



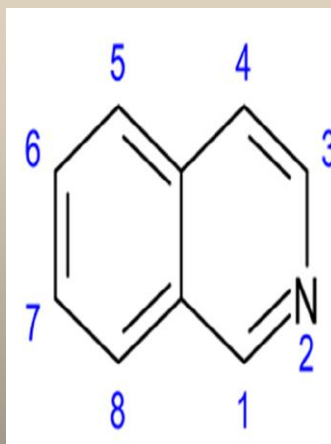
Pharmacognesy III

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

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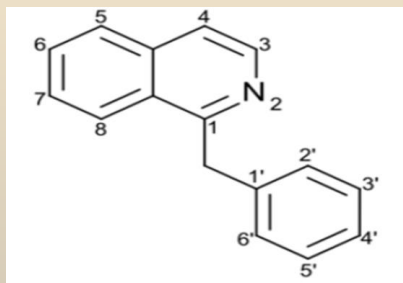
Isoquinoline alkaloids

- 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.

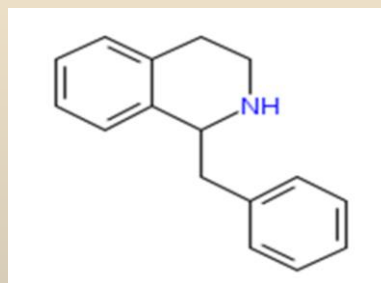


Classes of Isoquinoline Alkaloids

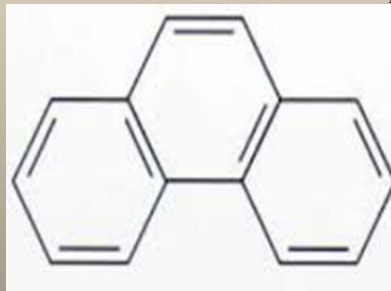
- **Benzylisoquinoline or BIQ alkaloids** About 4000 BIQ alkaloids are known. Many BIQ alkaloids are important in medicine. Others are **highly toxic**. Some are used as arrow poisons (Tubocurarine).
- **Tetrahydrobenzylisoquinoline or THBIQ alkaloids** The simplest alkaloids of this series are those in which the nitrogen-containing ring is completely saturated. 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.



Benzyl isoquinoline (BIQ)



Tetrahydrobenzyl isoquinoline (THBIQ)



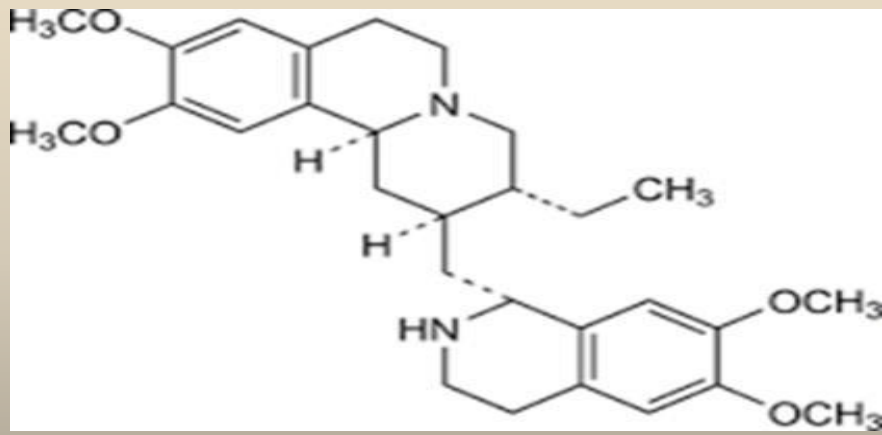
Phenanthrene

- **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, cephaline, & psychotrine**.

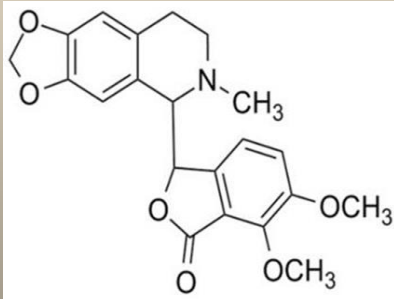


Emetine

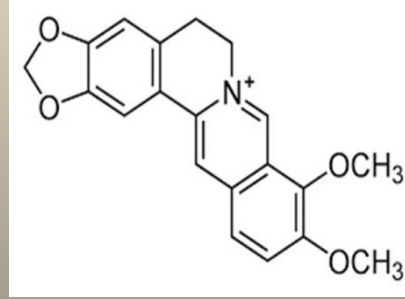
2- Hydrastis or golden seal:

- 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.

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



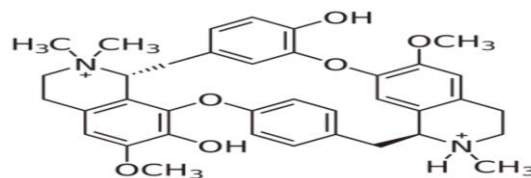
Hydrastine



Berberine

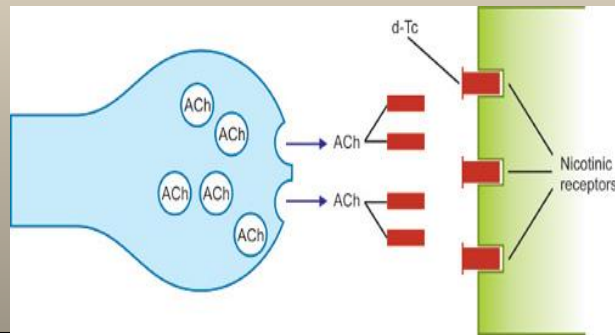
3- Curare:

- 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.



Tubocurarine

- 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.



- **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 neuropsychiatry & 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- 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.
- 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%

- 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 subclassified 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.

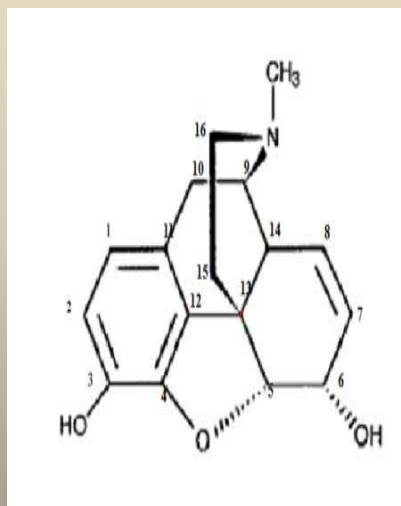
3. Phenylethylamine alkaloids: e.g. narceine

Classification of opioids

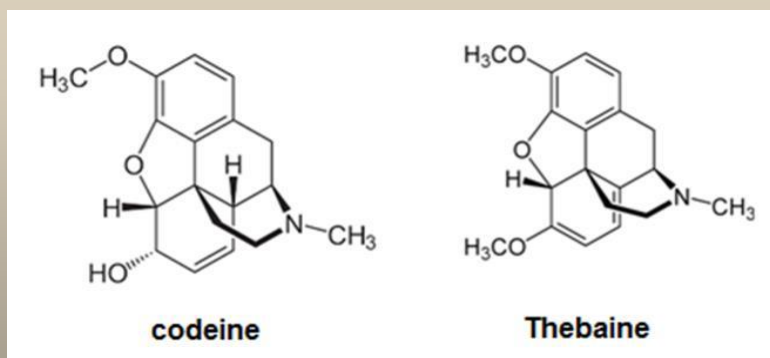
- According to their sources, opium alkaloids are classified into:
 - **Natural opiates:** morphine, codeine, and thebaine.
 - **Semi-synthetic opioids:** created from either the natural opiates or morphine esters, such as hydromorphone.
 - **Fully synthetic opioids:** such as pethidine, tramadol .
- 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.

Phanathrene derivatives

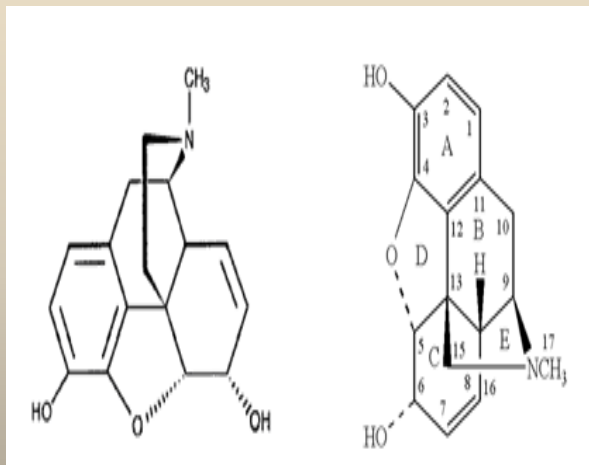
- **The structure contain:**
 - Benzene ring
 - Phenolic OH
 - N-CH₃ (tertiary amine)
 - Ether linkage.



- 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**.

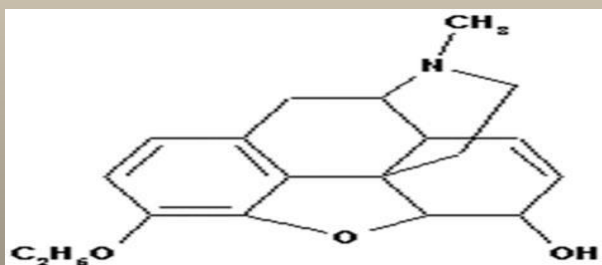


- **Morphine**
- It is the most important of the opium alkaloids.
- Morphine & related alkaloids are derivatives of phenanthrene.
- The molecule contains a phenolic & an alcoholic hydroxyl group. Morphine & its salts are classified as narcotic analgesics; they are strong hypnotics & narcotics.
- Their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



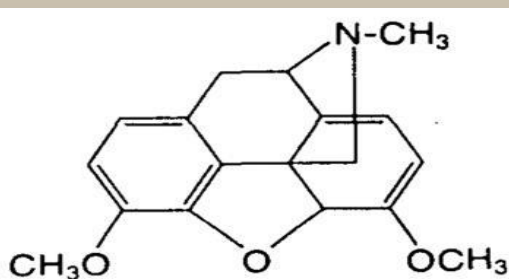
Morphine

- **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.

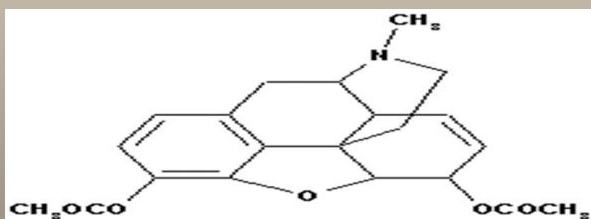


- **Codeine**
- Codeine & its salts are narcotic analgesics & antitussive.
- Although its action is similar to that of morphine but codeine is less toxic & less habit forming.
- **Thebaine**
- It is a phenanthrene derivative used as a CNS stimulant.

Thebaine



- **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.

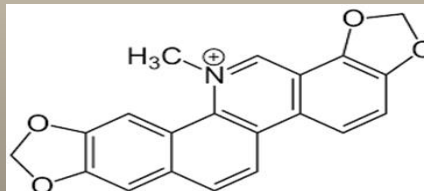


- **Apomorphine** Prepared by heating morphine in a sealed tube with HCl. It is used as emetic & particularly valuable in cases of poisoning.
- **Papaverine** It is a derivative of benzyloisoquinoline. It is a smooth muscle relaxant.
- **Noscapine** It is commonly called narcotine. It is also a derivative 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.

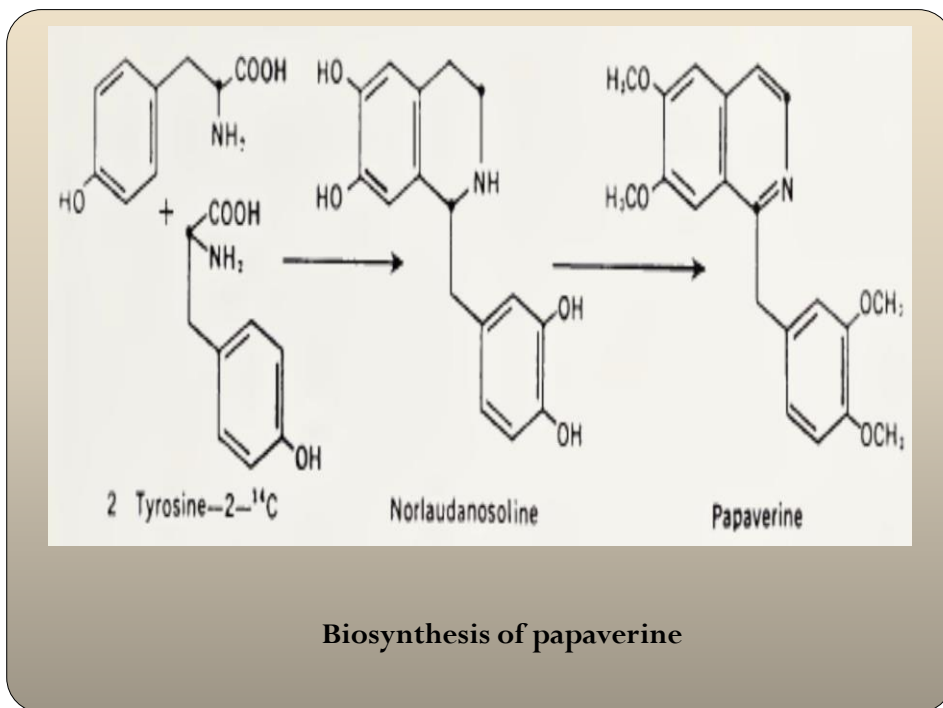
- Opioid is used for compounds which inhibit the pain reaction within the central nervous system, so: opioid is a psychoactive chemical that works by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the **gastrointestinal tract**.
- The receptors 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.

- **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.



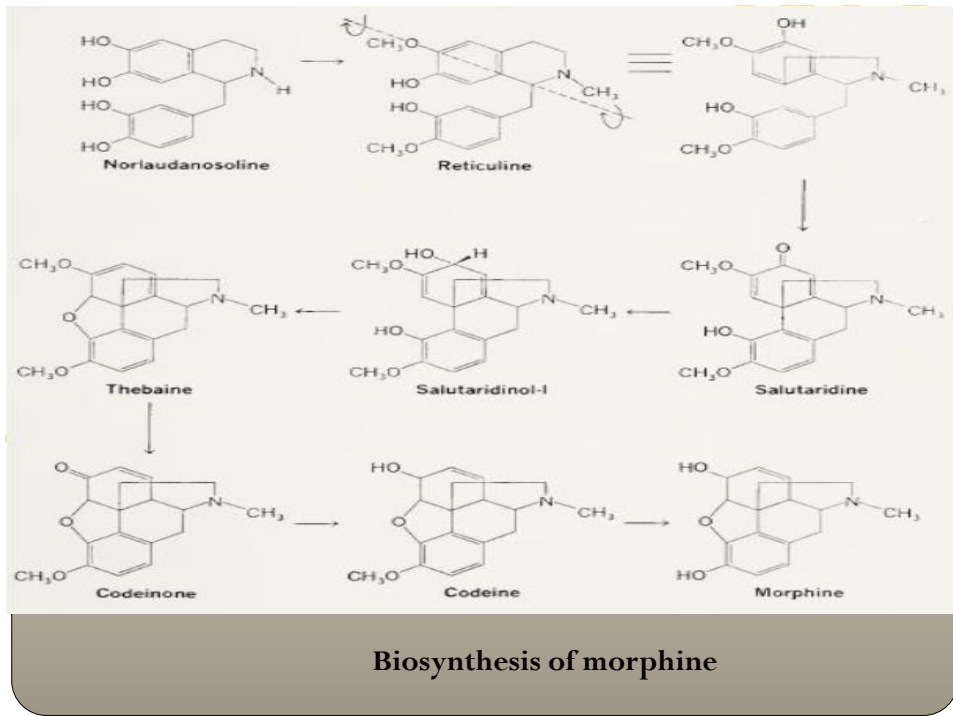
BIOSYNTHESIS OF ISOQUINOLINE ALKALOIDS

- 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-2-¹⁴C to *Papaver somniferum* resulted in the formation of papaverine labeled in corresponding positions.
- Norlaudanosoline is probably an intermediate in this reaction.



- Morphine is also formed from **two molecules of tyrosine**. This medicinally important alkaloid is derived from a benzyl- isoquinoline metabolite.
- 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, ***P. bracteatum* serves as** source of codeine without concomitant production of morphine which is more subject to abuse by drug addicts.



THANK YOU