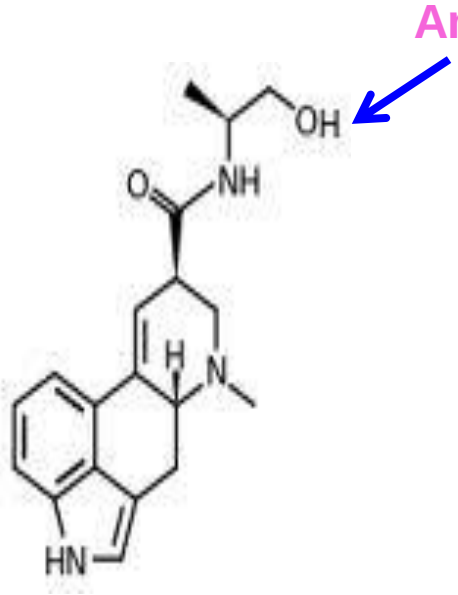
Ergot:

- **Ergometrine (ergonovine) structure:**

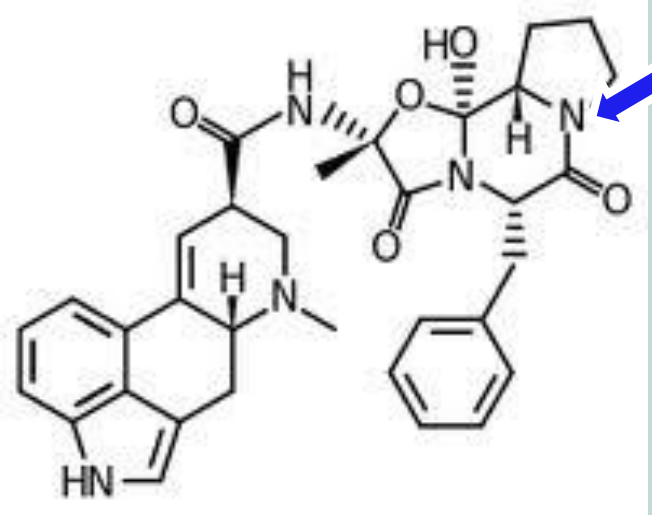


- This alkaloid causes prompt and vigorous contraction of the uterus (oxytocic action),
- As a result, it is used for prevention of hemorrhage after child birth.

Ergot:

- Ergotamine structu

❖ Ergotamine is a cyclic peptide containing the following amino acids: α-hydroxyalanine, proline, phenylalanine.



- The official salt is ergotamine tartrate.
- It is unstable, specially in aqueous solution and on exposure to light.
- On hydrogenation, **dihydroergotamine** is produced, which is used as **migraine analgesic** (**Cafergot®** tablets with caffeine)

Ergot:

lysergic acid ethylamide (LSD):

- LSD is a potent psychotic drug.
- It is thought to act by interfering with normal serotonergic transmission.
- The psychic effects are very marked (marks of psychosis ذهان, اضطراب عقلي):

I. Perceptual changes (shapes, sounds, colors).
II. Subjective time alteration {{Living in the past or future; refers to a person's subjective impression of the speed at which time passes}},
III. A disintegration of the self.
IV. An increase in suggestibility, i.e.

{{a person will accept the suggestions of another person and act accordingly}}.

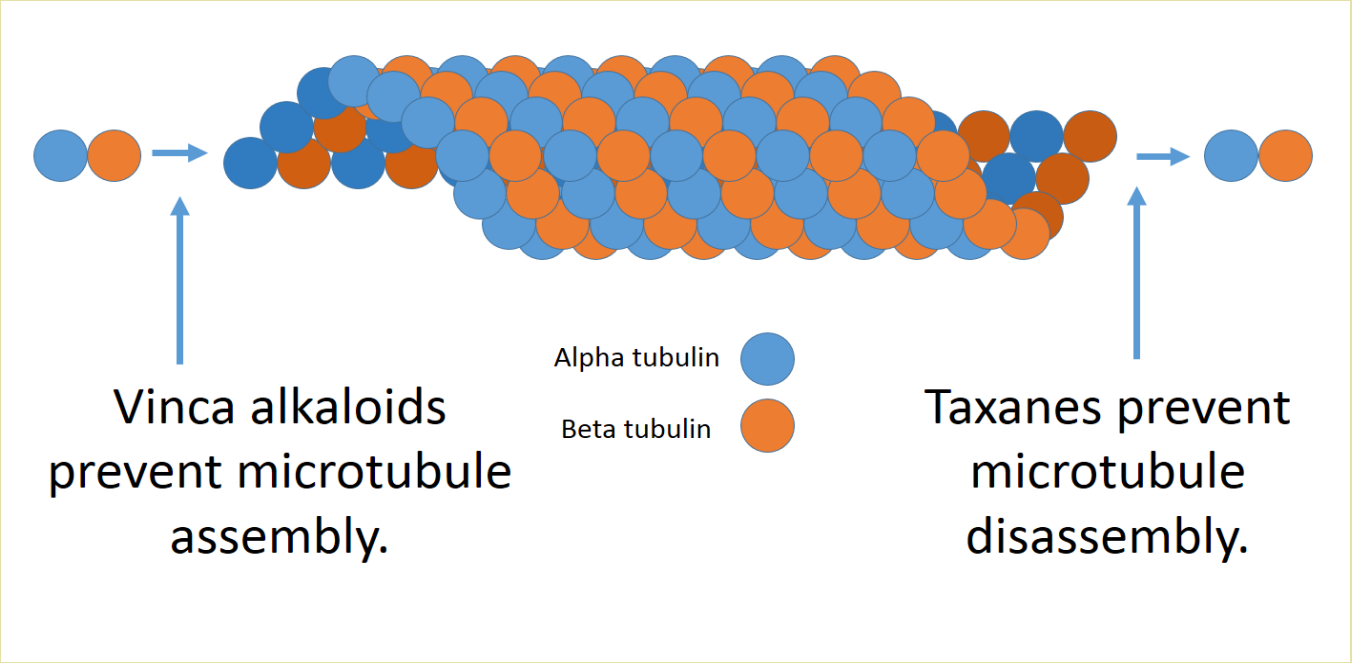
Vinca rosea alkaloids

Vincristine and vinblastine:

- These are obtained from *Catharanthus roseus* (Vinca rosea) which is a **Madagascar periwinkle**. **Apocynaceae.**
- Now, it is widely cultivated.
- It was used in Europe in folklore medicine for diabetes for centuries and had a reputation as magic plant.
- The alkaloids in this plant are referred to as Vinca alkaloids.

- A screening program at the Pharmaceutical company **Eli Lilly** revealed that this plant extracts inhibited growth of certain types of cancer cells.
- Bioassay –guided isolation of extracts of the plant led to the finding of these 2 alkaloids.
- The **problem** with this plant is that the content is too **low** (500 kg to produce 1 g of vincristine, and the extraction and purification are too complicated).
- Content of vinblastine is higher, but it is vincristine that is demanded more.
- The generic name {{**The chemical name of a drug. A term referring to the chemical makeup of a drug rather than to the advertised brand name under which the drug is sold. A term referring to any drug marketed under its chemical name without advertising**}} for it is **Oncovine** (**vincristine**, Eli Lily).
- Used for acute **leukemia**, **Hodgkin's disease** and other **lymphomas**.

- **Vinblastine:** the other drug which is used for Hodgkin's disease, lymphomas, advanced testicular and breast cancer.
- The generic name is **Velban**
- **Mode of action:** Inhibition of mitosis by binding to tubulin dimers preventing spindle formation by keeping the chromosomes aligned in the middle of the cell, thus preventing assembly of tubules (preventing polymerization).



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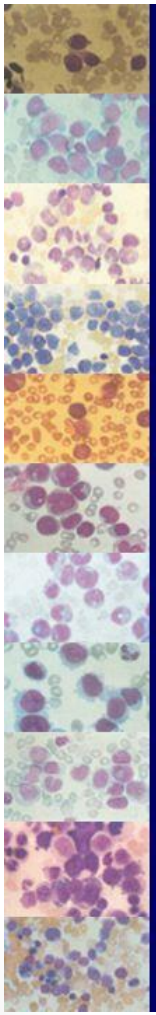


Vinca Alkaloids

- Mechanism of action
  - Bind to tubulin
  - Prevent polymerization of tubulin thus preventing microtubule formation
  - Chromosomes remain lined up in middle
  - Apoptosis
- Small differences in structure changes toxicity and activity
  - vincristine active in leukemia and is neurotoxic
  - vinblastine active in lymphomas and testicular cancer and is myelosuppressive
  - vinorelbine active in lung cancer and is neurotoxic and myelosuppressive

Biosynthesis of strictosidine-derived terpenoid indole alkaloids

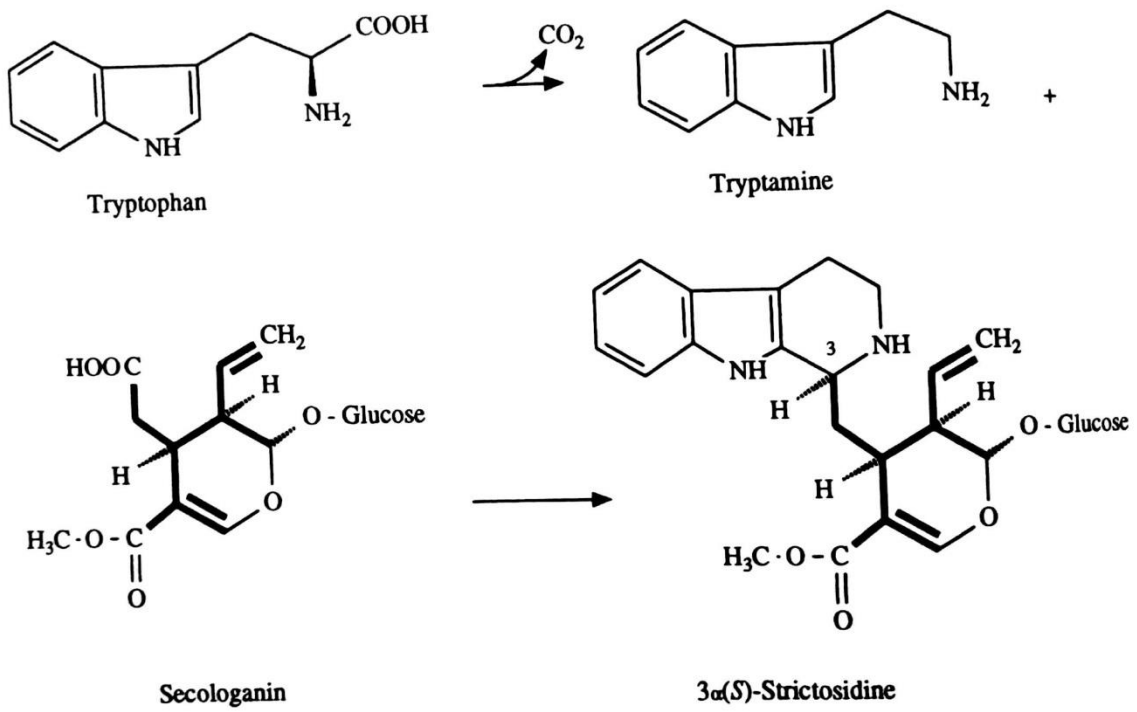
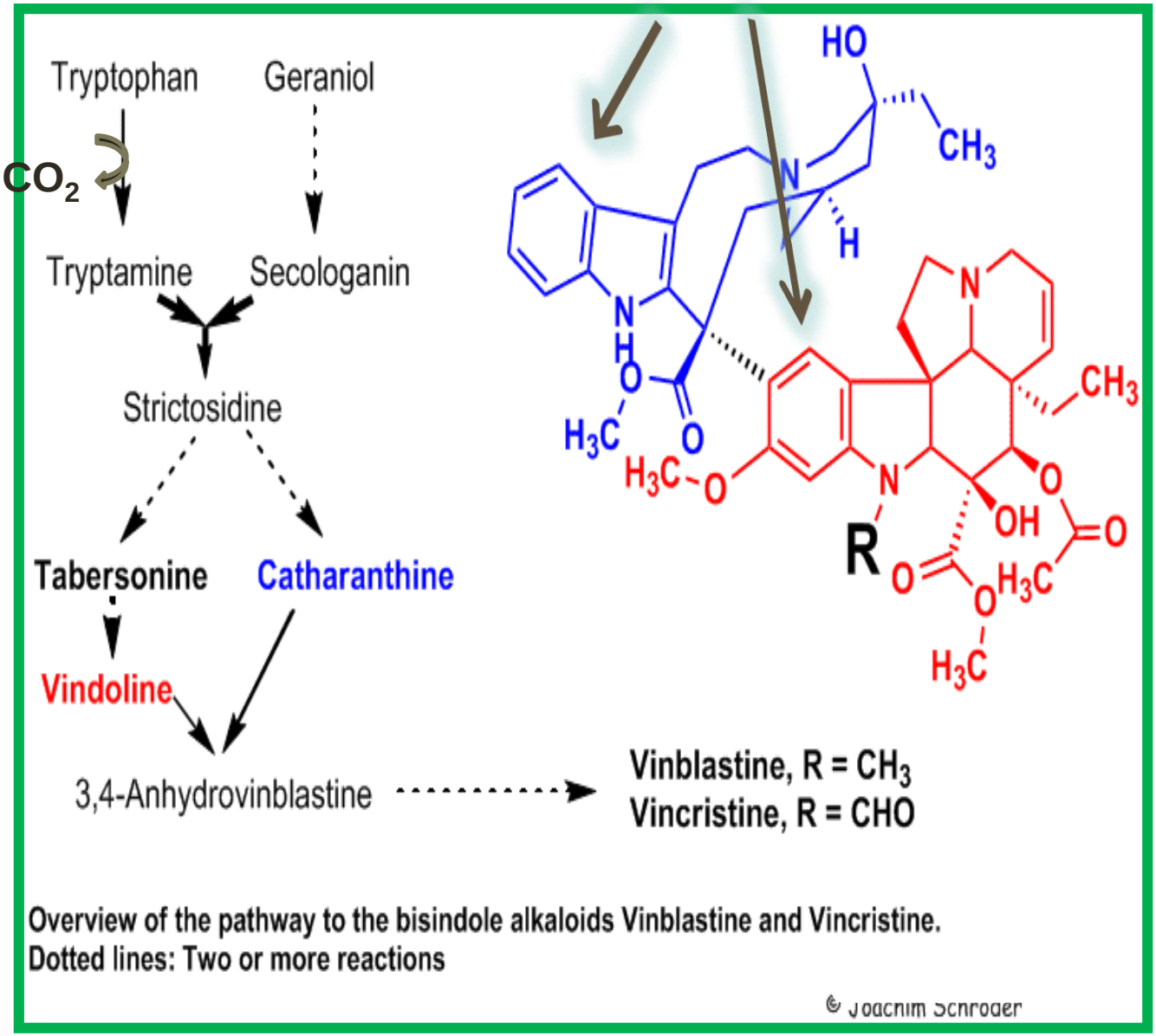


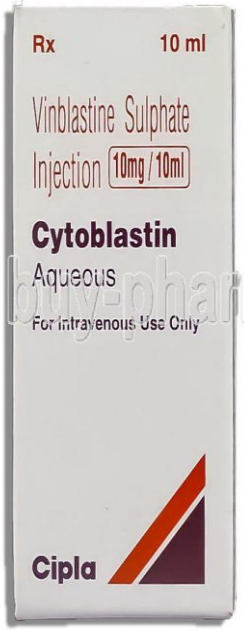
Fig. 222. Biosynthesis of 3α(S)-strictosidine

Bisindole alkaloids



Overview of the pathway to the bisindole alkaloids Vinblastine and Vincristine.
Dotted lines: Two or more reactions

© Joachim Schroder



Taxol

- Generic name: **paclitaxel**.
- Obtained from *Taxus brevifolia* tree.(**bark** of stem).

طقسوس قصير الأوراق أو طقسوس باسيفيكي أو طقسوس غربي

- Collected from USA on the pacific ocean. The mature tree is 100 years old.
- **Problem:** the plant yield is very small, 12 kg of bark yield 0,5 gm of taxol.

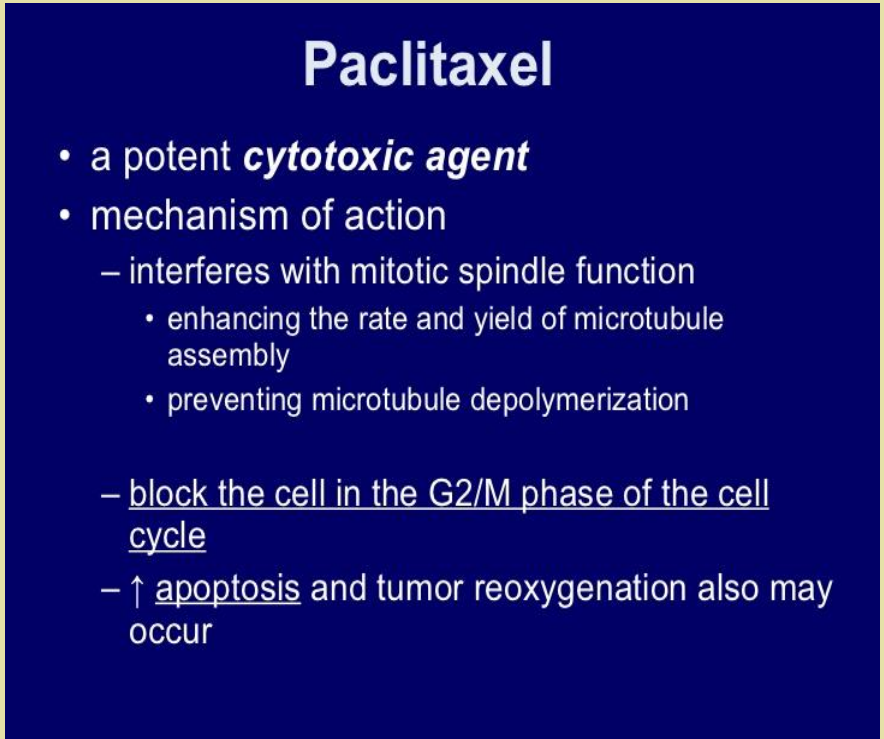
- To overcome this problem of the low yield:

1. The European species *Taxus baccata* that is known to yield considerable amounts of **10-deacetylbaccatin III (precursor for the anti-cancer drugs)**. This compound is then converted to taxol.
2. Also, by tissue culture.

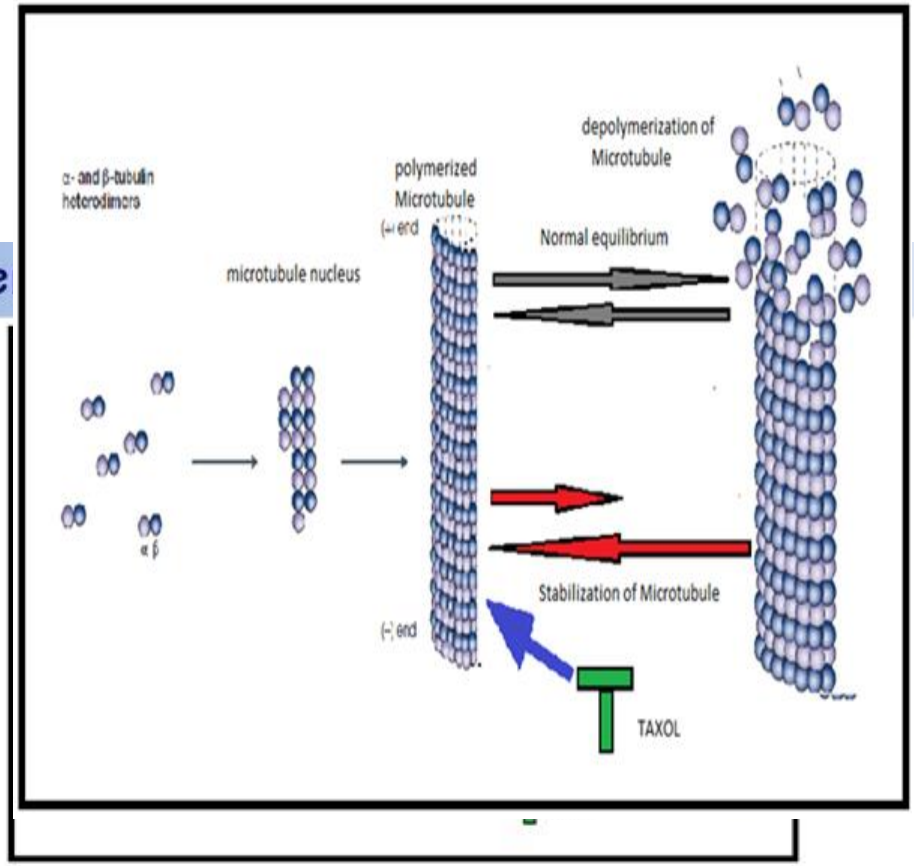
- It is active for **solid tumors**, **leukemia** and **melanoma cell line.**
- Taxol was marketed by **Bristol Myers Squibb** for:

1. Ovarian cancer.
2. Breast cancer.
3. Non-small cell lung cancer.

- **Mode of action:** prevents the mitotic spindle from being broken down by stabilizing microtubules bundles during cell division.



Anticance



Taxol promotes the polymerization of tubulin heterodimers to microtubules. At clinically relevant concentrations, taxol binds to microtubules resulting in their stabilization via suppressing their dynamic changes. Taxol thus interferes with the formation of mitotic spindle, which causes the chromosomes not to segregate, and consequently mitotic arrest.

- **Docetaxel:**

- Is more water-soluble than paclitaxel.
- A semi-synthetic drug from 10-deacetylbaccatin.
- It also works as paclitaxel by stabilizing the microtubules.
- Used as a single agent against **breast cancer** that is resistant to other agents or which has recurred after treatment.

Taxus baccata

Strychnine and Brucine:

Nux-vomica الجوز المقيء

Botanical source:

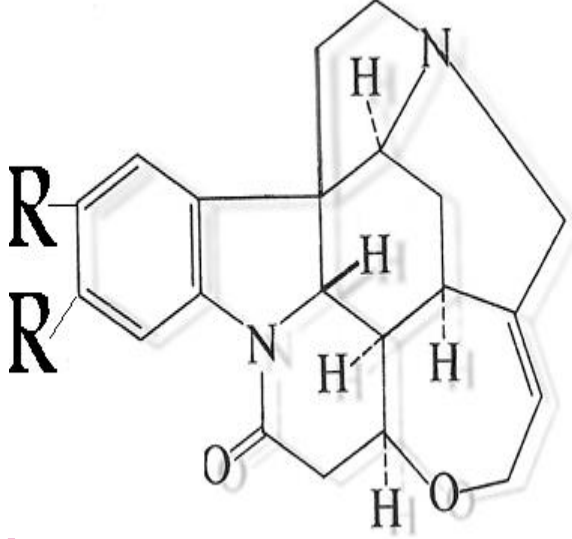
Seed of *Strychnos nux-vomica* - *Loganiaceae*.

Use: poison to kill birds and rodents

Very toxic compound which stimulates the CNS, greatly increasing the reflex excitability, presumably by preventing the effect of the inhibitory chemical signals that control muscle contractions by normally exerting a "switch-off" on them, so it causes spasms, glycine-antagonist---

Arched-back position

** Used only for studying the sympathetic and parasympathetic action of drug.



R= H: Strychnine

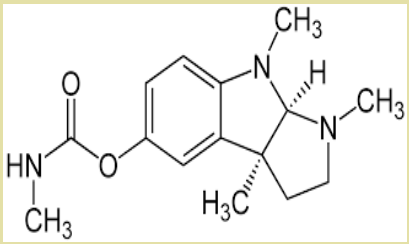
R= OCH3: Brucine

Physostigmine and Neostigmine Alkaloids:

Biosynthetic origin:

Botanical source: seed of *Physostigma venenosum* فول كالابر- *Fabaceae*.

Common name: Calabar been.



Pharmacological effect:

A reversible cholinesterase inhibitor (parasympathomimitic i.e increases the effect of acetylcholine).

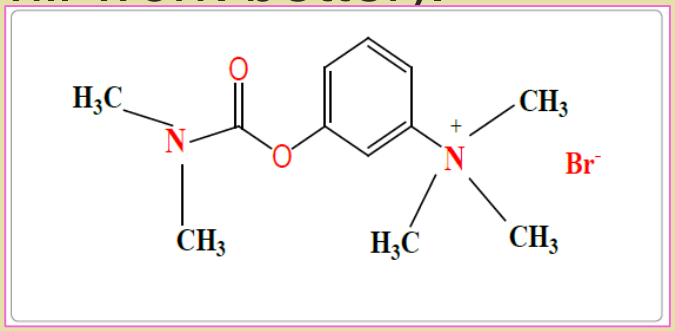
Used in acute open-angle glaucoma (in combination with pilocarpine).

1. It increases the contraction of ciliary
2. muscles and **2.** increases excretion of aqueous humor
3. decreases intraocular pressure (IOP).

- Given I.V or I.M for its toxicity, and because it is unstable compound as it is an (ester and amide).
- Antidote of choice against *Datura stramonium* poisoning.

Neostigmine: synthetic alkaloid.

- Not an **indole** alkaloid.
- Action: normalizes contraction of striated muscles by facilitating nerve impulse (muscles will work better).
- Has a positive charge (4° alkaloid),
- therefore it is soluble in water.
- Accordingly, it can be given S.C.



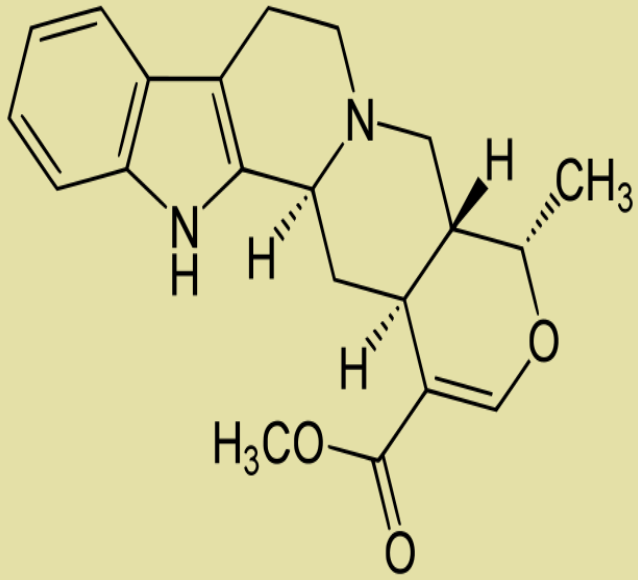
❑ Uses:

1. For diagnosis and treatment of **myasthenia gravis** (a rare chronic autoimmune disease marked by muscular weakness without atrophy, and caused by a defect in the action of acetylcholine at neuromuscular junctions).
2. Post-operation bladder surgery.
3. To reverse the effect of muscle relaxants e.g. tubocurarine.

- Side effect: miosis, convulsions, respiratory arrest, bradycardia (all are due to the cholinergic effect).

Ajmalicine

- An indole alkaloid obtained from the roots of *Vinca rosea* (***Catharanthus roseus***)and the roots of *Rauwolfia serpentina*.



Uses:

1. **Antihypertensive.**
2. **To increase the blood flow in the brain and in the peripheral parts of the body.**

Rauwolfia Alkaloids:

Botanical source: root of ***Rauwolfia serpentina*** (*Apocyneceae*).

Examples: reserpine and rescinnamine.

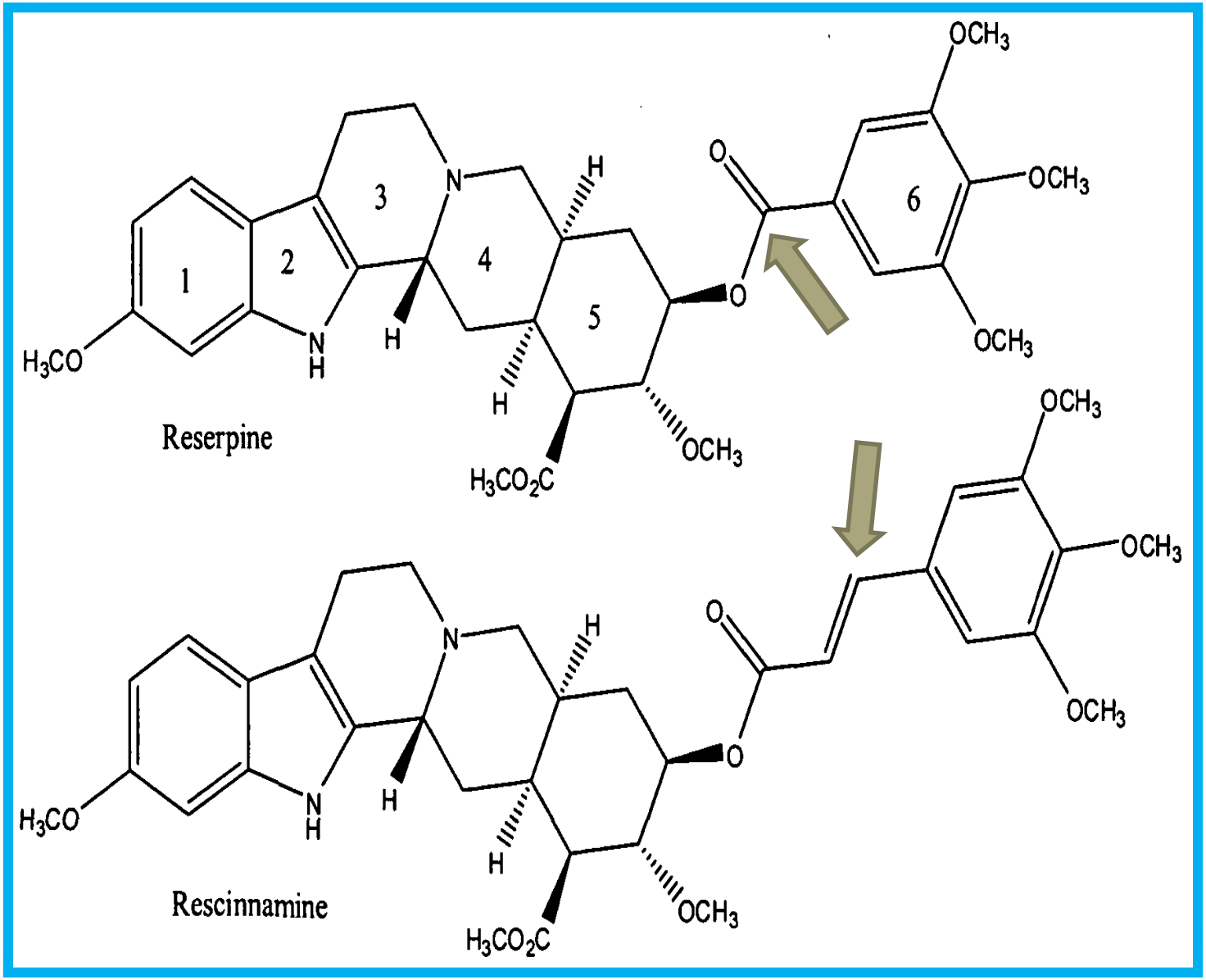
** Reserpine was an important antihypertensive drug.

** It also has a tranquilizing effect.

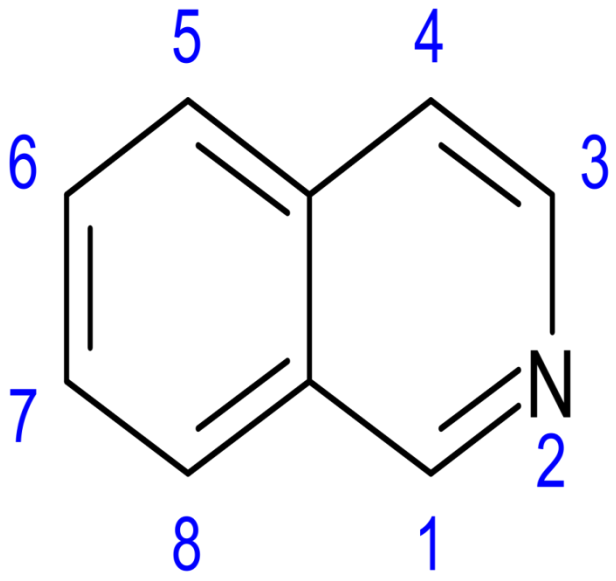
High doses could cause mental fatigue and depression.

Mechanism of action: anti-hypertensive; depletion of catecholamines peripherally (decrease in epinephrine and norepinephrine), depletion of central neurotransmitter (mainly serotonin and norepinepherine).

** Unstable compound due to existence of an ester linkage.


Reserpine
Rescinnamine

Isoquinoline Alkaloids



Dr. Yousef Abusamra

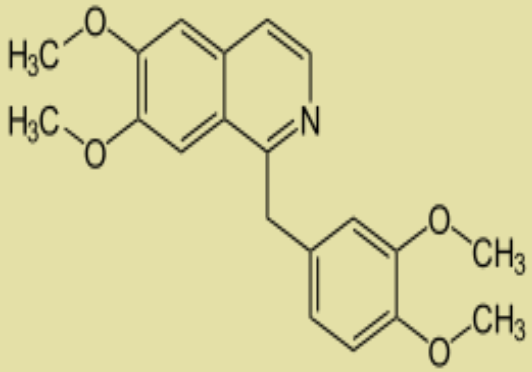
Isoquinoline alkaloids

- This group include the followings:

I. Benzyl isoquinoline type:

Papaverine:

- An opiate alkaloid isolated from the plant *Papaver somniferum*, الخشخاش المنوم and is also produced synthetically.
- Effect: a direct-acting smooth muscle relaxant.



Morphinan type alkaloids:

Morphinan: the prototype structure of numerous drugs

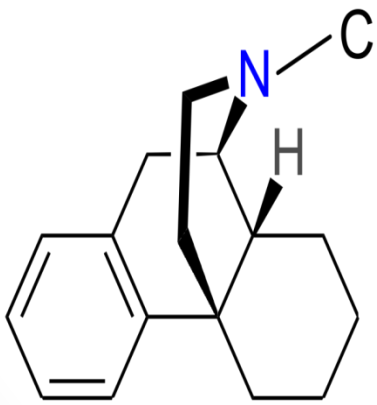
Including opiate analgesics, cough supressants…etc.

Opium alkaloids:

Botanical source:

- Dried latex of *Pappaver somniferum* الخشخاش المنوم -

Papaveraceae



Morphinan

Pharmacology:

1. **Papaverine** decreases the tone of smooth muscles, thus, It has a spasmolytic and vasodilating effect {used to increase blood flow}.
2. It is neither narcotic nor addictive.
3. It is of a beneficial effect on angina pectoris.
4. It is used for treatment of pulmonary embolism and cerebrovascular thrombosis.
5. Anti-arrhythmic.

Pharmacological action and medicinal uses:

Morphine:

1. potent analgesic and pain-killer in several cases and ailments such as: myocardial infarction, cancer, renal colic, bone and joint pain ..etc.
2. Cough supressant and anti-diarrheal (severe). However they are other more convenient drugs for these two cases.

Codeine:

1. Analgesic to treat mild to moderate pain.
2. Anti-tussive.
3. Anti-diarrheal.

Thebaine (codeine methyl enol ether):

- Thebaine is **not** used for therapeutic or recreational purposes, but is **converted** industrially into a variety of compounds including **oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, buprenorphine**.

Papaverine:

1. Used to increase blood flow throughout the body, including the heart and the brain. Papaverine is a vasodilator. It works by relaxing the muscles in the blood vessels.
2. Papaverine is also an antiarrhythmic medication that treats certain abnormal heartbeats (ventricular arrhythmias).

Heroin:

1. Strong analgesic and pain-killer, like morphine, to relieve severe pain (e.g. myocardial infarction, injuries …etc)
2. As a maintenance drug among heroin addicts.
3. As a substitute for morphine as a pain-killer as it is more lipid-soluble.

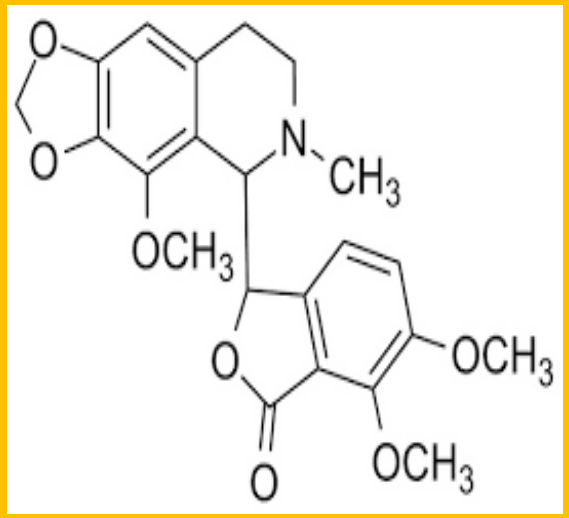
Noscapine: is devoid of pain-killing properties.

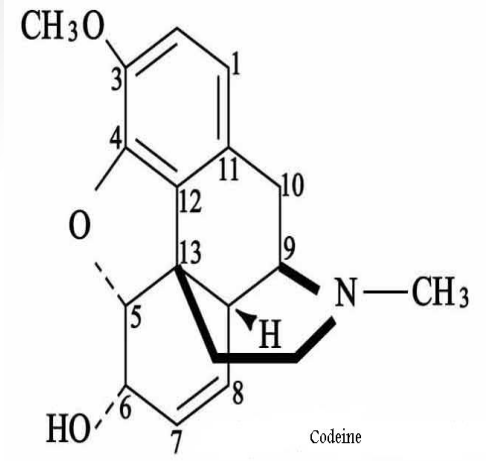
- Anti-tussive.

- **Noscapine** (previously narcotine):
  - It is a benzylisoquinoline (like papaverine).
  - Found in *Papaver somniferum* (opium) 4-8%.

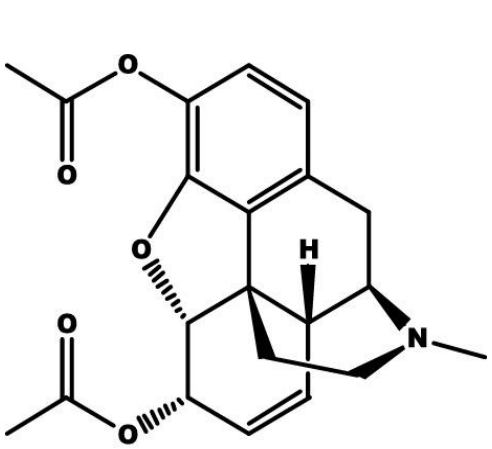
Pharmacology:

- Smooth muscle relaxant effect.
- It is used as antitussive with no **analgesia** or **sedation**.
- It is devoid of any narcotic or hypnotic activity.

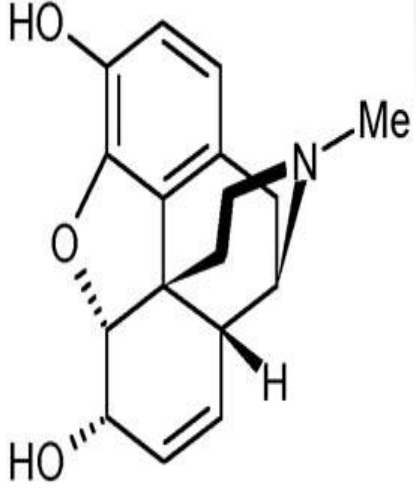




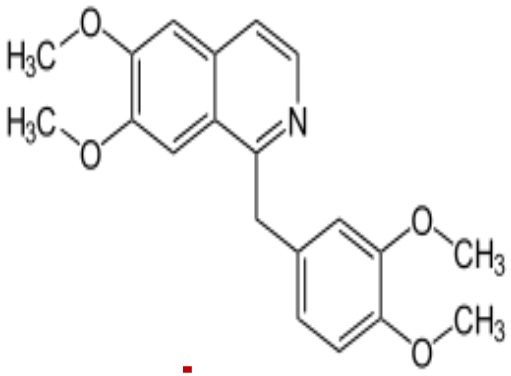
Codeine



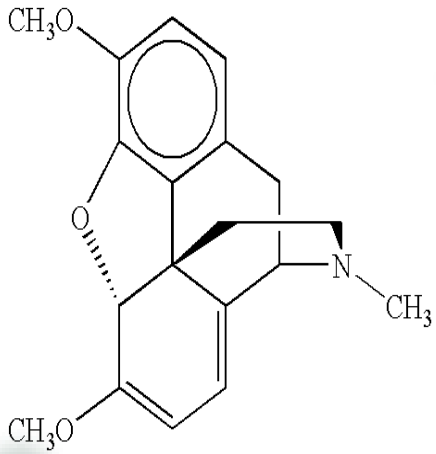
Heroin



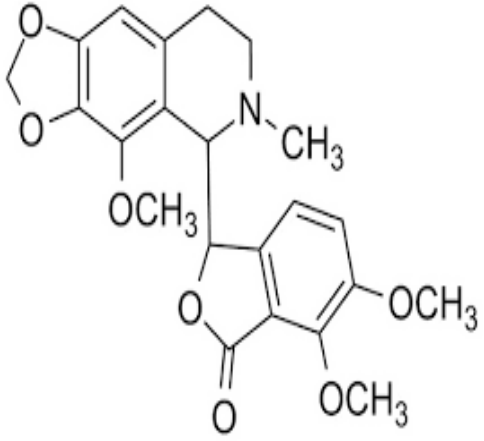
Morphine



Papaverine



Thebaine:
6-methoxy codeine



Noscapine (Narcotine)

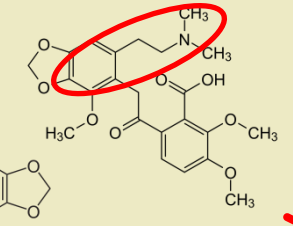
Opium Alkaloids

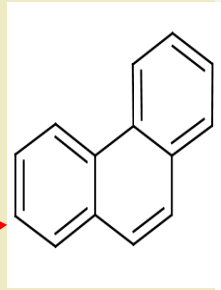
- OPIUM is the air-dried milky exudates (latex) obtained after the incision of the unripe capsules of ***Papaver somniferum***, {family: **Papaveraceae**}.
- The word opium comes from a Greek word which means "poppy juice".
- The name "morphine" was derived from a Greek word "Morpheus": the god of dreams.
- Opium is reported to contain many alkaloids (about 40), the most important of them are :

Morphine, codeine, thebaine, papaverine, noscapine and narceine.

➢ **They are divided into 4 groups according to structures:**

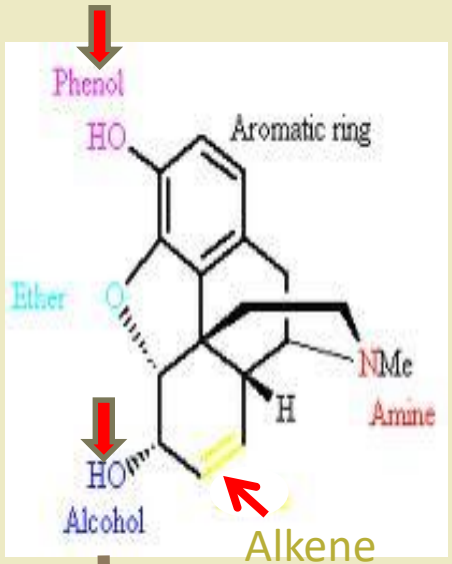
1. **Benzylisoquinoline**: like papaverine.
2. **Phenylethylamine**: e.g., narceine.
3. **Diisoquinoline**:e.g., cryptopine.
4. **Phenanthrene**: e.g., morphine, codeine, thebaine.

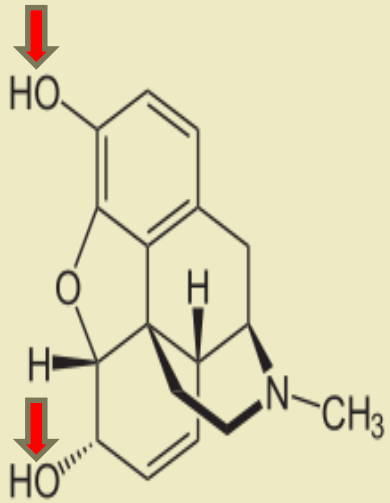




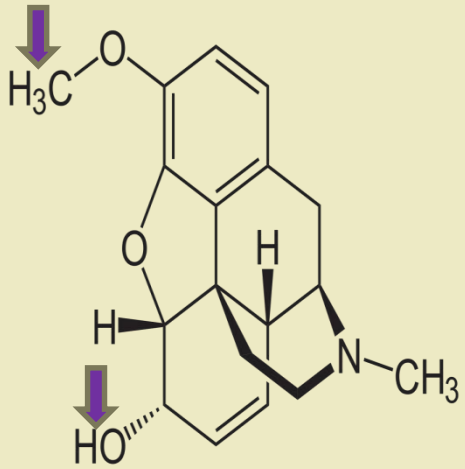
- **Phenanthrene alkaloids:**

➢ These are important alkaloids in opium, morphine (8-10 %), codeine (0.5-2%) and thebaine (0.1-1%).



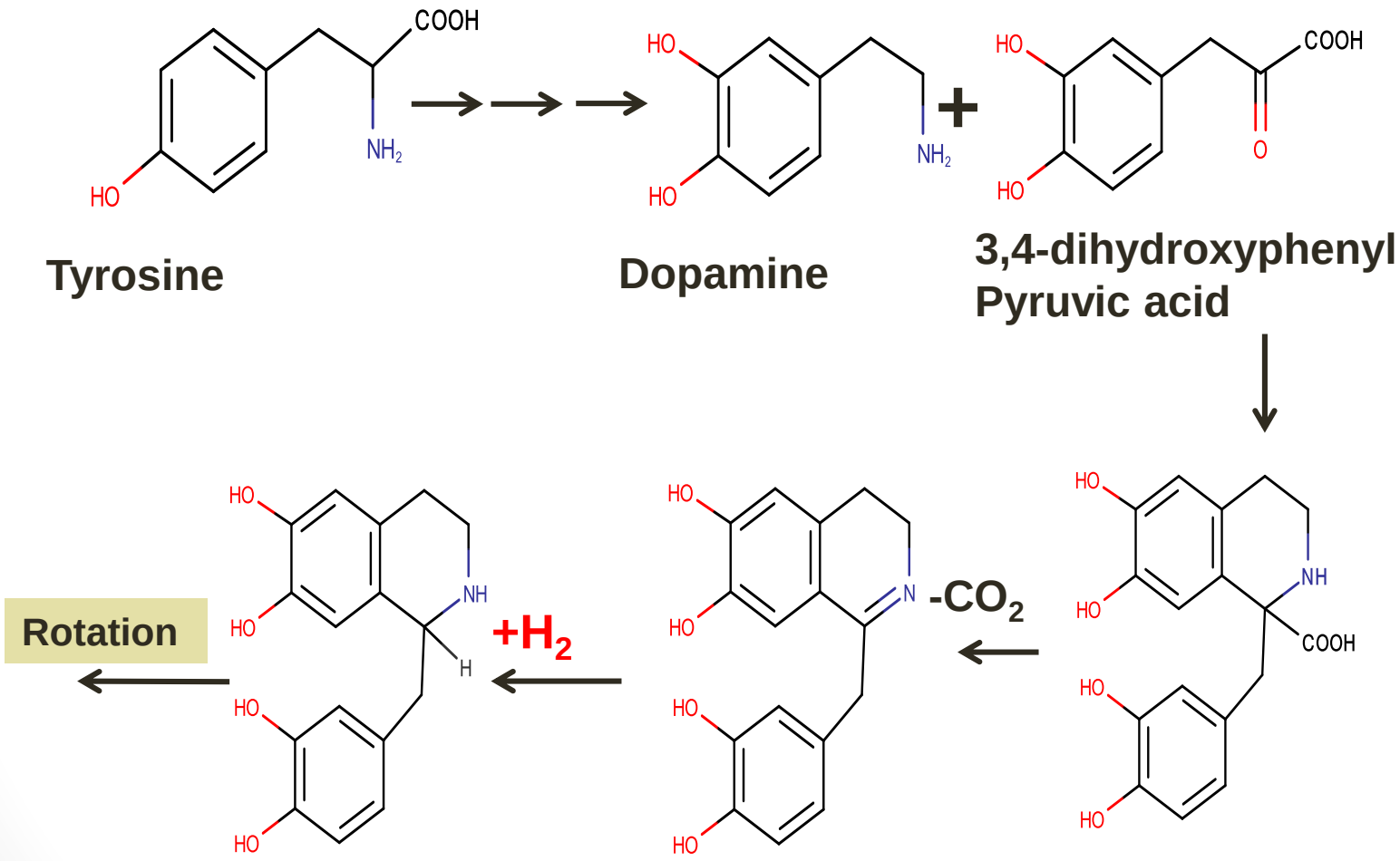


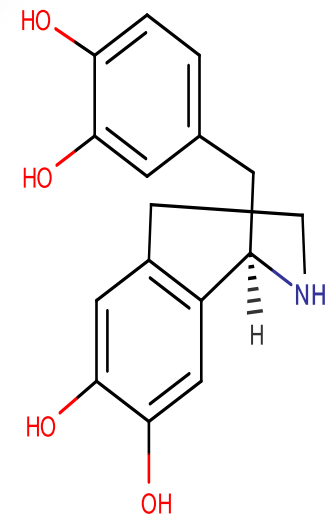
Morphine



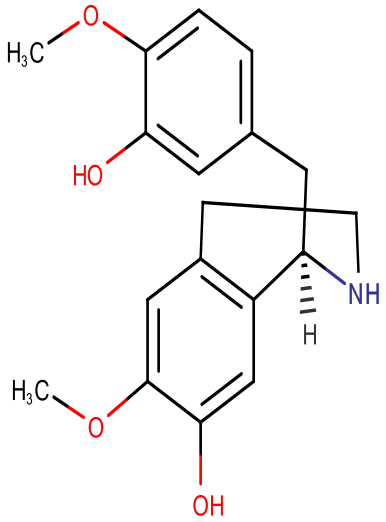
Codeine

Biosynthesis of opium alkaloids



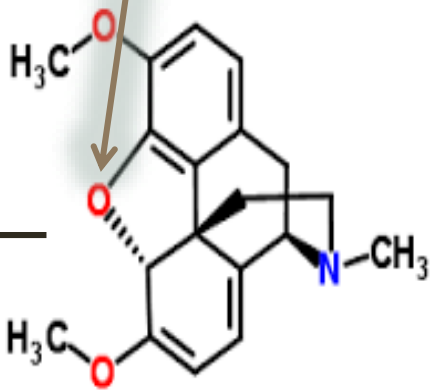


Nor-landanosoline

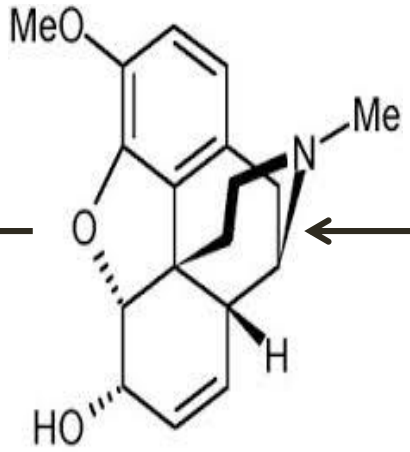


Reticuline

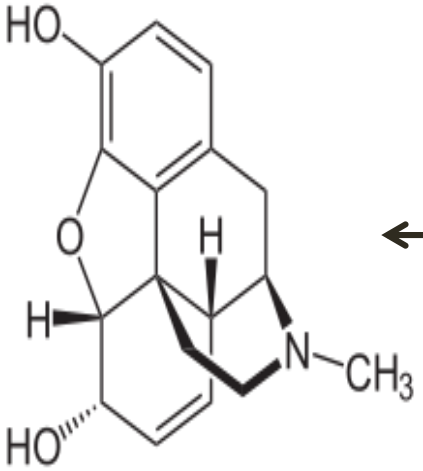
Phenolic oxidative coupling



Thebaine



Codeine



Morphine

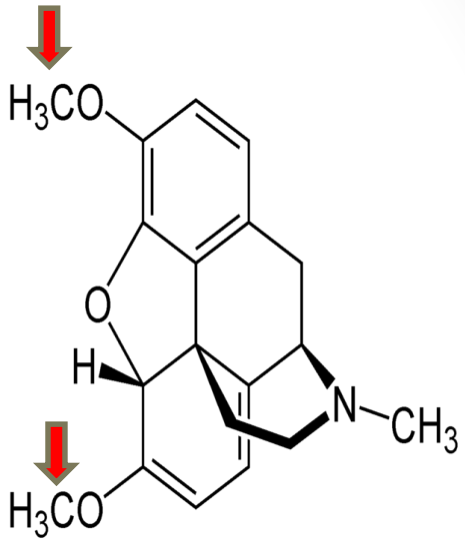
Pharmacology:

- The pharmacological action of opium is mainly due to morphine.
- It acts first as a stimulant, then as a sedative and hypnotic depressing the CNS.

❖ Effect:

1. Analgesia.
2. Miosis (differentiate from meiosis).
3. Euphoria.
4. Respiratory depression.
5. Sedation.
6. Physical dependence.
7. Bradycardia.
8. Constipation.

Thebaine



Adverse effects:

1. Constipation.
2. Sedation.
3. Nausea and vomiting.
4. Respiratory depression.
5. Hypersensitivity.
6. Anticholinergic effect: dry mouth, urinary retention.
7. CNS excitation.
8. Tolerance: an increase in dose is required to maintain analgesia.
9. Dependence: addiction, if used for a long time.

Withdrawal symptoms:

1. Anxiety.
2. Irritability.
3. Insomnia.
4. Chills.
5. Salivation.
6. Diaphoresis.
7. Nausea.
8. Vomiting.
9. GI cramping and diarrhea.

❖ These symptoms last for about **10-14** days, unless a further dose of morphine is taken.

Uses:

Morphine:

1. Post-operative analgesic for major operations.
2. Cancer pain (terminal pain).

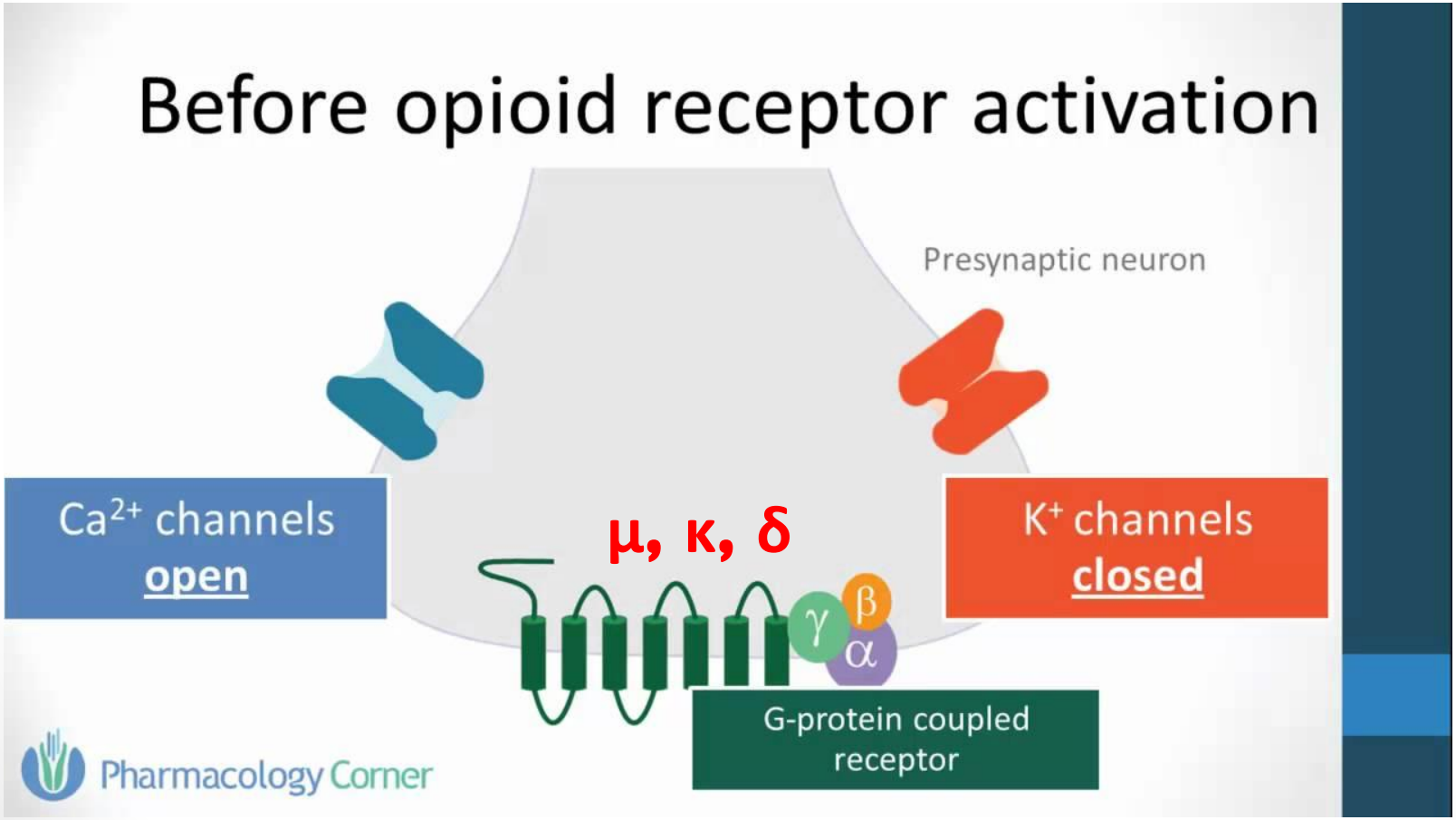
Codeine:

- Mainly used as **antitussive**, it suppresses the coughing center in brain.
- Codeine is less toxic and much weaker in action than morphine with less development of tolerance.


Boots
PHARMACEUTICALS
PARACETAMOL
& CODEINE
Effervescent Tablets
Co-Codamol
Can cause addiction
For 3 days use only
DUAL ACTION PAIN RELIEF
Effective pain relief
32
New advice for drivers - see leaflet


MORPHINE
Sulfate Inj, USP
(25 mg/mL)* 250
10 mL
MORPHINE
Sulfate Inj, USP
5 mg/10 mL
Morphine Sulfate
Injection, USP

Mechanism of action



Mechanism of action

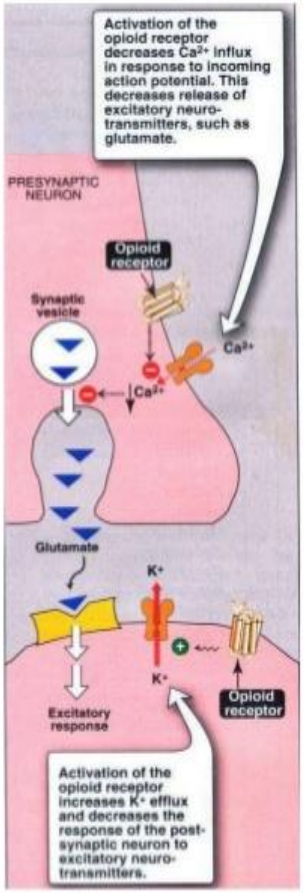
Mechanism of Action

All opioid receptors are G-protein coupled receptors and inhibit adenylate cyclase.

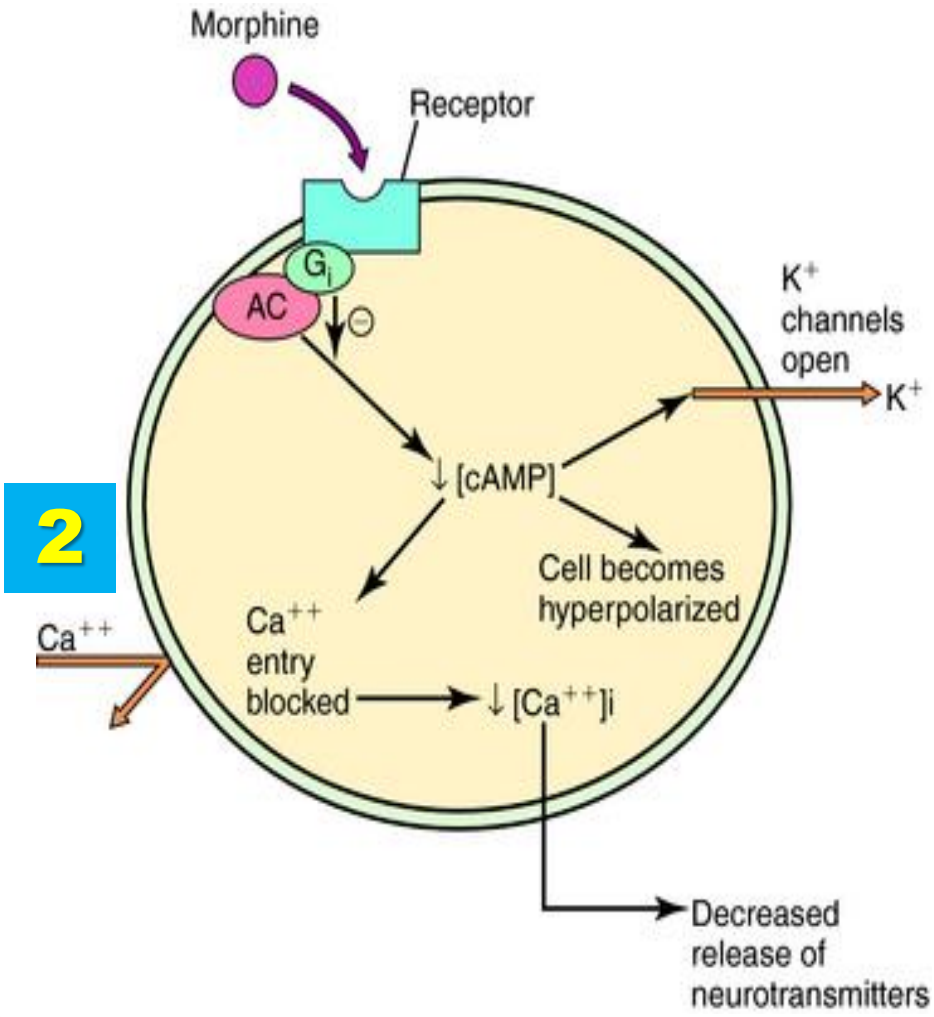
They are also involved in

- Postsynaptic hyperpolarization (increasing K+ efflux)
- Reducing presynaptic Ca^{++} influx

thus inhibits neuronal activity.



Mechanism of action



1

In the postsynaptic neuron

2

3

In the presynaptic neuron

e.g. glutamate a stimulatory neurotransmitter

- Opium is the dried milky exudates, or latex, obtained by incising the unripe capsules of opium poppy.
- The plant is an annual herb with large solitary (sole, alone) flowers, either white or pink in color.
- The latex is obtained by incision of the ripening capsule (that is changing in color from blue-green to yellow).
- The incision is made at night.
- The milky exudates ooze out (filtrate out), and they rapidly turn brown and coagulate.
- They are collected the next morning by scrapping (scratching) from the capsule.
- The raw opium is molded into balls or blocks (lumps) and wrapped in poppy leaves and shade-dried.

- **The plant is cultivated for Black Market in the following countries:**

1. Asia Minor (Turkey).
2. Afghanistan.
3. Burma (Myanmar).
4. Laos (Near Thailand).
5. Latin America (Mexico and Columbia).

- **Official drug is cultivated in:**

1. India.
2. China.

Semisynthetic preparations

1. **Heroin:**
   - It is morphine diacetate.
   - Highly addictive analgesic, with more lipophilicity.
   - More abused drug.

2. Apomorphine:

- Injection of the drug is used for its **emetic** properties to treat intoxication when vomiting is not contraindicated (as in case of poisoning by caustic alkali, or when the patient is in coma) .
- Vomiting is induced by injecting 10 mg of alkaloid subcutaneously).
- The alkaloid is also available as sublingual tablets which are used sometimes in recovery of alcoholism.
- Nowadays, it is less frequently used for this purpose, but is used to control the symptoms of Parkinson's disease, **as it is a stimulator to dopamine receptors.**

3.Nalorphine:

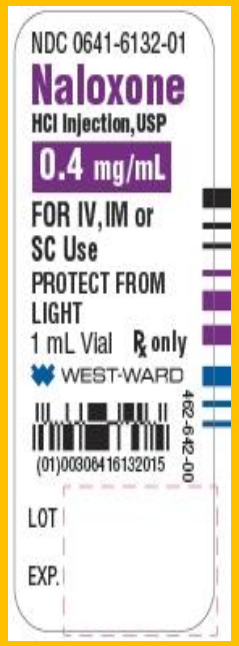
- It is an opioid antagonist and partial agonist.
- It interrupts the effect of morphine by displacing it from the receptors to where it binds.

- It is used to treat the respiratory insufficiency due to opiates.
- It is **contraindicated** in drug-addicted patients with risk of withdrawal syndrome.

Totally synthetic drugs related to morphine:

1. Naloxone:

- It is an antagonist to morphine.
- Is used to treat opiate poisoning including children born to opiate addicts.

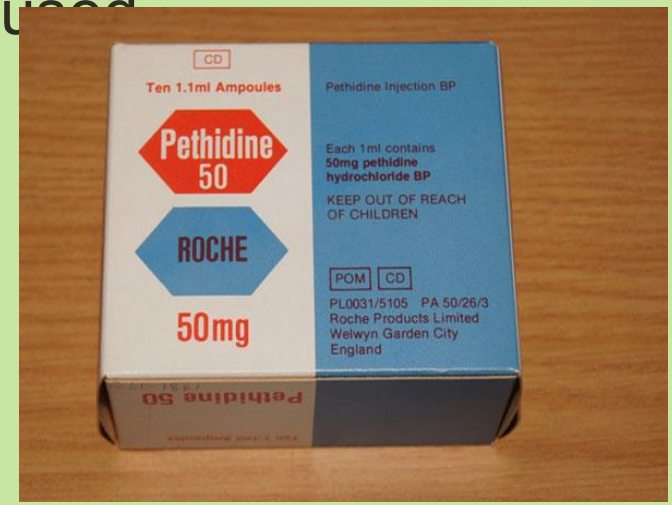


2. Dextromethorphan:

- Antitussive effect like codeine with no analgesic and narcotic effect.

3. Pethidine (generic name: meperidine):

- It is less potent than morphine, with a shorter duration of action.
- It is used by addict people.
- {{Used as: **an analgesic for moderate to severe pain --- Mostly used during labor and delivery and after surgeries in general**}}.
- Less constipating (than morphine).
- Not a first-choice drug to control pain.
- Not used for chrong pain (else caused addiction).

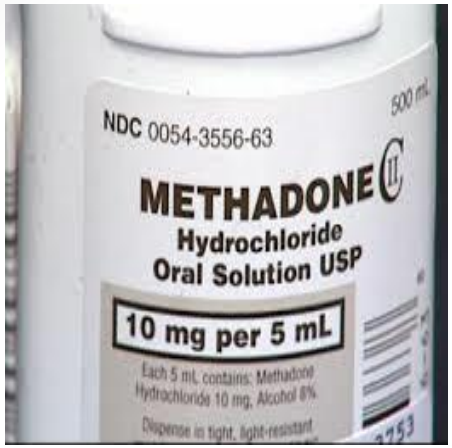


4. Fentanyl:

- It is 50-100 times more potent as analgesic than morphine.

5. Methadone:

- Has a similar activity to morphine with longer duration of action and different withdrawal symptoms.
- Is used in rehabilitation program for addict patients.



6. Tramadol:

- A new analgesic drug.
- It acts by 2 mechanisms; morphine mechanism and serotonin-adrenergic pathway.
- It produces typical morphine side effects.

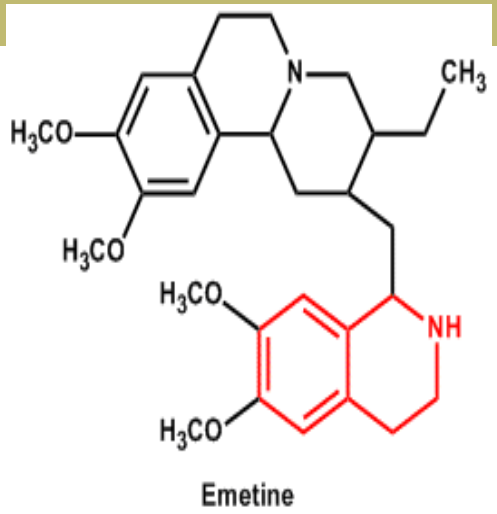
7. Etorphine:

- It is 5000 -10,000 times more potent than morphine.
- It is used as an analgesic in large animals like elephants.

2. Benzyltetrahydroisoquinoline:

Ipecacuahna alkaloids:

- Rhizome *of Cephaelis ipecacuhana* (*Rubiaceae*)
- **Emetine:** anti-protozoal and to induce vomiting.
- **Cephaeline**: to induce vomiting (emesis).



Emetine

2-benzyltetrahydroisoquinoline: Ipecac alkaloids

- Emetine, cephaeline, psychotrine : obtained from the roots of *Cephaelis ipecacuana*, (family **Rubiaceae**), a shrubby small plant native to tropical rain forest of Brazil .
- It causes vomiting and has local reputation for use for dysentery.

Pharmacology:

- 1. For dysentery (*Entamoeba histolytica*): by ***inhibiting protein synthesis in the protozoal cell by binding to 40S ribosomal subunit.***
- 2. For poisoning cases in hospitals.
- 3. In small doses, emetine and cephaline are expectorants.
- 4. It has anticancer effect , but its effect is marginal and toxic to heart.

Mode of action as emetic: locally by irritation of the mucous membrane of stomach and intestine.

- **These days its use as emetic is less because of this effect and its toxic effect on heart and liver.**

Goldenseal:خاتم الذهب

Root and rhizome of ***Hydrastis canadensis*** (***Ranunculaceae***).

Catarrha: inflammation of a mucous membrane, especially of the respiratory tract, accompanied by excessive secretions.

Uses: anti-catarrhal, anti-inflammatory, antispetic, astringent, bitter tonic (stimulate apetite), anti-diabetic.