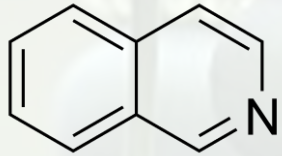
College of pharmacy /Al-Nahrain University

3rd stage/ 2nd coarse

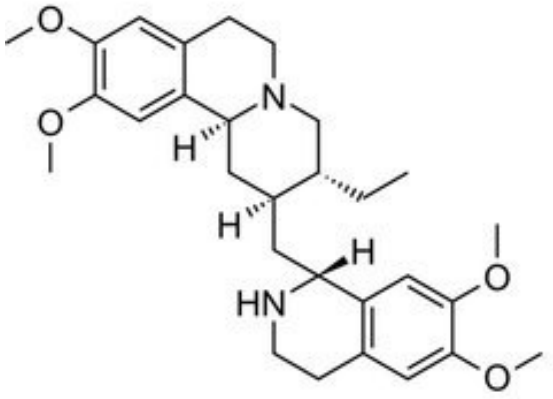
Isoquinoline Alkaloids



Pharmacognosy-Lecture 5

Lecturer Ayah Al-Qrimli/MSc pharmacognosy

Ipecac



- Ipecac is derived from the dried **rhizomes** and **roots** of the *Cephaelis ipecacuanha*.
- Alkaloids found in Ipecac are **Emetine, Cephaeline and Psychotrine**.
- It is used to induce vomiting by irritating the lining of the stomach gastric mucosa and by stimulating part of the brain called the medullary chemoreceptor trigger zone. CR-T-Zone. Ipecac syrup was used in treatment of drug **overdose and in certain poisonings**.
- **Mechanism of action**: The actions of ipecac are mainly those of its major alkaloids, emetine (methyl cephaeline) and cephaeline.
- They both act **locally** by **irritating the gastric mucosa** and **centrally** by **stimulating the medullary chemoreceptor trigger zone to induce vomiting**
- **Biosynthetic precursor**: **Phenyl alanine and terpenoid (secologanin).**
- **Terpenoid -Tetrahydro –Isoquinoline.**

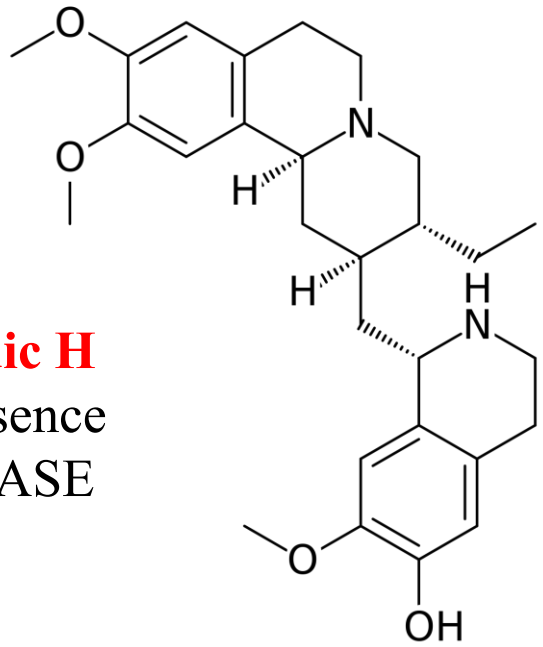




Both are soluble in organic solvent

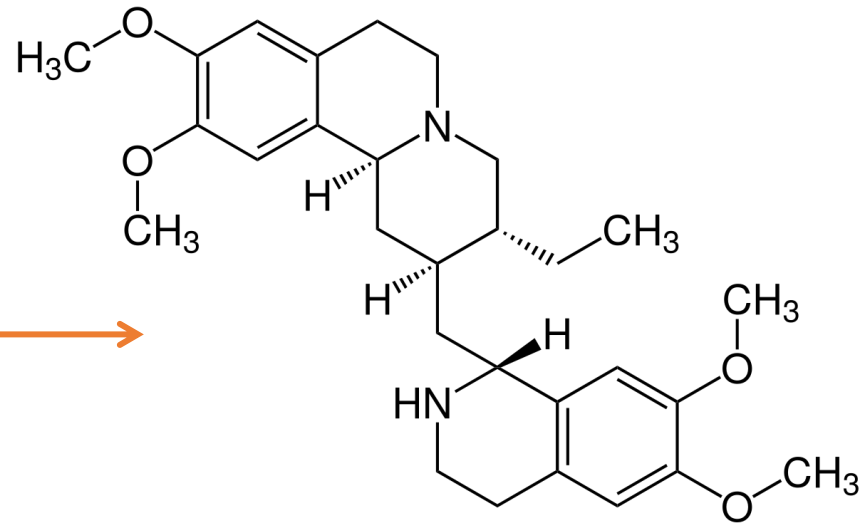
Both are soluble in organic solvents, but **only cephaeline is soluble in aqueous** base due to phenolic salt formation.

Phenolic acidic H
Soluble in presence of Aqueous BASE (SALT)



Cephaeline
Phenolic (Acidic)

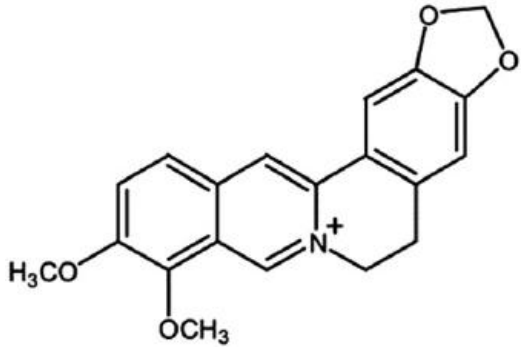
Methylation



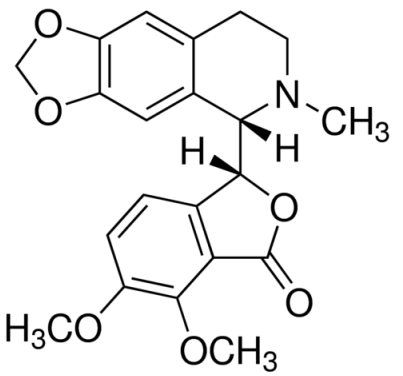
Emetine
Non-phenolic (nonacidic character)

Hydrastis or golden seal:

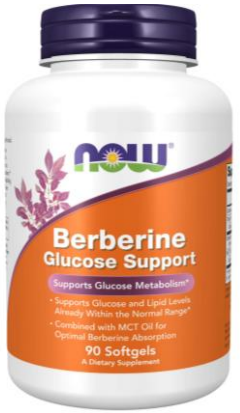




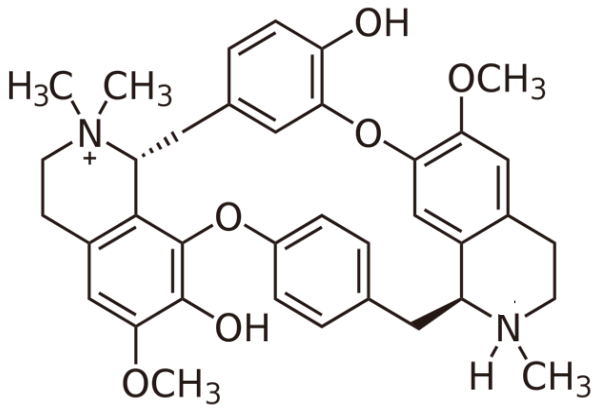
- It consists of the **dried rhizomes & roots** of *Hydrastis canadensis*.
- Three alkaloids have been isolated from Hydrastis namely **hydrastine, berberine,** and **canadine.** Of these, hydrastine is the most important while Berberine is a quaternary alkaloid.
- **The biosynthesis precursor** is from **phenylalanine &glycine.**
- Uses:
- Hydrastine & berberine are used as **astringents in inflammation of the mucous membrane.** Hydrastine is toxic internally however, locally it treats mucous membrane.
- Berberine is used in supplements by diabetic patients **due to its ability to reduce blood sugar levels, and lower cholesterol level.**
- In vitro studies proved powerful anti-cancer, anti-microbial (anti bacterial and antiparasitic) and anti-inflammatory properties.





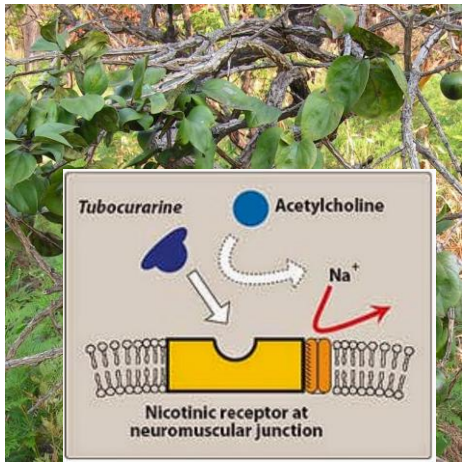


Curare

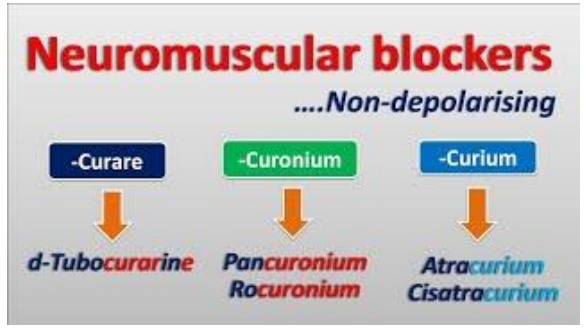


- **Curare or arrow poison**, which is the dried crude extract of the **bark** and **stems** of *strychnos castelnaei* F: Loganiaceae. Traditionally used by South American tribes as **arrow poison.** The term curare is derived from woorari, an Indian word for poison.
- The most important alkaloid of which is **(+)-Tubocurarine**, which is a **bis-benzyl tetrahydroisoquinoline Quaternary alkaloid**
- **Produces paralysis of voluntary skeletal muscles (curariform effect).**
- Acts by blocking nerve impulse transmission at the **neuromuscular junction Mechanism** (blocks nicotinic acetylcholine receptors **so Prevents acetylcholine from activating skeletal muscle contraction**) , **charged N^+ is essential for binding to nicotinic receptors at the neuromuscular junction.**
- SE: causes **histamine release** causing **bronchospasm** and **hypotension**.
- Tubocurarine contains **one quaternary ammonium nitrogen** with **permanent positive charge** and **one tertiary amine nitrogen** that is **not permanently charged;** this **explains its poor CNS penetration and neuromuscular blocking activity. No effect on consciousness, No effect on pain sensation**





Tubocurarine



- Tubocurarine is **the first used skeletal muscle relaxant in surgical procedures without deep anesthesia.** used adjunctively in anesthesia to **provide skeletal muscle relaxation during surgery or mechanical ventilation**.
- It is also used to control of severe muscle spasms in **strychnine poisoning and of tetanus**.
- Tubocurarine was given as **injections** because its **poorly absorbed orally** also it **can't cross BBB.**
- Drug Classification: **Non-depolarizing neuromuscular blocking agent**, **Long-acting nicotinic receptor antagonist**
- Tubocurarine is classified as **a long-duration**, antagonist for nicotinic acetylcholine receptor.
- Rarely used today due to **Histamine-related adverse effects** and Availability of safer alternatives Examples of newer agents **Atracurium** and **Rocuronium**
- The **quaternary ammonium structure** restricts it to **peripheral action** and inspired the design of synthetic non-depolarizing neuromuscular blockers with improved safety profiles.



Opium

- Opium or gum opium, is **the air-dried milky exudates** obtained by incising the **unripe capsules** of *Papaver somniferoum* F: Papaveraceae.
- The term **opium** is from Greek opium meaning **poppy juice**; **Papaver** is the Latin name for the **poppy; somniferoum** 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.
- The drug contains many alkaloids that are essential & cannot be substituted by any other preparations.
- The Turkish variety contains 10-20% of morphine & it is used for pharmaceutical purposes. The Indian variety contains 13% morphine & the Chinese 4-10%.







Cultivation:



- It is collected 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
- **Morphine , Codeine , Noscapine (Narcotine) , Papaverine ,and Thebaine.**
- Opium also contains 3-5% of, **Meconic acid** which exists, free or in combination with morphine, codeine & other alkaloid , it gives a **red color in solution of ferric chloride (meconic acid–Fe^{3+} complex formation)**. The color is not altered when dilute **HCI** is added (**dilute HCl does not break the Fe^{3+}–meconate complex)**. Because meconic acid is found only in opium. this test may be used for th**e detection of opium.**

Generally, Opium alkaloids can be classified into:

1. **Benzyl isoquinoline** derivatives:

- These have little action on the CNS but mainly act as **antispasmodic and vasodilator** (smooth muscles relaxant) like: **Papaverine and Noscapine.**

2. **Phenanthrene** derivatives:

- They act primarily on the **CNS to produce depressant** effects like: **Morphine, Codeine and Thebaine.**

3- **Phenylethyl amine** alkaloids like **Narceine**

Structure Activity Relationship of Morphine alkaloids

- **Aromatic ring** with a **free phenolic –OH** (usually at position 3)

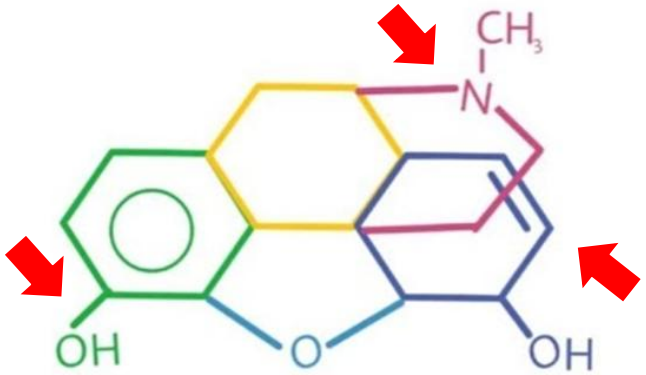
➢Forms **hydrogen bonding with opioid receptor**, Essential for **high analgesic potency** (Free –OH → ↑ activity , O-methylation → ↓ activity like in codeine)

- **A tertiary amine (N) that is NOT quaternary**

➢Required for **ionic binding to μ-opioid receptors** (receptor binding)

➢ Must be **unionized** → **to cross BBB**

- **Phenanthrene nucleus** → essential **CNS activity**
- Morphinan nucleus that **maintain distance (3C Aromatic –Nitrogen)**
- **Structure may look different but must mimic morphine geometry**



Structure of Morphine

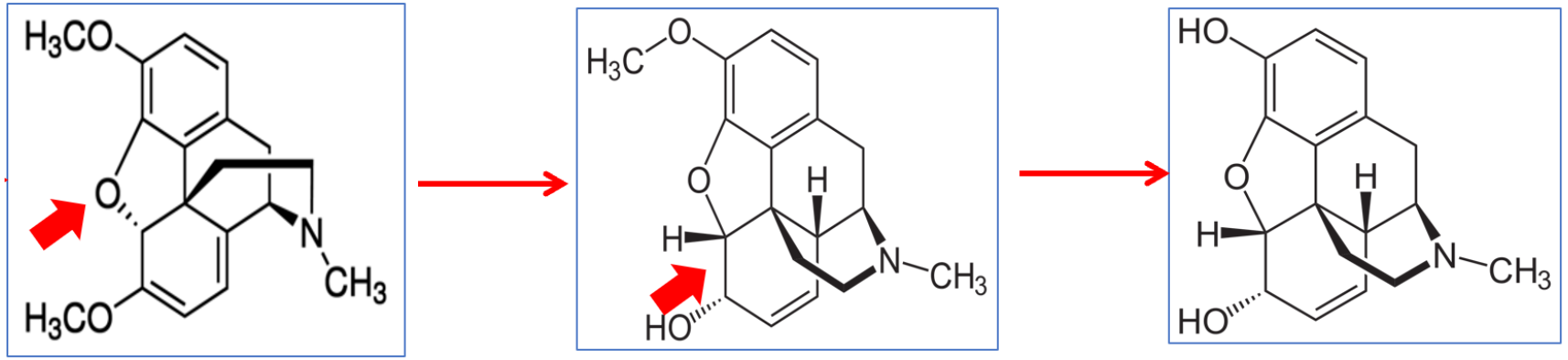
Effect of Chemical Modification

- Morphine: **Strong analgesic** and **High addiction potential**
- Codeine: **Moderate** analgesic and **Lower** addiction

➢If **OH** at position-3 is changed to **OCH3** we get **Codeine**

- Thebaine: **No analgesic** and used as **Synthetic precursor**

➢if the other OH is changed to **OCH3** with changing of the **double bonds** we end up with **Thebaine**.



Thebaine

Reduction demethylation

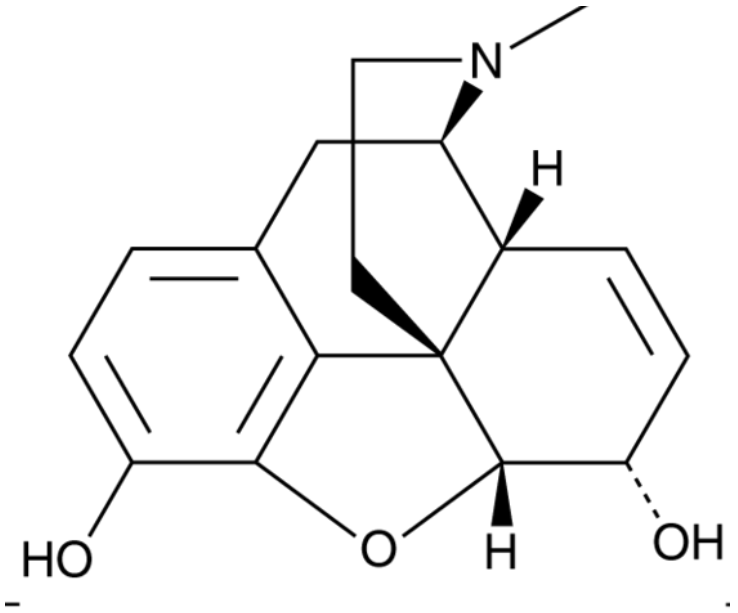
Codeine

Morphine

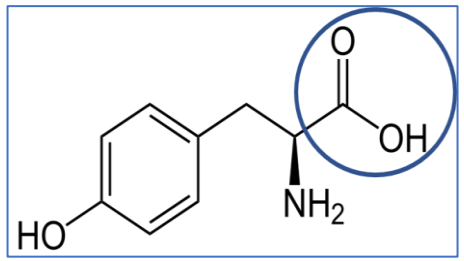
1. Morphine



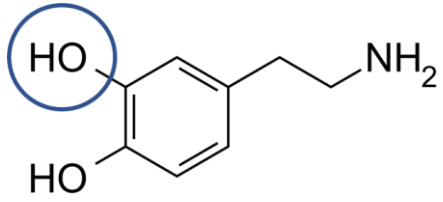
- It is the most important of the opium alkaloids. Morphine & related alkaloids are derivatives of phenanthrene. The molecule contains a **phenolic & an alcoholic hydroxyl groups.**
- Morphine & its salts, are classified as(**narcotic analgesics**) they are strong hypnotics, analgesic and narcotic acting **centrally on opioid receptors** to inhibit pain pathways.
- Their use induces **sedation, nausea, vomiting**, **constipation**, and habit forming.



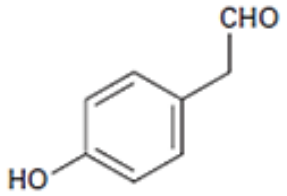
Biosynthesis of Morphine



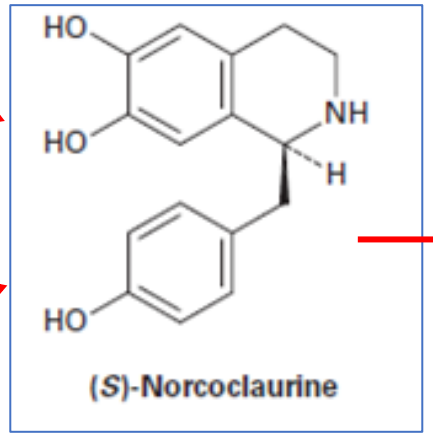
Tyrosine



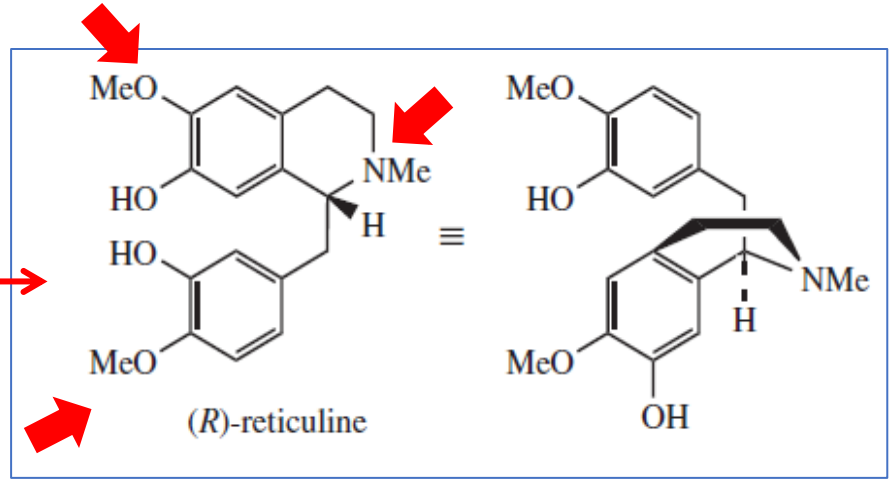
Dopamine



p-Hydroxyphenyl-acetaldehyde

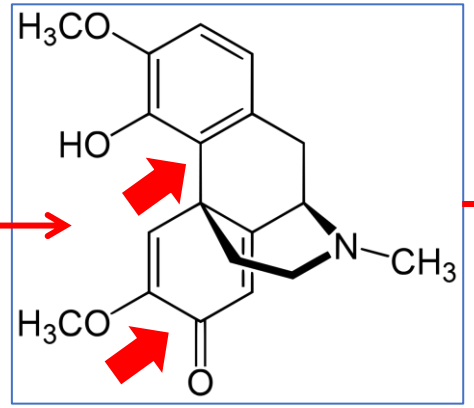


(*S*)-Norcoclaurine



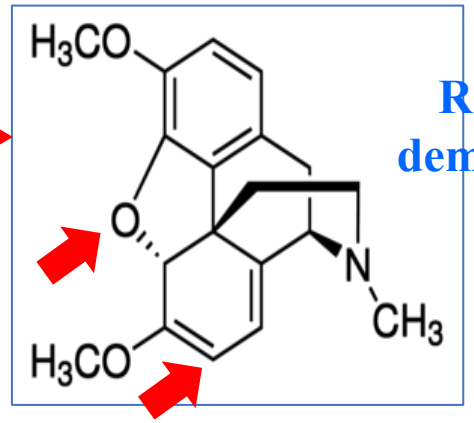
(*R*)-reticuline

Phenolic oxidative coupling



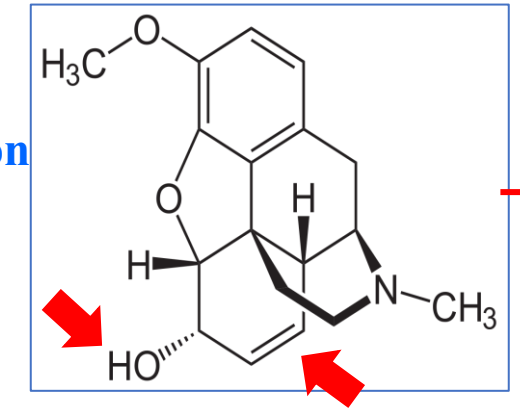
Salutaridine

Reduction
Cyclization (4,5-epoxy bridge)



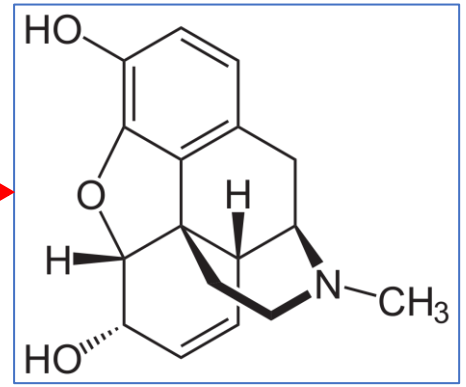
Thebaine

Reduction
demethylation



Codeine

Demethylation

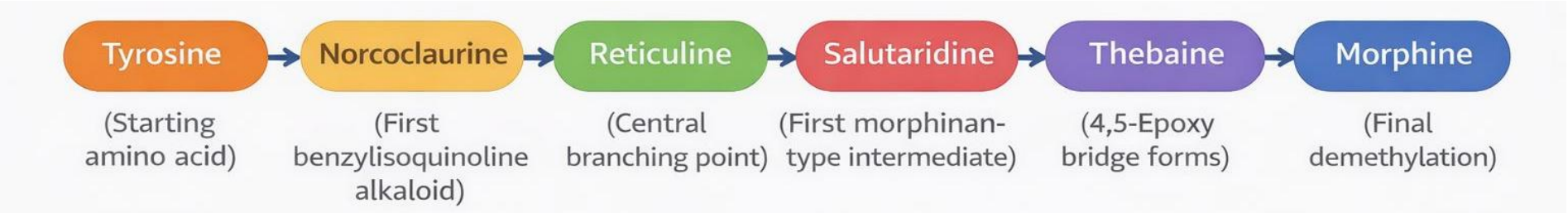


Morphine

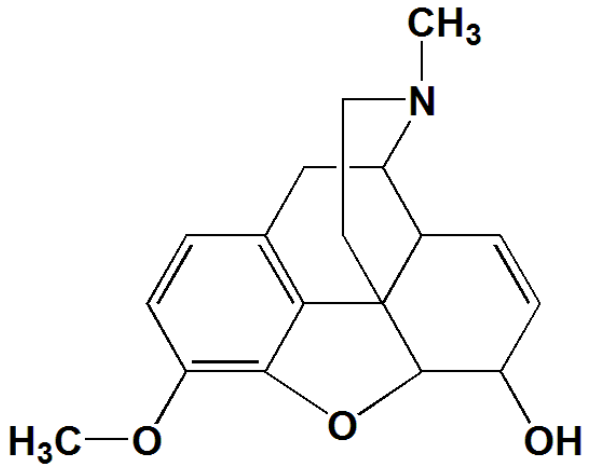
first morphinan-type intermediate.

Biosynthesis of Morphine

- It starts from the amino acid **tyrosine. Tyrosine** is converted into two simple molecules: **dopamine** and **p-hydroxyphenylacetaldehyde**.
- These two molecules combine to form **(S)-norcoclaurine**. This is **the first benzylisoquinoline alkaloid**, which is the basic building block for many opium alkaloids."
- **Methylation** and **rearrangement,** norcoclaurine becomes **reticuline**.**Reticuline** is the **central branching point in opium alkaloid biosynthesis**.
- **Phenolic oxidative coupling,** step changes the flexible molecule into a **rigid structure and produces salutaridine** the **first morphinan-type intermediate**.
- **Ring closure and bridge formation** :Salutaridine undergoes **reduction** and **cyclization** to form **thebaine (the characteristic 4,5-epoxy bridge of morphinan alkaloids appears.)**
- Final **demethylation steps,** thebaine is converted first into codeine, and then by demethylation into morphine.



2. Codeine



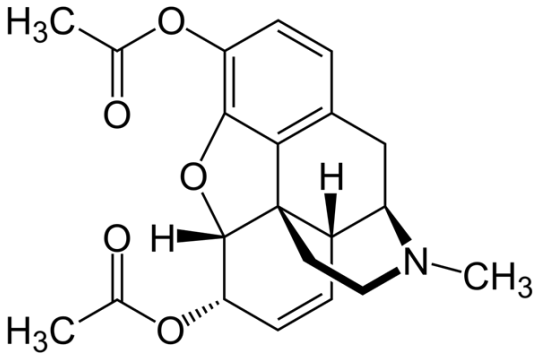
Codeine

- Codeine & its salts are narcotic analgesics & **central antitussive.**
- Although its action is like that of morphine, **but codeine is less toxic and less habit forming.**
- **Methylation blocks OH permanently → weaker receptor binding.**
- Codeine is the most widely used opium alkaloid, its obtained either **naturally** from opium plant or prepared from **morphine** by **methylation** (methylation of phenolic OH group) or from **Thebaine** by appropriate **reduction and demethylation**.
- It has **less narcotic analgesic than morphine**. **It is mainly used as anti-tussive.**



3-Diacetylmorphine (Heroin)

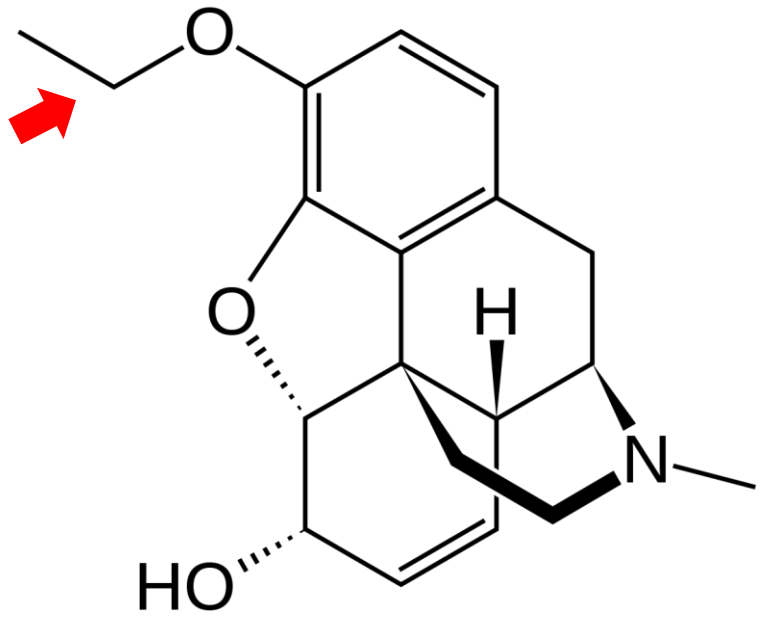
- Diacetylmorphine (Heroin) is formed by the **acetylation of morphine**; **the hydrogen atom of both phenolic & alcoholic OH-group are replaced by acetyl group**,
- Its action is like morphine**, but it is more potent than morphine** (100 times stronger), so because of its potency and the **danger of habit formation, its manufacture in the USA is forbidden by law, and its use in medicine has been discontinued.**
- Heroin crosses BBB very rapidly it is a **prodrug (**It is **enzymatically deacetylated to morphine**)
- **More drug reaches the brain faster** → greater potency and **intense effect**
- **Acetylation hides OH temporarily → better brain entry → stronger effect**.
- It has similar medicinal effects however, it is a **recreational drug**, in which case the user is seeking **euphoria.** Frequent and regular administration is associated with **tolerance and physical dependence**.





4- Ethyl morphine (dionine)

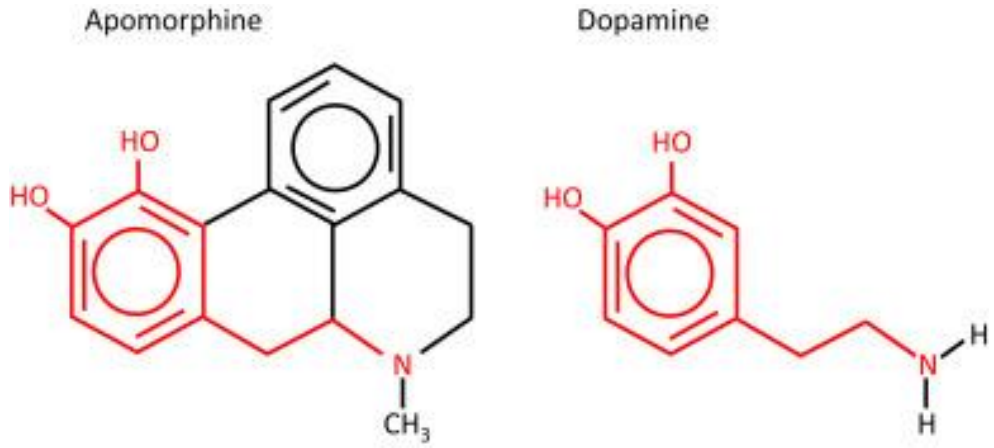
- Is formed by the **Ethylation of phenolic OH of morphine**.
- It is used in **ophthalmology as an analgesic, especially in glaucoma.**
- It is used to less extent as codeine.
- Eye drops are used topically & eye ointment as **miotic.**

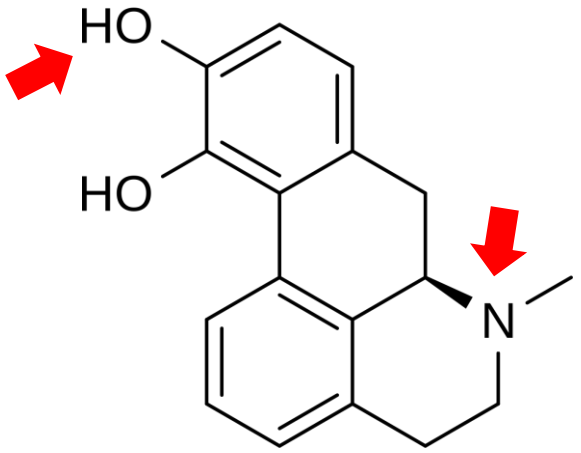


5. Apomorphine

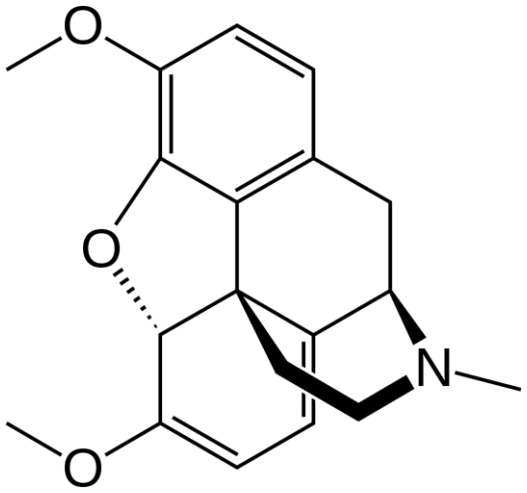
- **Prepared by heating morphine in a sealed tube with HCL.**
- **Acid-induced rearrangement** of morphine, which **destroys the opioid structure** and produces a **dopamine-like molecule** that acts as a D2 receptor agonist,
- It is used as **emetic** ,Also, it's an **agonist on dopamine D2 receptors** in the brain used as an **anti-parkinsonian** agent.



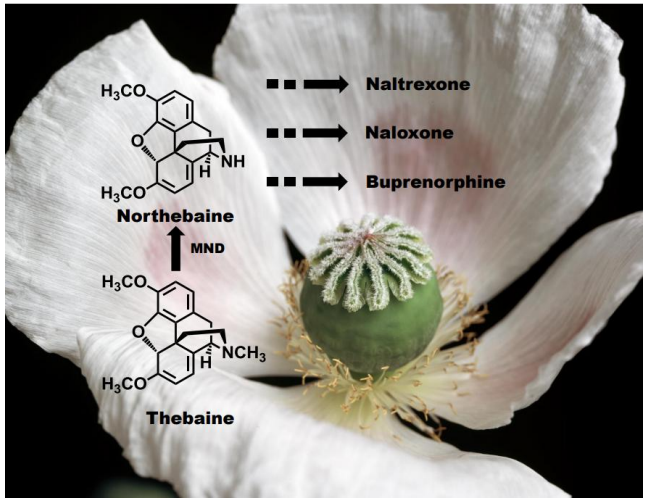




6-Thebaine



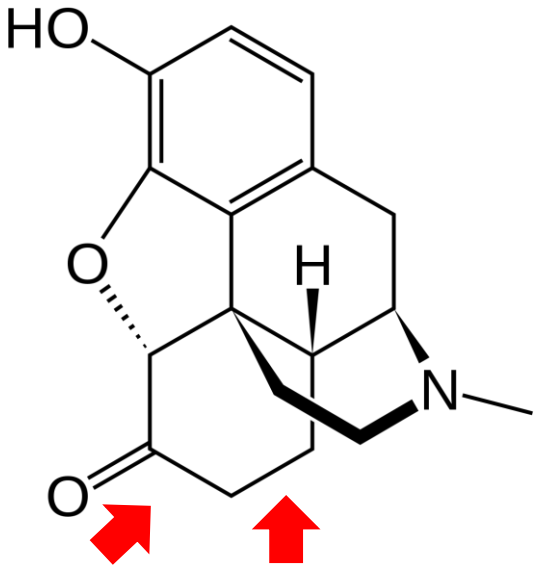
- It is a **phenanthrene derivative** of Opiate alkaloids, it is a minor constituents of opium.
- It has **CNS stimulant** effect rather than depressant effect and at high doses can cause convulsions.
- It is not used therapeutically , its is only used to prepare synthetic opioid agonists and antagonists.



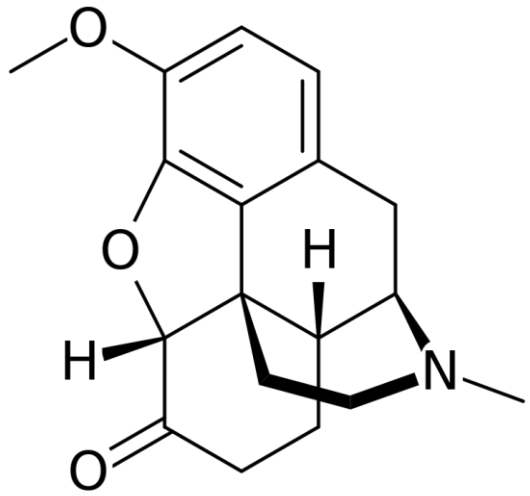
Synthetic Opioid analgesic

- Hydromorphones are formed by **reduction of-7 double bond** of morphine accompanied by **oxidation of OH at C-6 to ketone.**
- **Keton instead of alcoholic OH:** Binds **strongly to μ-opioid receptors,** Produces **intense analgesia**
- BUT: Has **shorter receptor residence time, Produces less sustained dopamine signaling in reward centers**
- It is a **powerful narcotic analgesic** tends to **strongly depress the respiratory mechanism**, but it is **less habit-forming** (however, **still addictive**).



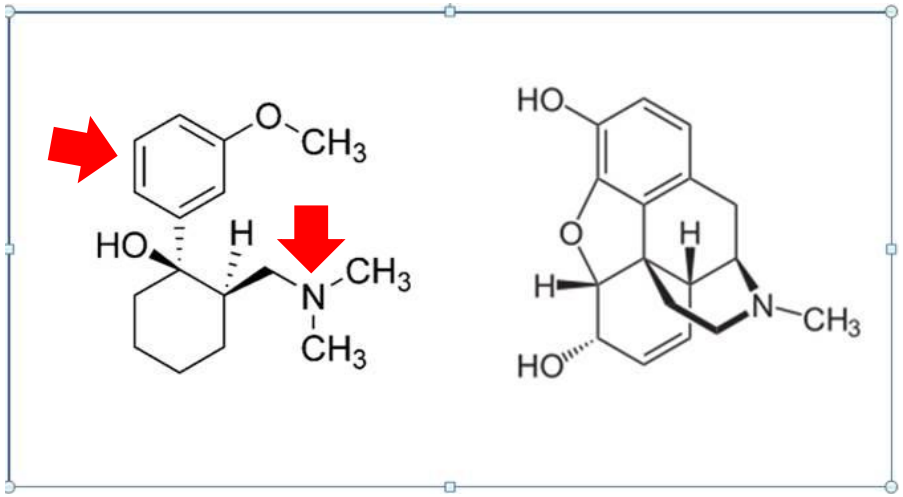


Hydromorphone



Hydrocodone

Tramadol



- Is a synthetic opioid , **centrally acting analgesic**.

→ **weaker opioid activity** but CNS analgesia is preserved, acts **centrally and peripherally**.

- **It mimics morphine:**
- **Has aromatic ring**
- **Has tertiary amine**
- **Maintains aromatic–N distance** (**3C bridge**)
- **Key differences** :
- No phenolic –OH
- Flexible, non-rigid structure



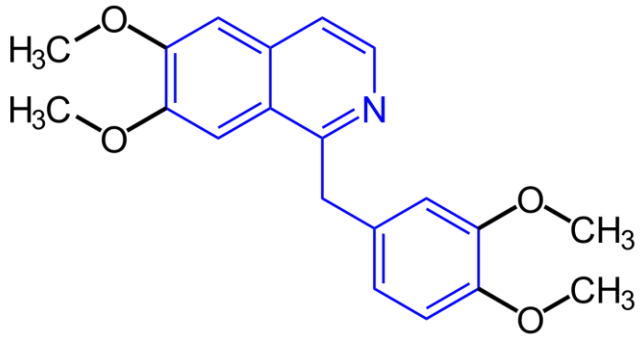


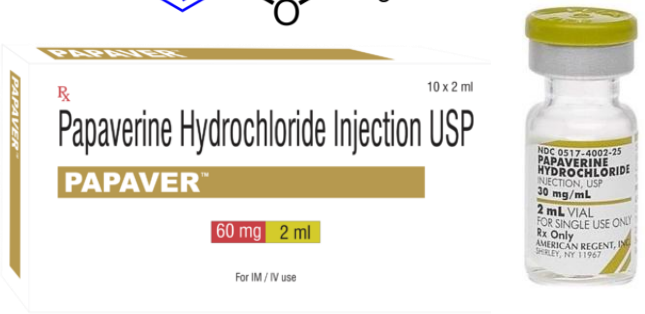


Benzyl isoquinoline Derivatives

Papaverine

- It is a derivative of **Benzyl isoquinoline**. It is a smooth muscle relaxant , anti-spasmodic and as a vasodilator.
- Used mostly by cardiologists.





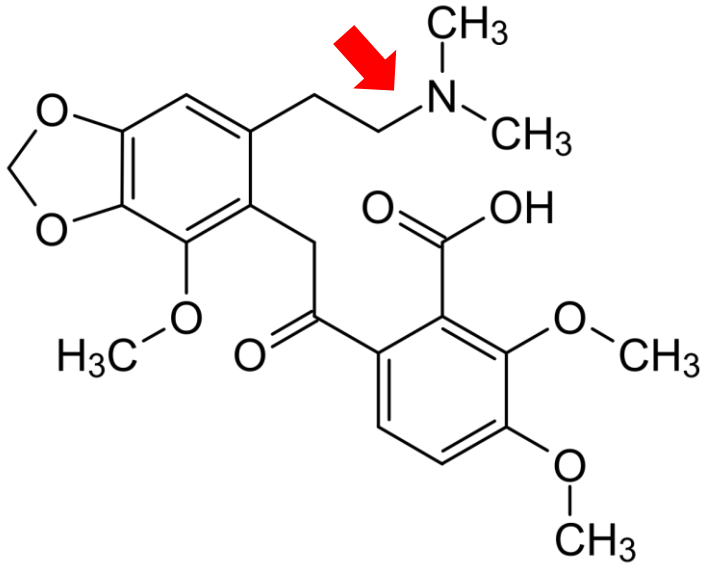
Noscapine (Narcotine) / (Anarcotine)

- 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**.



Narceine (**phenyl alkyl amine**)

- Is a **tertiary alkaloid**, where the tertiary nitrogen is part of **alkyl chain**.
- It is a **narcotic opium alkaloid**. (**not an isoquinoline alkaloid)**
- It has a **tertiary amine → can interact with CNS receptors**
- It is sufficiently lipophilic to reach the brain (produces central depressant effects)
- It is **amphoteric alkaloid** since it contains a **carboxylic acid group.**
- **More ionization** → less BBB penetration→ weaker narcotic effect
- This explains why narceine is **Narcotic** But **much weaker than morphine**

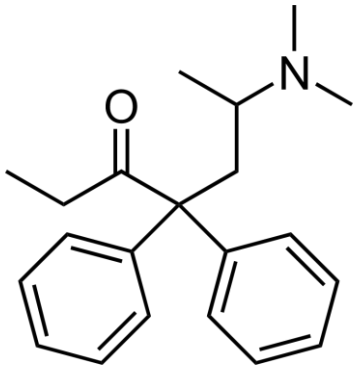


Opioids and Opiates

- **An opioid is any chemical that resembles morphine or other opiates in its pharmacological effects** by binding to opioid receptors, which are found principally in the **central and peripheral nervous system and the gastrointestinal tract.**
- 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 somniferous),***
- **Opioid** refers to **both opiates and synthetic substances, as well as to opioid peptides.**
- Many synthetic morphine-like compounds offer the same **narcotic & pain-relieving properties as morphine,** but they **are not as habit-forming** , others posses **cough relieving activity of codeine but are not addictive like morphinan opioids, Methadone** & **Meperidine.**

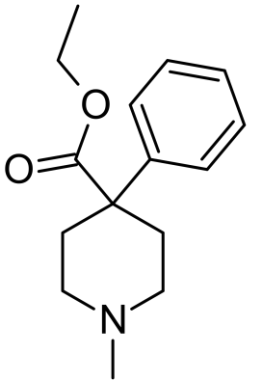
Opioids

- **Methadone** has **Tertiary amine** present, **distance (3C)** and orientation preserved, with **No phenolic OH, No rigid morphinan nucleus,**
- It has **Long half-life** and **High lipophilicity → strong CNS penetration**
- **Meperidine (Pethidine)** : **Tertiary amine present, distance (3C)** and orientation preserved the **Ester group increases** also has **No phenolic OH**
- **Moderate analgesic potency and Short duration of action.**



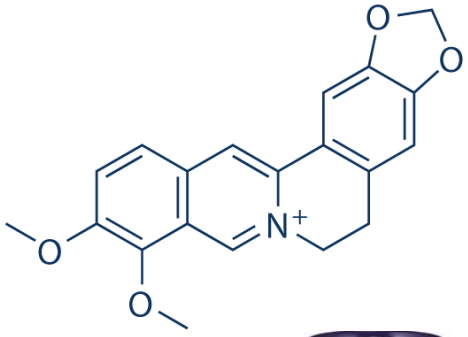
Methadone





Meperidine

Berberis



- Many isoquinoline alkaloids were isolated from **fruit** and **root** of *Berbers vulgaris*.
- The Berbers vulgaris **root** has **a yellow color which indicates content of berberine**. Berberine is isolated as a main alkaloid from the **roots and bark** of Berberis vulgaris. The main alkaloid is the **quaternary ammonium isoquinoline alkaloid berberine**.





- Poor oral absorption, Does NOT cross BBB, and Acts mainly peripherally
- Traditionally it is an **Antimicrobial,Antiparasitic (e.g. amoebiasis),Antiinflammatory**
- Modern supplements nowadays used as Hypoglycemic (↓ blood glucose) and Hypolipidemic (↓ cholesterol)



- Not recommended in, Pregnancy and can cause GI irritation at high doses
- **Drug–enzyme interactions** (affect how your liver processes medications, caution with **blood thinners or diabetes medication**.)
- Barberry is an abundant, **fast-growing shrub**, while Goldenseal is a **slow-growing** woodland plant that has been **over-harvested to the point of being endangered** in many areas (**so though goldenseal provides more berberine however due to barberry abundance makes it the current source of berberine**)





The end