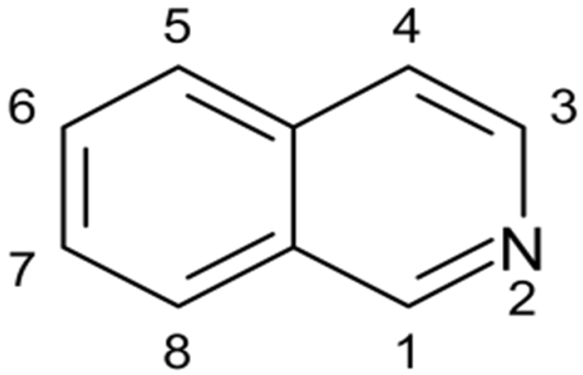
PharmacognosyIII

Lec. 5 **3rd stage 2nd semester** **Year 23-24**

Lecturer: Dr. Jamel Fani

ALKALOIDS

Isoquinoline alkaloids



Isoquinoline alkaloids

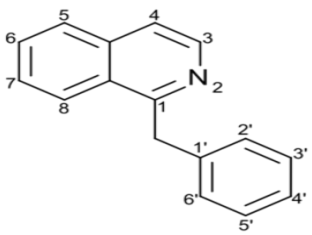
Isoquinoline is a heterocyclic aromatic organic compound. It is a structural isomer of quinoline.

Isoquinoline and quinoline are benzo pyridines derivatives, which are composed of a benzene ring fused to a pyridine ring.

Types of isoquinoline alkaloids:

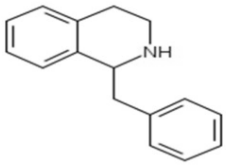
Benzylisoquinoline or BIQ alkaloids

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.



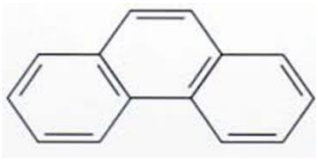
Tetrahydrobenzylisoquinoline or THBIQ alkaloids

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 and related alkaloids.



The important drugs and their alkaloids in this group are:

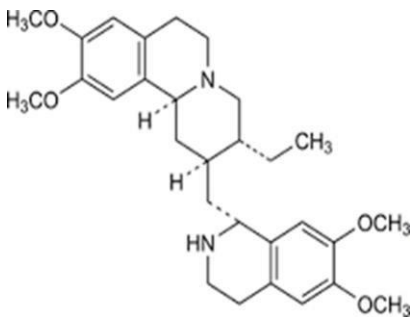
- Ipecac which contains emetine.
- Hydrastis which contains hydrastine.
- Curare which contains (+)-tubocurarine.
- Berberis which contains berberine.
- Opium which contains morphine and related alkaloids.
- Sanguinaria which contains sanguinarine.

Drugs containing isoquinoline alkaloids:

Ipecac

- It consists of the dried rhizomes and roots of *Cephaelis ipecacuanha* (*Brazilian ipecac*) or *Cephaelis acuminate* (*Nicaragua* or *Panama ipecac*) F: Rubiaceae.

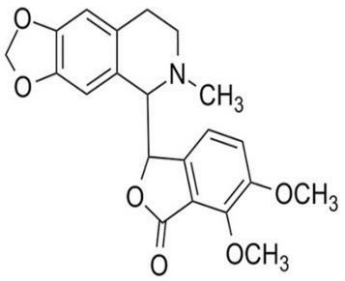
- Ipecac yields not less than 2% of ether-soluble alkaloids.
- Ipecac contains five alkaloids, 3 main alkaloids namely: emetine, cephailine, and psychotrine.



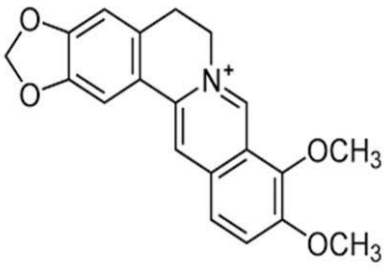
Emetine

Hydrastis or golden seal

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



Hydrastine

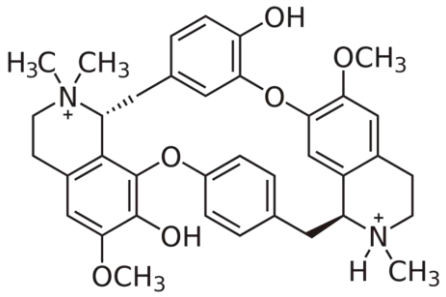


Berberine

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

Curare

- Curare or South American arrow poison is a crude dried extract from the bark and stems of *Strychnos castelnaei* or *S. crevauxii* F: Loganiaceae.
- The drug contains several alkaloids and 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.



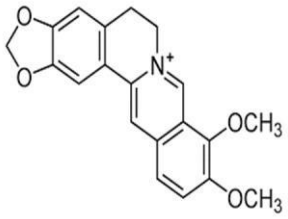
Tubocurarine

Uses:

- Tubocurarine is used as a skeletal muscle relaxant in surgical procedures without deep anesthesia.
- It is also used to control convulsions of strychnine poisoning and of tetanus.
- It is an adjunct therapy in neuro psychiatry and 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.

Berberis (barberry)

- Sixteen isoquinoline alkaloids were isolated from *Berberis vulgaris*, F: Berberidaceae.
- In addition to quaternary proto berberines and bisbenzyl isoquinolines, a new secobisbenzyl 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

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 and 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 and 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 and unripe, each plant contains 5-8 poppy (fruit) and then it is superficially cut and a milky juice is obtained, left for one day and collected in the second day.

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

- morphine 4-21%
- codeine 0.8-2.5%
- noscapine (narcotine) 4-8%
- papaverine 0.5-2.5%
- thebaine 0.5-2%
- Other alkaloids include narceine, protopine, laudanine, codamine, cryptopine…..

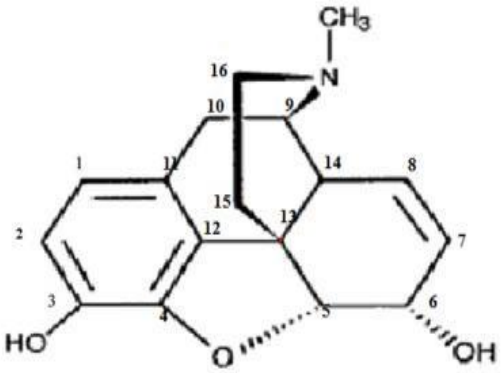
Opium also contains 3-5% of meconic acid which exists free or in combination with morphine, codeine and other alkaloids. It gives a red color in solution of ferric chloride. The color is not altered when dilute HCl is added. Because meconic acid is found only in opium, this test may be used for the detection 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 and they stimulate the contraction of the smooth muscles e.g. morphine, codeine and thebaine.

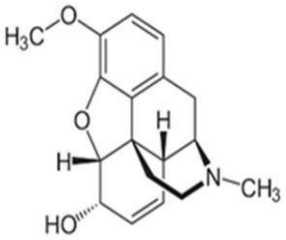
2. Benzylisoquinoline alkaloids: these have little action on the CNS but mainly act as antispasmodic (smooth muscles relaxant) e.g. papaverine and noscapine.
3. Phenylethylamine alkaloids: e.g. narceine.



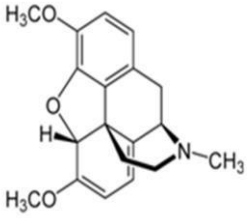
Phenanthrene derivatives

The structure contain:

- Benzene ring.
- Phenolic OH.
- N-CH_3 (tertiary amine).
- Ether linkage.
- If OH at position-3 is changed to OCH_3 we get codeine, and if the other OH is changed to OCH_3 with changing of the double bonds we end up with thebaine.



codeine

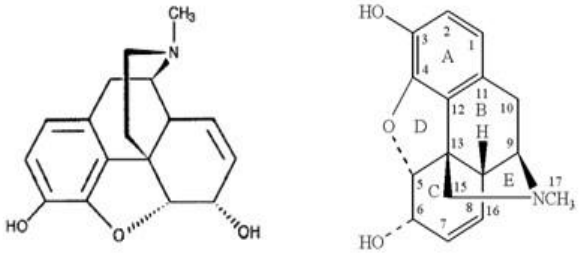


Thebaine

Alkaloids of opium:

Morphine

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



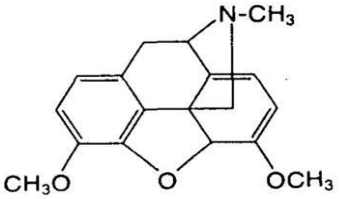
Morphine

Codeine

- Codeine and its salts are narcotic analgesics and antitussive.
- Although its action is similar to that of morphine but codeine is less toxic and less habit-forming.

Thebaine

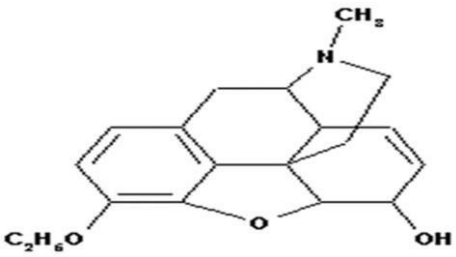
- It is a phenanthrene derivative used as a CNS stimulant.



Ethyl morphine (dionine)

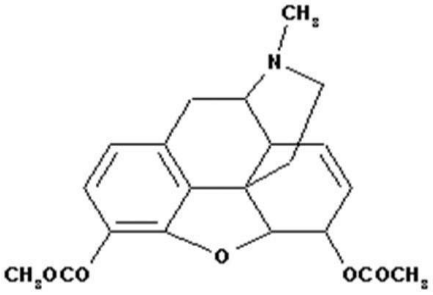
- It is used to less extent as codeine.
- Is formed by the ethylation of phenolic OH of morphine.

- It is used in ophthalmology as analgesic.



Diacetyl morphine (heroine)

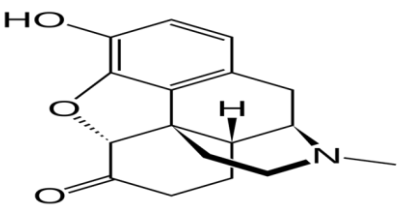
- It is formed by acetylation of morphine.
- It is very toxic and expensive.
- It is 100 times stronger than morphine.
- It is a drug of addiction.
- Heroin is sometimes available in free base form, dulling the sheen and consistency to a matte-white powder.
- Because of its lower boiling point, the freebase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



heroine

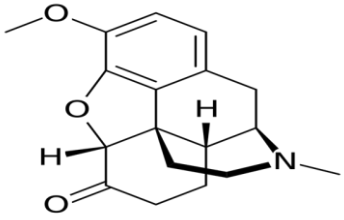
Hydromorphone, also known as dihydromorphinone

- It prepares 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 and tends to strongly depress the respiratory mechanism.



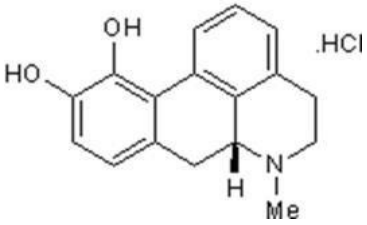
Hydrocodone, also known as dihydrocodeinone

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



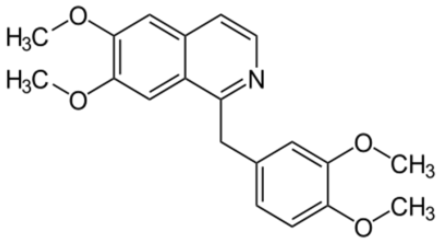
Apomorphine

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



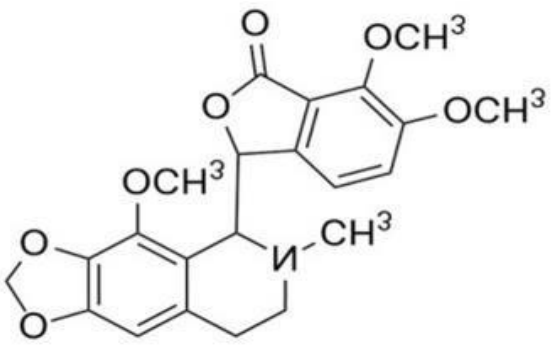
Papaverine

- 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 and 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 if the synergistic effect.

Opioid

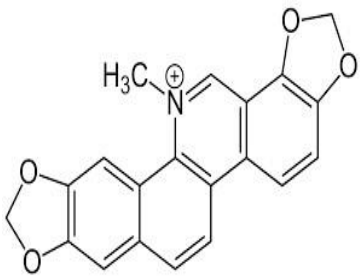
- Opioid is used for compounds which inhibit the pain reaction within the central nervous system, so opioid is a psychoactive chemical that works by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the gastrointestinal tract. The receptors in these 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.
- It refers to the synthetic morphine like compounds.
- Many of these substances offer the same narcotic and 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 and meperidine.

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.

Sanguinaria (blood root)

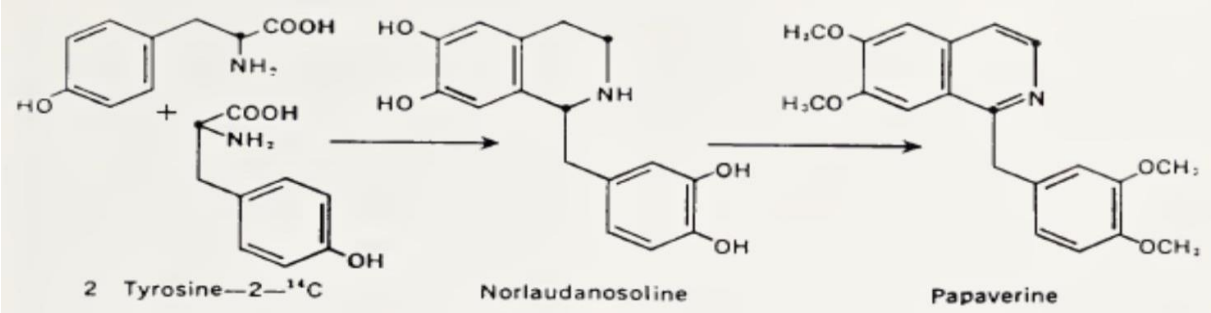
- It consists of the dried rhizomes and roots of *Sanguinaria canadensis* F: Papaveraceae.
- It contains the benzyl phenanthridine alkaloids sanguinarine, chelerythrine, protopine.
- Sanguinarine and chelerythrine although they are colorless, form red and yellow salts respectively.
- The drug also contains red resin and 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-2-14C to *Papaver somniferum* resulted in the formation of papaverine labeled in corresponding positions. Norlaudanosoline is probably an intermediate in this reaction.



Biosynthesis of papaverine

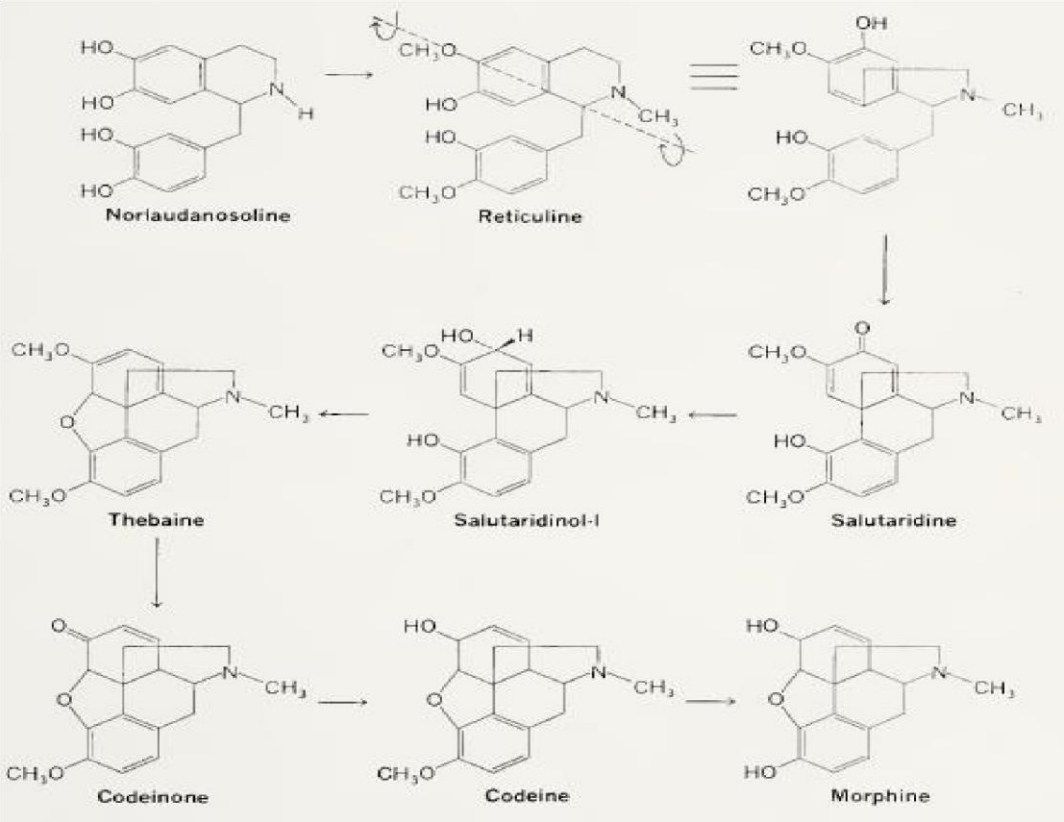
Morphine is also formed from two molecules of tyrosine. This medicinally important alkaloid is derived from a benzyl- isoquinoline metabolite. The biosynthesis of morphine and related alkaloids has been studied extensively, and these experiments provide some of the most complete and detailed observations available for any secondary plant constituent. The biosynthetic pathway starting with nor laudanosoline 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 morphin