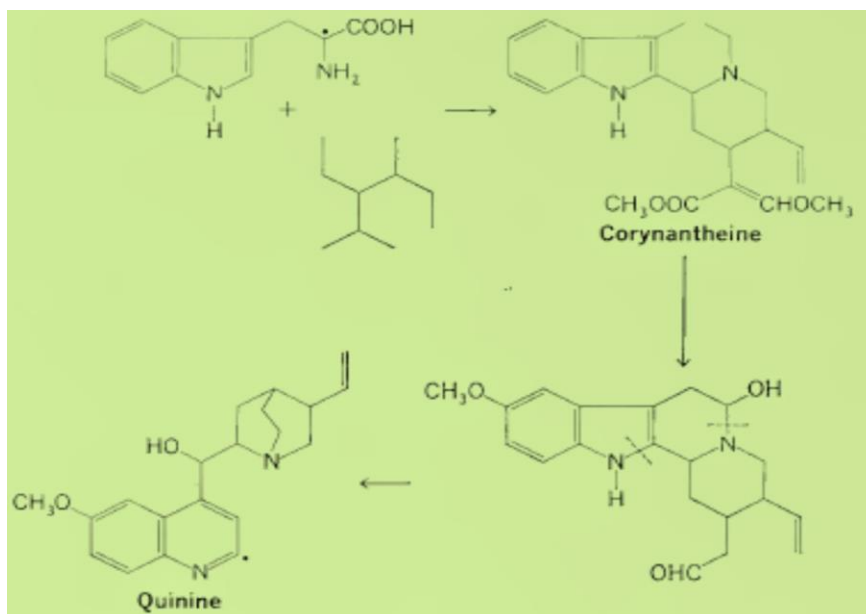
R = OMe, (-)-quinine
R = H, (-)-cinchonidine



R = OMe, (+)-quinidine
R = H, (+)-cinchonine

Biosynthetic pathway

- Studies with labeled geraniol and tryptophan indicate that quinine is metabolically derived from the monoterpenoid-tryptophan pathway.



Identification Tests of Quinine

1- Fluorescence Test: Quinine gives a distinct and strong blue fluorescence when treated with an *oxygenated acid*, such as: acetic acid, sulphuric acid.

- This test is very marked and pronounced even to a few mg concentration of quinine.
- Note: The hydrochloride and hydroiodide salts of quinine do not respond to this fluorescence test.

Identification Tests of Quinine

2- Thalleioquin Test: Add to 2-3 ml of a weakly acidic solution of a quinine salt a few drops of bromine-water followed by 0.5 ml of strong ammonia solution, a distinct and characteristic emerald green color is produced.

Identification Tests of Quinine

- The colored product is termed as **thalleioquin**, the chemical composition of which is yet to be established.
- This test is so sensitive that quinine may be detected to a concentration as low as 0.005%.
- **Notes: Quinidine gives also a positive response to this test; but cinchonine and cinchonidine give a negative test.**

Uses

1- Cinchona & its alkaloids have been used in the treatment of malaria fever for many years.

Quinine sulfate continues to be used for malaria in many parts of the world (it poison the protozoa), as tonic, analgesic, in the treatment of cold.

2- Quinidine is used to treat various cardiac arrhythmias e.g. arterial & ventricular tachycardia, atria fibrillation & ventricular contraction.

Quinidine is found as salts (sulfate & gluconate). It depresses myocardial excitability, conduction velocity & contractility.

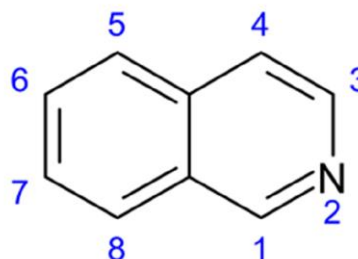
- **Totaquine** : It is a mixture of total alkaloids, containing not less than 7% & not more than 12% of anhydrous quinine.
- It should contain 70-80% of total alkaloids.
- It is used as anti malarial & for cold but it cannot be used as cardiac depressant. Usual dose 600mg.

Cinchonism or quinism

- Treatment with cinchona products result in symptoms of mild cinchonism (which may occur from standard therapeutic doses of quinine).
 - These symptoms include flushed and sweaty skin, ringing of the ears (tinnitus), blurred vision, impaired hearing, confusion, reversible high-frequency hearing loss, head ache, abdominal pain, rashes, dysphoria, nausea, vomiting and diarrhea.
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- Ringing in the ears is a symptom of toxicity.
 - When these symptoms are produced as the result of continuous use of cinchona or of quinine the condition has been called **cinchonism**.

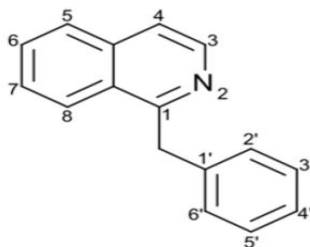
Isoquinoline alkaloids

- Isoquinoline is a heterocyclic aromatic organic compound.
- It is a structural isomer of quinoline.
- Isoquinoline and quinoline are benzo pyridines derivatives , which are composed of benzene ring fused to a pyridine ring.



Benzylisoquinoline or BIQ alkaloids

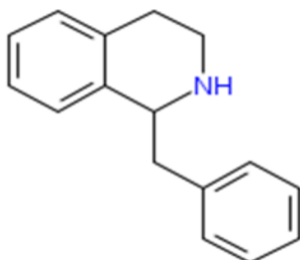
- About 4000 BIQ alkaloids are known.
- There are many important structural types.
- Many BIQ alkaloids are important in medicine. Others **are highly toxic**. Some are used as arrow poisons.



Tetrahydrobenzylisoquinoline or THBIQ alkaloids

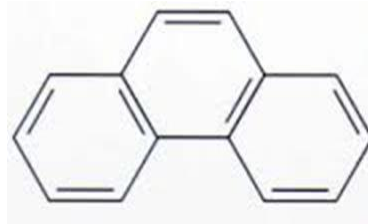
- The simplest alkaloids of this series are those in which the nitrogen-containing ring is completely saturated.
- These alkaloids are found in almost all families that contain BIQ alkaloids.
- About 100 compounds of this type are known.

- The most important compound from a biosynthetic point of view is (+)-reticuline.



Phenanthrene alkaloids

They are mainly found in papaveraceae family as morphine & related alkaloids.

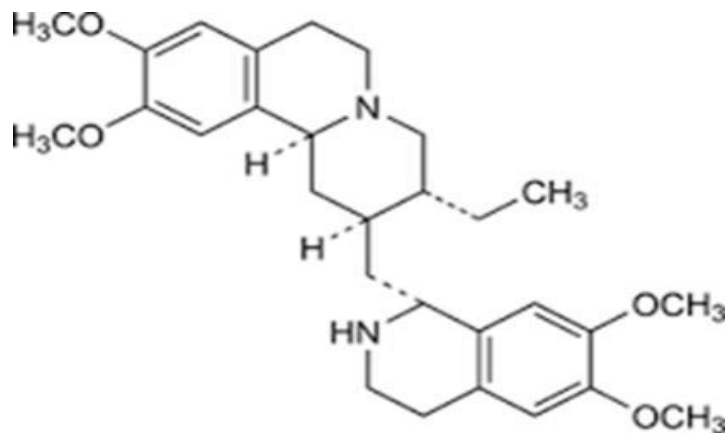


- **The important drugs & their alkaloids in this group are:**
- **Ipecac which contains emetine.**
- **Hydrastis which contains hydrastine .**
- **Curare which contains (+)-tubocurarine .**
- **Berberis which contains berberine.**
- **Opium which contains morphine & related alkaloids .**
- **Sanguinaria which contains sanguinarine.**

Drugs containing isoquinoline alkaloids

1- Ipecac:

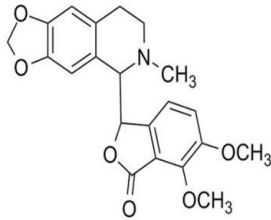
- It consists of the dried rhizomes & roots of *Cephaelis ipecacuanha* (Brazilian ipecac) or *Cephaelis acuminata* (Nicaragua or Panama ipecac). F: Rubiaceae.
- Ipecac yields not less than 2% of ether-soluble alkaloids.
- Ipecac contains five alkaloids, 3 main alkaloids namely: emetine, cephailine, & psychotrine.



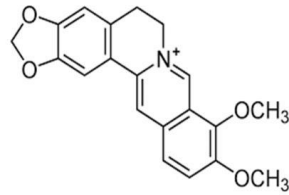
Emetine

2- Hydrastis or golden seal:

- It consists of the dried rhizomes & roots of *Hydrastis canadensis*. F: Rununculaceae.
- Three alkaloids have been isolated from hydrastis namely: hydrastine, berberine, & canadine.
- Of these, hydrastine (1.5-4%) is the most important.
- Hydrastis yields not less than 2.5% of anhydrous ether-soluble alkaloids.



Hydrastine

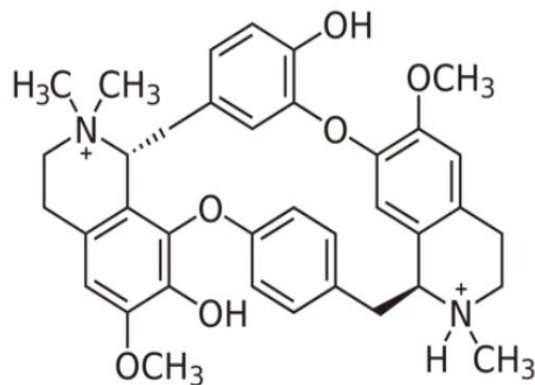


Berberine

- **Uses:**
- Hydrastine & berberine are used as astringents in inflammation of the mucous membrane.

3- Curare:

- Curare or South American arrow poison, is a crude dried extract from the bark & stems of *Strychnos castelnaei* or *S. crevauxii* F: Loganiaceae.
- The drug contains several alkaloids & quaternary compounds, the most important of which is (+)-tubocurarine, which is a quaternary compound that contains a bis-benzyl isoquinoline structure.
- The crude extract exhibits a paralyzing effect on the voluntary muscles (curariform effect) by blocking nerve impulses to skeletal muscles. It also produces a toxic action on blood vessels.



Tubocurarine

- **Uses:**

1- Tubocurarine is used as a skeletal muscle relaxant in surgical procedures without deep anesthesia.

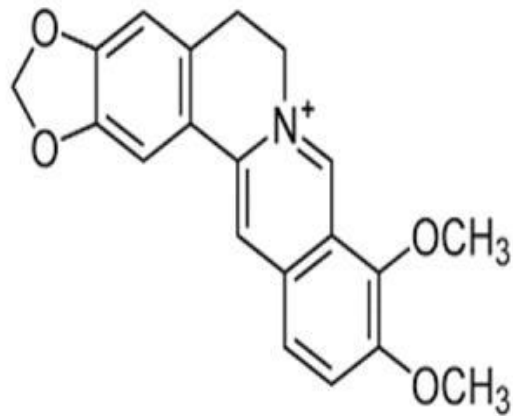
2- It is also used to control convulsions of strychnine poisoning & of tetanus.

3- It is an adjunct therapy in neuro psychiatry & as a diagnostic aid in myasthenia gravis.

Currently, tubocurarine is rarely used as an adjunct for clinical anesthesia because several alternatives, such as cisatracurium and rocuronium, are available.

4- Berberis (barberry):

- Sixteen isoquinoline alkaloids were isolated from *Berberis vulgaris*.
- In addition to quaternary proto berberines and bisbenzyl isoquinolines, a new seco-bisbenzyl isoquinoline, (-)-tejedine, is reported.
- Barberry is considered to be antibacterial, anti-inflammatory, hypertensive, haemostatic, diuretic and vasodilator.
- Due to its constituent berberine, Barberry can act as a very efficient remedy against bacterial, viral, fungal and parasitic infections.



Berberine

5- Opium:

- Opium or gum opium, is the air-dried milky exudates obtained by incising the unripe capsules of *Papaver somniferum*. F: Papaveraceae.
- The term opium is from Greek opion meaning poppy juice; papaver is the Latin name for the poppy; somniferum is Latin & means to produce sleep.
- The cultivation of opium poppy is controlled internationally by the International Narcotic Control Board of the United Nations.

Lately it was decided to be grown in Turkey, India, Russia, Romania, Australia, France, China & Spain.

- **Cultivation:**

- It is cultivated by planting in October.
- In spring, the plant reaches 15cm height, then the fruit appears.
- In June or July when it is fully grown & unripe, each plant contains 5-8 poppy (fruit) & then it is superficially cut & a milky juice is obtained, left for one day & collected in the second day.

- The main constituents are 30 different alkaloids, the most important of which are:

- 1- morphine 4-21%
- 2- codeine 0.8-2.5%
- 3- noscapine (narcotine) 4-8%
- 4- papaverine 0.5-2.5%
- 5- thebaine 0.5- 2%

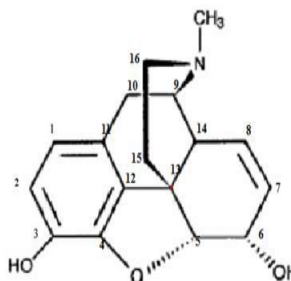
- Other alkaloids include narceine, protopine, laudanine, codamine, cryptopine.....
- Opium also contains 3-5% of meconic acid which exists free or in combination with morphine, codeine & other alkaloids.
- **It gives a red color in solution of ferric chloride.**
- **The color is not altered when dilute HCl is added.**
- **Because meconic acid is found only in opium, this test may be used for the detection of opium.**

Classification of opium alkaloids

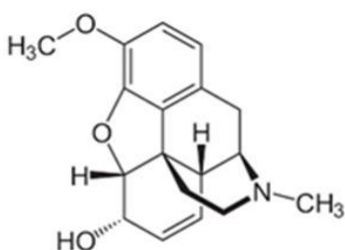
- Opium alkaloids can be sub-classified into 3 main groups with different basic nuclei:
 - 1. Phenanthrene alkaloids:** they act primarily on the CNS to produce depressant effect & they stimulate the contraction of the smooth muscles e.g. morphine, codeine, thebaine
 - 2. Benzyloquinoline alkaloids:** these have little action on the CNS but mainly act as antispasmodic (smooth muscles relaxant) e.g. papaverine & noscapine.
 - 3. Phenylethylamine alkaloids:** e.g. narceine

Phanathrene derivatives

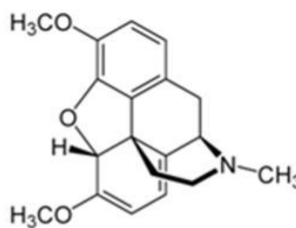
- The structure contain:
- benzene ring
- phenolic OH
- N-CH₃ (tertiary amine)
- ether linkage.



- If OH at position-3 is changed to OCH₃ we get codeine, & if the other OH is changed to OCH₃ with changing of the double bonds we end up with thebaine.



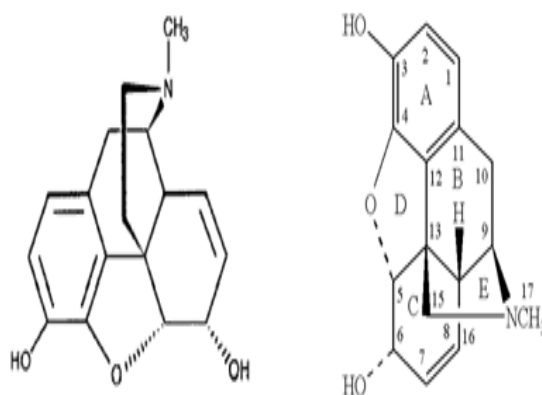
codeine



Thebaine

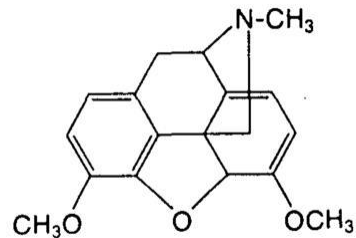
Alkaloids of opium

- **Morphine**
- It is the most important of the opium alkaloids.
- Morphine & related alkaloids are derivatives of phenanthrene.
- The molecule contains a phenolic & an alcoholic hydroxyl group. Morphine & its salts are classified as narcotic analgesics; they are strong hypnotics & narcotics.
- Their use induces nausea, vomiting, constipation, & habit forming.

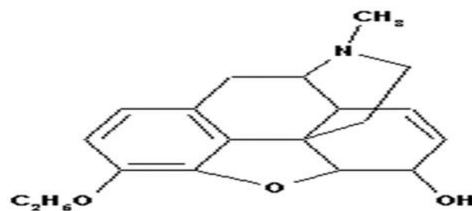


Morphine

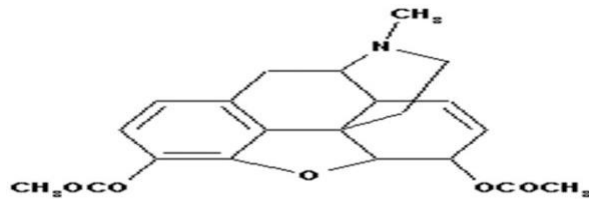
- **Codeine**
- Codeine & its salts are narcotic analgesics & antitussive.
- Although its action is similar to that of morphine but codeine is less toxic & less habit forming.
- Thebaine It is a phenanthrene derivative used as a CNS stimulant.



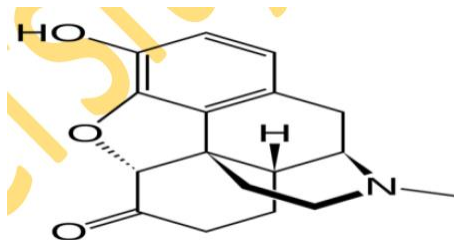
- **Ethyl morphine (dionine)**
- It is used to less extent as codeine.
- is formed by the ethylation of phenolic OH of morphine, it is used in ophthalmology as analgesic.



- **Diacetyl morphine (heroin)**
- It is formed by acetylation of morphine. It is very toxic & expensive.
- It is 100 times stronger than morphine. It is a drug of addiction. Heroin is sometimes available in free base form, dulling the sheen and consistency to a matte-white powder.
- Because of its lower boiling point, the free base form of heroin is also smokable.

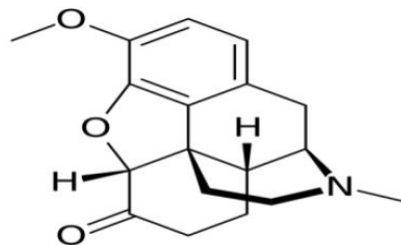


- **Hydromorphone, also known as dihydromorphinone:**
- Prepared by reducing morphine in HCL solution (one of OH group replaced by ketone group and adjacent double bond is removed) , this drug is a powerful narcotic analgesic & tends to strongly depress the respiratory mechanism .

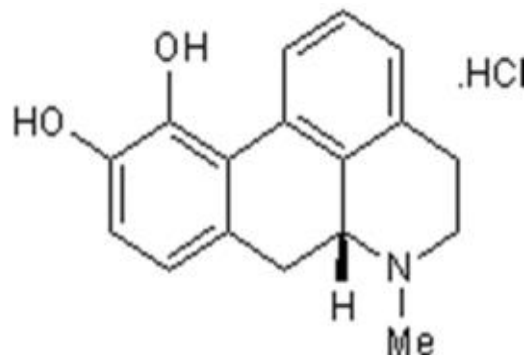


- **Hydrocodone, also known as dihydrocodeinone:**

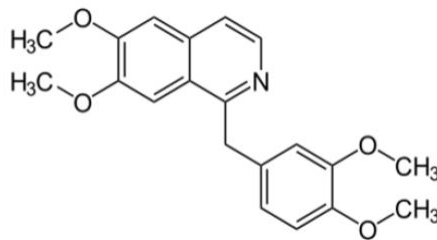
bears the same relation to codeine as hydromorphone dose to morphine, used mainly as a cough suppressant agent.



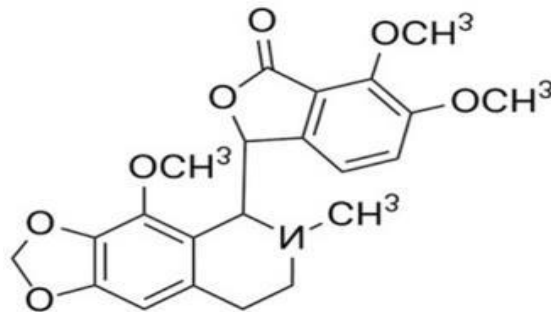
- **Apomorphine** Prepared by heating morphine in a sealed tube with HCl.
- It is used as emetic & particularly valuable in cases of poisoning.



- **Papaverine** It is a derivative of benzylisoquinoline. It is a smooth muscle relaxant.



- **Noscapine** It is commonly called narcotine. It is also a derivative of benzyl isoquinoline. It has no narcotic properties & therefore sometimes called anarcotine. It is used as anti-tussive.



- **Pantopon:**
 - It refers to a preparation of the total alkaloids of opium deprived or excluded from any other non alkaloidal material.
 - The alkaloids are found in the same proportion as it is found inside the opium drug. It contains about 50% morphine.
 - It is more preferable to be prescribed than morphine alone because of the synergistic effect.
-
- Opioid is used for compounds which inhibit the pain reaction within the central nervous system, so: opioid is a psychoactive chemical that works by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the **gastrointestinal tract**.
 - The receptors in these organ systems mediate both the beneficial effects and the side effects of opioids. The analgesic (painkiller) effects of opioids are due to decreased perception of pain, decreased reaction to pain as well as increased pain tolerance. The side effects of opioids include sedation, respiratory depression, constipation, and a strong sense of euphoria.

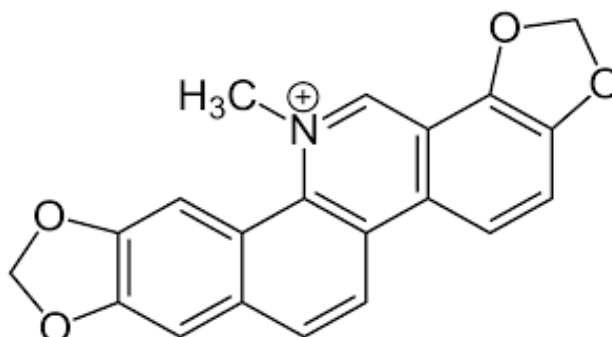
Classification of opioids

- **Natural opiates:** morphine, codeine, and thebaine.
- **Semi-synthetic opioids:** created from either the natural opiates or morphine esters, such as hydromorphone.
- **Fully synthetic opioids:** such as pethidine, tramadol .
- Although the term *opiate* is often used as a synonym for *opioid*, the term *opiate* is properly limited to the natural alkaloids found in the resin of the opium poppy (*Papaver somniferum*), while *opioid* refers to both opiates and synthetic substances, as well as to opioid peptides.

Opioid

- It refers to the synthetic morphine like compounds.
- Many of these substances offer the same narcotic & pain-relieving properties as morphine, but they are not as habit-forming.
- Others possess cough relieving activity of codeine but are not addictive e.g. morphinan opioids, methadone & meperidine.

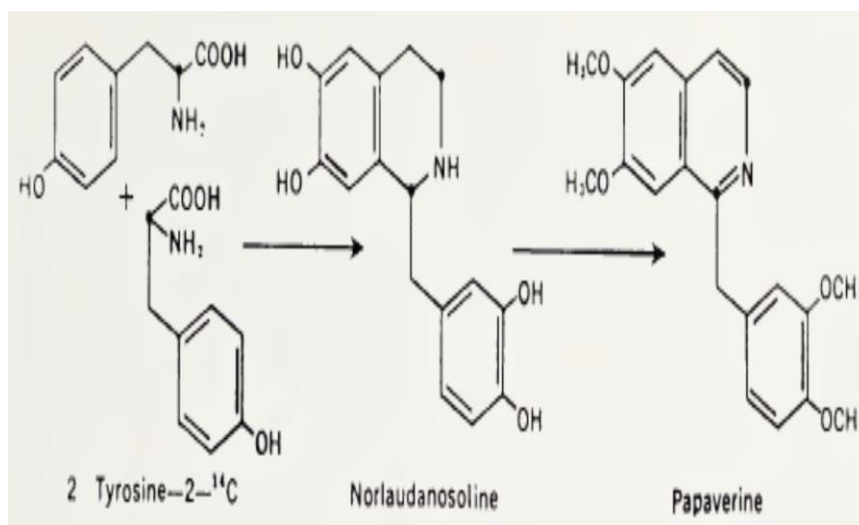
- **Sanguinaria (blood root):**
- It consists of the dried rhizomes & roots of *Sanguinaria canadensis* F: Papaveraceae.
- It contains the benzyl phenanthridine alkaloids sanguinarine, chelerythrine, protopine.
- Sanguinarine & chelerythrine although they are colorless, form red & yellow salts respectively.
- The drug also contains red resin & starch.
- Sanguinaria is mainly used as ingredient of compound white pine syrup.
- Sanguinarine as colchicine, causes doubling of the chromosomes in the cell.



Sanguinarine

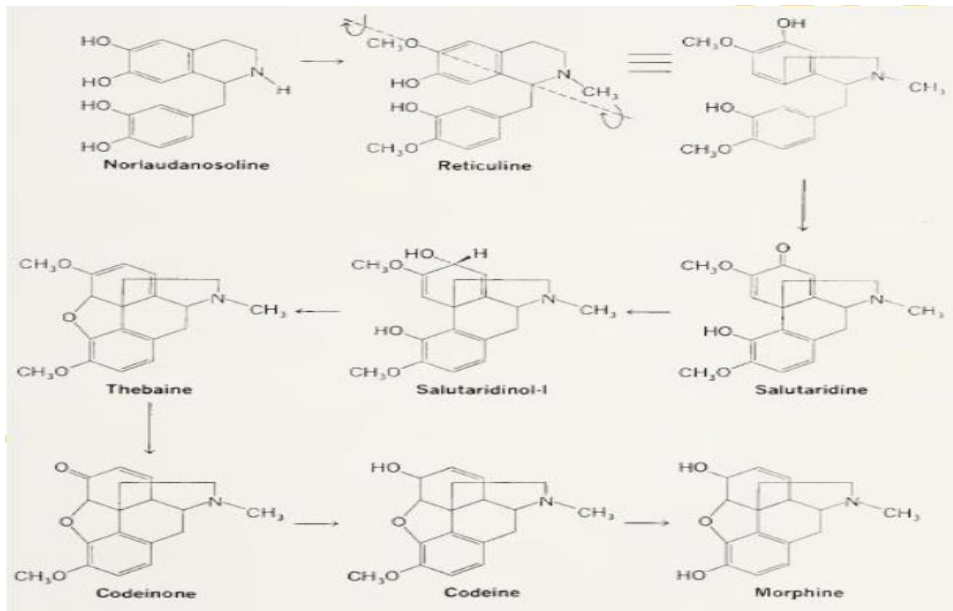
BIOSYNTHESIS OF ISOQUINOLINE ALKALOIDS

- Although the isoquinoline alkaloids possess relatively complex structures, the basic biosynthetic reactions which account for their formation in plants are relatively simple.
- These compounds result from the condensation of a phenylethylamine derivative with a phenylacetaldehyde derivative. Both of these moieties are derived from phenylalanine or tyrosine.
- Administration of tyrosine-2- ^{14}C to *Papaver somniferum* resulted in the formation of papaverine labeled in corresponding positions.
- Norlaudanosoline is probably an intermediate in this reaction.



Biosynthesis of papaverine

- Morphine is also formed from two molecules of tyrosine. This medicinally important alkaloid is derived from a benzyl- isoquinoline metabolite.
 - The biosynthesis of morphine and related alkaloids has been studied extensively, and these experiments provide some of the most complete and detailed observations available for any secondary plant constituent.
 - The biosynthetic pathway starting with norlaudanosoline and leading to morphine.
 - A key feature of this pathway is the enzymatically controlled methylation pattern which gives rise to reticuline; this facilitates formation of the dienone, salutaridine, which is the first intermediate with a phenanthrene nucleus.
-
- Another interesting aspect of this pathway is the biosynthetic relationship of thebaine, codeine, and morphine; stepwise demethylation of the therapeutically unimportant thebaine leads first to the relatively mild analgesic codeine and then to the potent narcotic morphine.
 - *P. somniferum* has a highly evolved and useful secondary metabolism which culminates, at least from the therapeutic viewpoint, in morphine. *P. bracteatum*, a thebaine-producing poppy, appears to lack any significant demethylation capability; this feature is not only useful for biosynthetic studies, but it has recently become commercially significant.
 - Since thebaine can be converted to codeine semisynthetically, a source of the latter alkaloid is assured without concomitant production of morphine which is more subject to abuse by drug addicts.
 - These two species emphasize the subtle metabolic difference which so frequently separates useful plants from those of only scientific interest.



Biosynthesis of morphine

THANK YOU