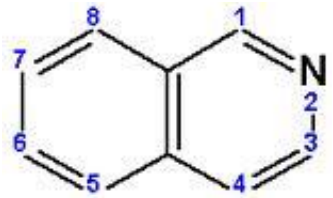
Quinoline Alkaloids, Isoquinoline Alkaloids and Benzylisoquinoline

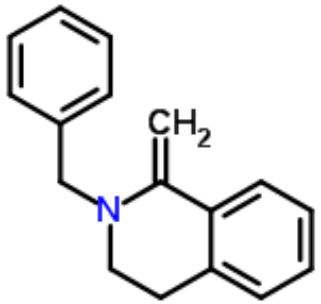
Dr. Rand Shahin

- In this chapter we will discuss very important compounds (Opium, Morphinan) alkaloids as well as alkaloids of curare and the alkaloids of ipecac.

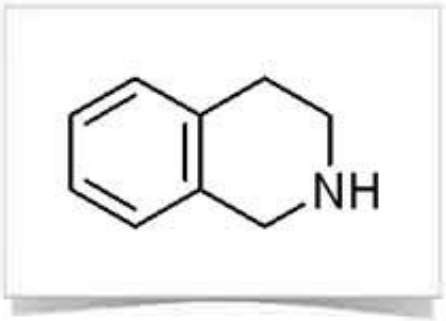
This is the basic structure of Isoquinoline and Tetrahydroisoquinoline.



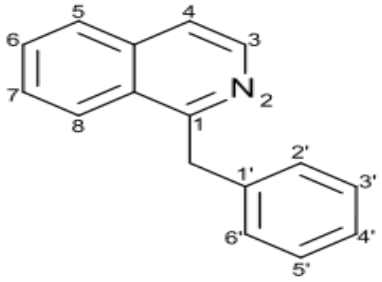
Isoquinoline



Benzyltetrahydroisoquinoline



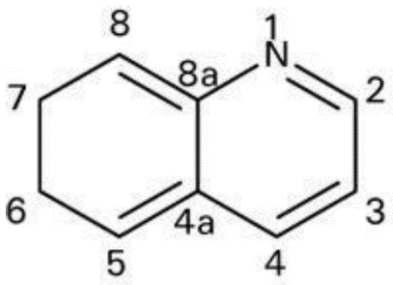
Tetrahydroisoquinoline



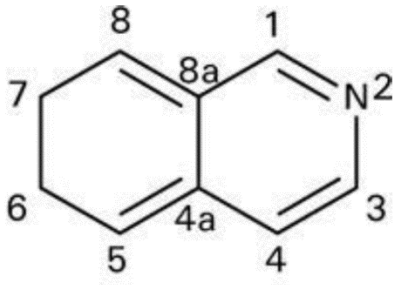
Benzylisoquinoline

Quinoline alkaloids:

- **Isoquinoline** alkaloids come form **tyrosine**, while **quinolines** come from **tryptophan**, the **difference** between quinoline and isoquinoline is the place of the **nitrogen atom**.
- In **isoquinoline**: nitrogen atom located at position number **2**.
- In **quinoline**: nitrogen atom located at position number **1**.

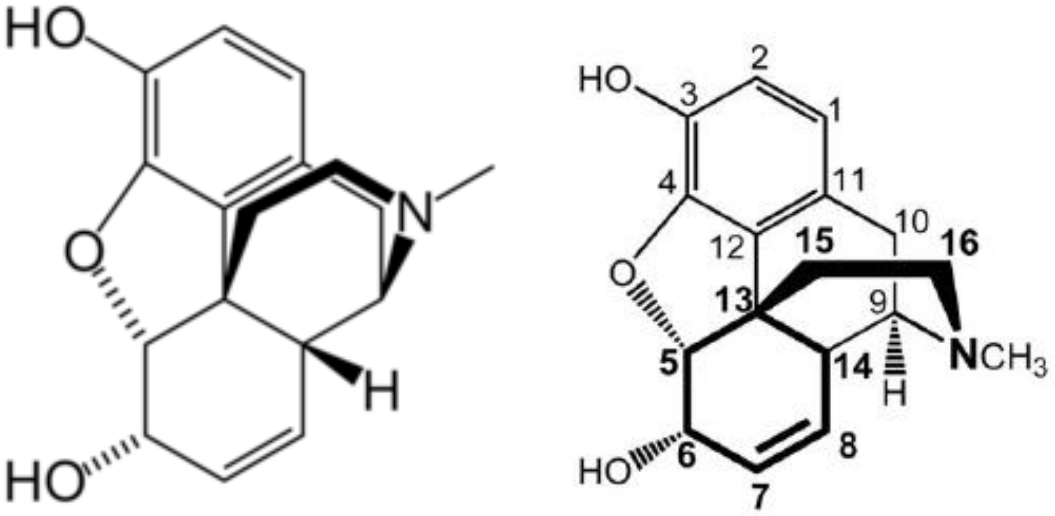


quinoline

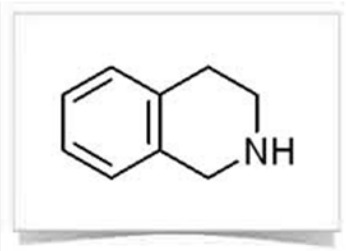


isoquinoline

What are Opioids? (A quick review!)



Morphine



Tetrahydroisoquinoline

- Opioids are a class of drugs that act primarily on the body's opioid receptors.
- Opioids are often referred to as narcotics.
- They act by blocking μ, κ, σ and possibly δ receptor classes.
- Most opioid receptors are found in the CNS and in the gastrointestinal tract.
- Opioids are used primarily for their analgesic effects but also for their cough suppressant properties.

Opium Alkaloids

- Now we'll talk about the opium alkaloids that are until the moment being manufactured from the opium powder. And there is no way that it can be prepared in the lab to give the exact effect.

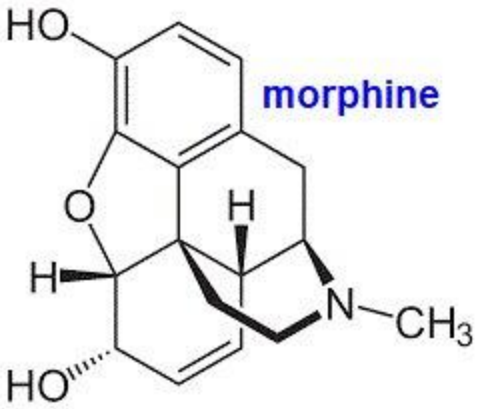
- The understanding of these compounds and how they work led to alternatives that would give the analgesic effect but without the addiction which is one of the drawbacks of opium alkaloids that are used as analgesics and known as **narcotic analgesic** compounds.

- The narcotic effect is different from one compound to another, and the most narcotic effect is found in morphine

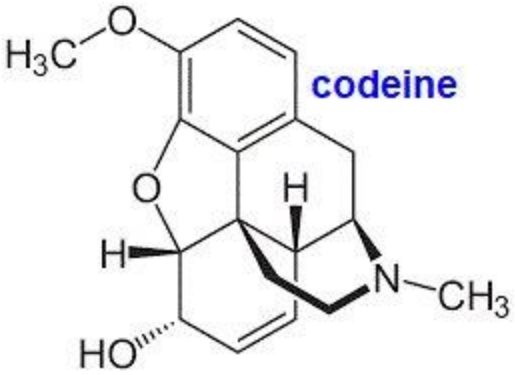
Opium Alkaloids

- Opium is considered among the first compounds that were used and studied by human. It was used to treat **diarrhea** since it has **constipating** effect. Moreover, it was used to treat **pain** and in surgeries, and its use goes back to 4000 years B.C in many countries (except Africa).
- **Morphine** was the first product to be isolated from the opium powder. Its structure was identified by the chemists according to the old techniques like the **hydrolytic method** which means that we extensively study the hydrolytic products to be able to know the original compound, and this method Is before NMR or mass spectroscopy were invented.
- Today India is the country licensed to grow the opium puppy for the extraction of active products for industrial purposes

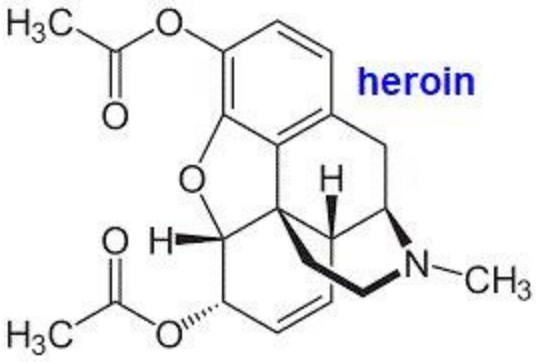
New drugs from old poisons



morphine



codeine



heroin

Examples of opium alkaloids - 'opiates'

Opium

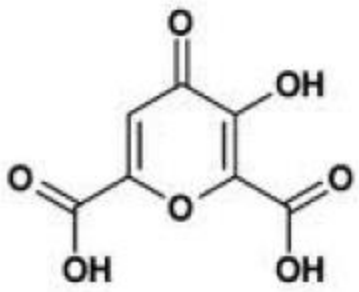
- Origin: is the **air-dried latex or milky exudate** obtained by incision from the **unripe capsules** of *Papaver somniferum*: Papaveraceae.

Opium alkaloids

- It contains **9-12 % morphine**.
- The latex contains also Codeine, Thebaine, Papaverine, Noscapine and Narcotine.
- Opium powder is colored brown not white like the cocaine!
- There are people who take opium as injection. others smoke it and some even eat it and all of that leads to addiction.
- the poppy seeds does not contain any addictive material. They are used sometimes at the bakery stores and on certain types of bread
- The capsule is v. small, if we didn't cut it to get the latex out then the capsule will turn into a beautiful flower that is similar to النعمان شقائق but the later flower has no opium alkaloids at all!

Opium Alkaloids

- Opiates are anything prepared from the natural opium powder, and the percentage of morphine in it is 10% and called standardized opium powder and we use lactose as diluent and some poor countries may use coconut hair.
- To make sure that my opium powder sample has the needed amount of opium alkaloids we do an analysis to inspect the presence of meconic acid.

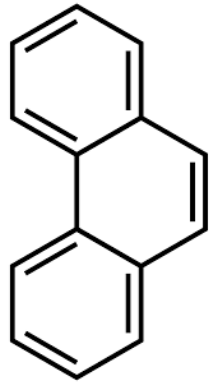


Meconic Acid

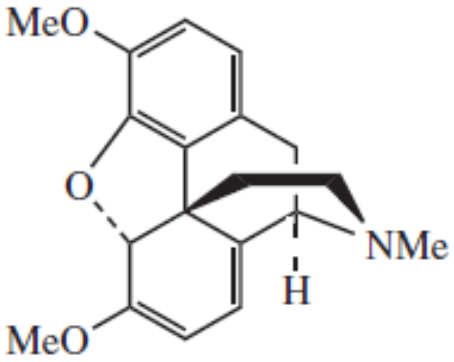
History of use

- Crude opium has been used as **analgesic** and **sleep-inducer** (narcotic) and for the **treatment of coughs**
- Powdered opium was *combined* with powdered Ipecacuanha to give a **sedative and diaphoretic** effect to take at the onsets of colds and influenza
- It has traditionally been smoked for pleasure

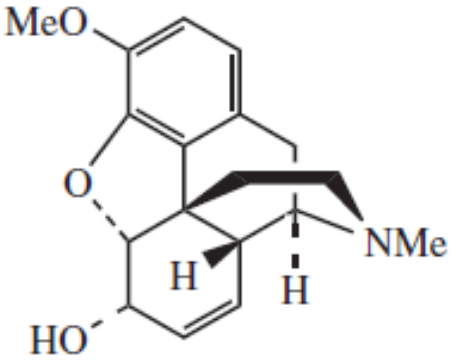
The biosynthesis of Morphine started with the methylated compound (Thebaine) and by demethylation we obtain morphine



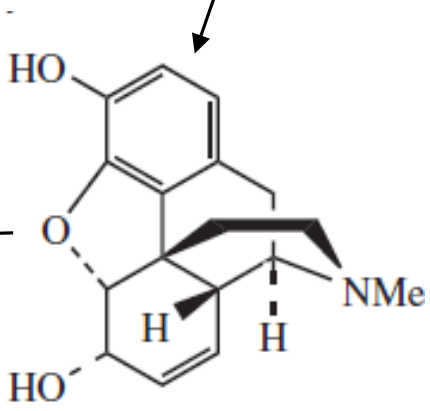
phenanthrene



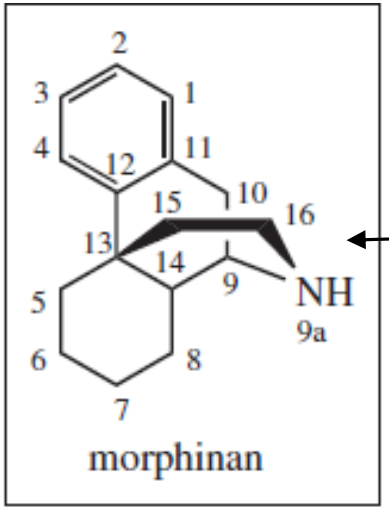
thebaine



codeine



morphine

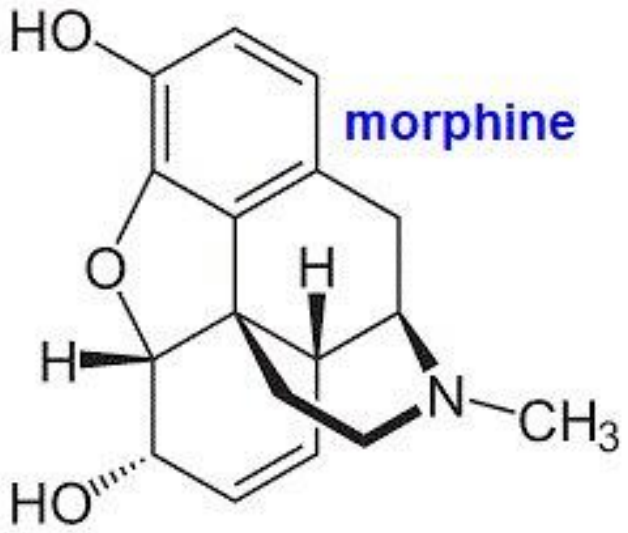


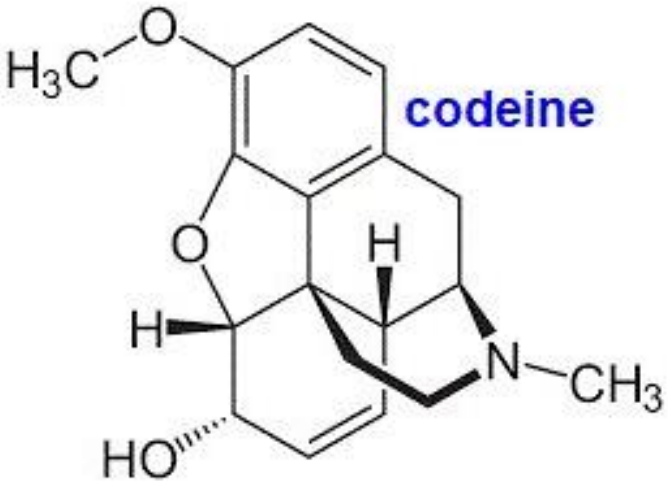
morphinan

*** Morphinan alkaloids are Thebaine, Codeine and Morphine only.**

* Morphinans are a phenanthrene structure and at the second ring of this structure we have a carbon-nitrogen ring at C13 (2 carbon bridge-N bridge)

* To distinguish morphine as a powder from codeine (both have a white powder) then we can use the phenolic grp of the morphine which can easily react with strong basic compounds like NaOH or KOH





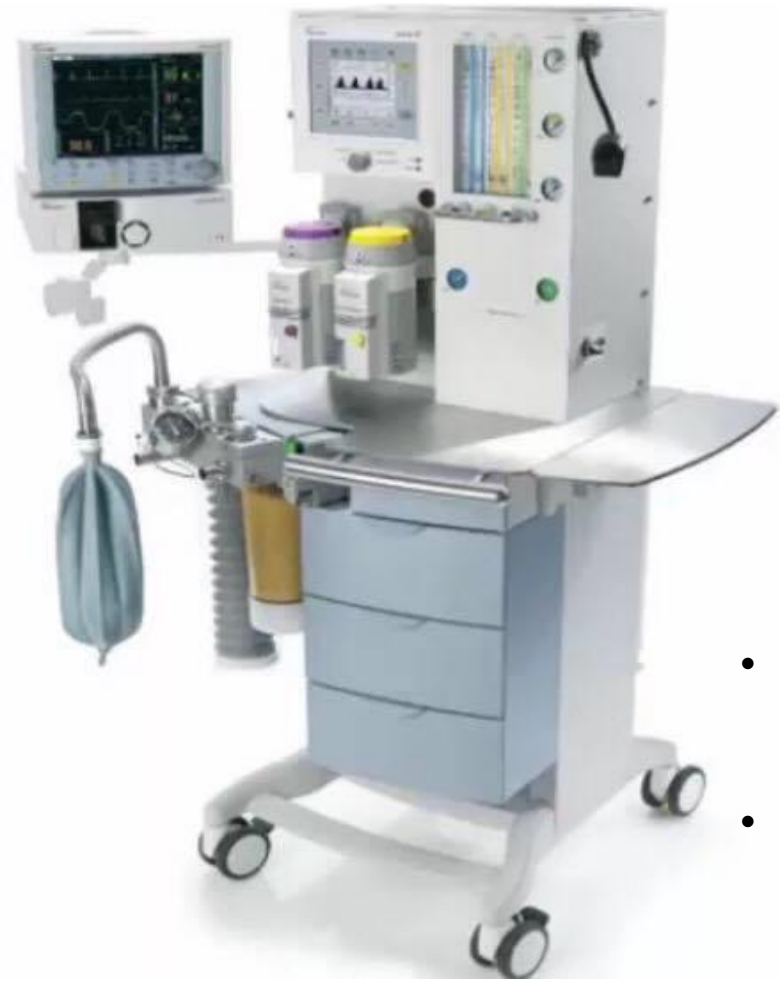
Morphine

- Morphine is a narcotic compound (easily separated) that causes euphoria and addiction.
- And one of its adverse effects is the **constipating effect** (that's why they use it as a treatment for diarrhea).
- Withdrawal symptoms need a long time for the person to get rid of it (takes from 2-3 weeks
- Another problem about morphine is the **nausea** and **vomiting** associated with its use and so we usually give the patient an anti-nauseating agent along with the drug.
- Morphine has both injectable and oral form (tablet form and is under strict observation from the government and only by a prescription).

Codeine

- In fact, it is the most widely therapeutically used opium alkaloids (main representative).
- Antitussive and mild analgesic agent.
- it is 3-O methyl morphine.
- it can be metabolized partially by liver enzymes (de-methylated) to produce **morphine** →so it produces morphine-like analgesic effects but little euphoria.
- it's about one –tenth (1/10) the potency of morphine.
- →So, relatively it is a safe non-addictive medium analgesic –for sure- when used within the therapeutic doses, if exceeded or used for a **prolong period of time** there will be -definitely- dependence, addiction and also **constipation**.

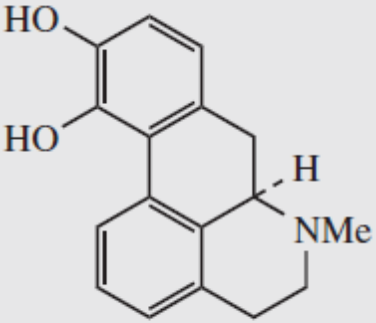
Inhalation Anesthetics



- Ibn al- Quff was an Arab physician and surgeon and author , he used anesthesia by inhalation, by using anesthetic spong.
- The sponge was soaked in a boiled solution made of water with cannabis (from Arabic hasheesh حشيش), opium(from Arabic afiun افيون) and belladonna (from Arabic cit alhuscin ست الحسن).
- The anesthetic sponge was placed it over the patient face, the liquid which is absorbed by the mucous membrane of nose and mouth .

Apomorphine

- Obtained by heating morphine in the presence of acid which lead to a completely changed structure (ex; the ether linkage is eliminated)
- has **no** analgesic properties, but morphine's side-effects of **nausea and vomiting** are **highly** emphasized.
- is a powerful emetic and can be injected for emergency treatment of poisoning (differs from other emetics in being parentally rather than orally).

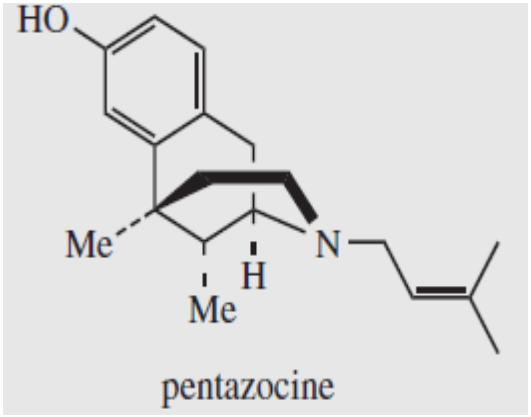


apomorphine

Synthetic derivatives:
Dextromethorphan:

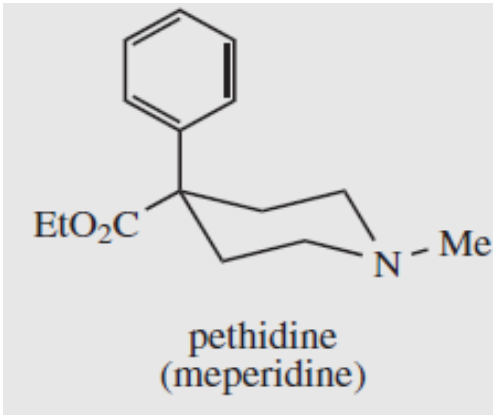
- One of the most widely used morphine analogues in the therapeutic purposes.
- potent antitussive agent.
- in lab preparations we obtain both isomers: **dextromethorphan** and **levomethorphan** but it has been found that **dextromethorphan** is **lacking** the analgestic activity with **potentiated antitussive activity**. While levomethorphan is possessing analgesic and antitussive activities.
- → Since this combination is not requested, dextromethorphan alone is the preferred drug material, being completely non-addictive.
- **Now**, the other synthetic derivatives of morphine which we will discuss now, all are possessing analgesic activity differing in their duration of action …etc

Synthetic derivatives of Morphine



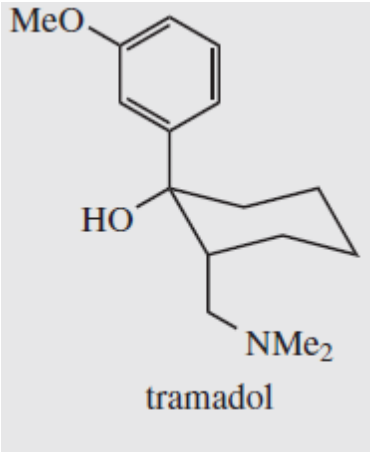
pentazocine

has competitive agonist properties, and although it is a good analgesic, it can induce withdrawal symptoms.



pethidine
(meperidine)

Short-acting, quick and short-duration analgesia, used nowadays as a pain killer parentally in surgery.

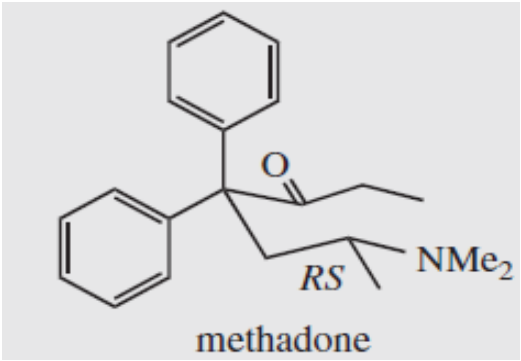


tramadol

synthesized in 1980 as an analgesic, it wasn't causing addiction, but recent studies show that tolerance can be developed.

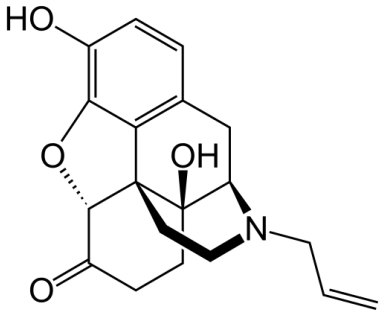
Note: all synthetic cpds do possess CNS euphoria addiction and tolerance.

Synthetic derivatives of Morphine



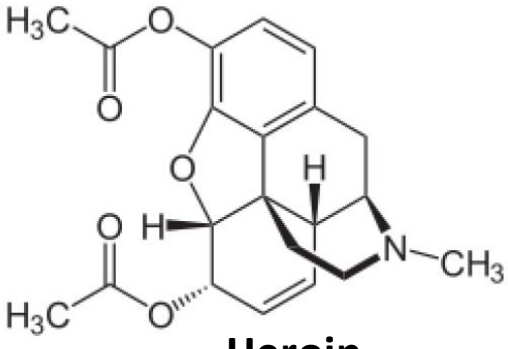
methadone

* Orally active, has similar activity to morphine, but is less euphorigenic and has a longer duration of action. Although it is as potentially addictive as morphine.
* Widely used for the **treatment and rehabilitation of heroin addicts**.



Naloxone

* Pure opioid antagonist. works by reversing the depression of the CNS and respiratory system caused by opioids.
* Approved for opioid overdose by the FDA in 1971.



Heroin

Heroin

- (it's also known as di acetyl morphine)
- This compound isn't natural occurring, it's **highly addictive analgesic and hypnotic** semi synthetic derivative. Heroin cause **euphoria** (عدم الاحساس بالمحيط الخارجي)
- - It's obtained from morphine but the difference between them is in 2 hydroxyl gp in morphine while in heroin 2 hydroxyl in morphine gps are replaced with acetate function gps (named so as diacetyl bond).
- Morphine too is addicting from the first dose.
- Heroin is more addictive and each time the body need a higher dose than the previous one (has tolerance)

Derivates of Natural Products

BAYER Pharmaceutical Products

HEROIN—HYDROCHLORIDE

is pre-eminently adapted for the manufacture of cough elixirs, cough balsams, cough drops, cough lozenges, and cough medicines of any kind. Price in 1 oz. packages, $4.85 per ounce; less in larger quantities. The efficient dose being very small (1-48 to 1-24 gr.), it is

The Cheapest Specific for the Relief of Coughs

(In bronchitis, phthisis, whooping cough, etc., etc.)

WRITE FOR LITERATURE TO

FARBENFABRIKEN OF ELBERFELD COMPANY

SELLING AGENTS

P. O. Box 2160 40 Stone Street, NEW YORK

BAYER

PHARMACEUTICAL PRODUCTS.

We are now sending to **Physicians** throughout the United States literature and **samples** of

ASPIRIN

The substitute for the Salicylates, agreeable of taste, free from unpleasant after-effects.

HEROIN

The Sedative for Coughs,

HEROIN HYDROCHLORIDE

Its water-soluble salt.

You will have call for them. Order a supply from your jobber.

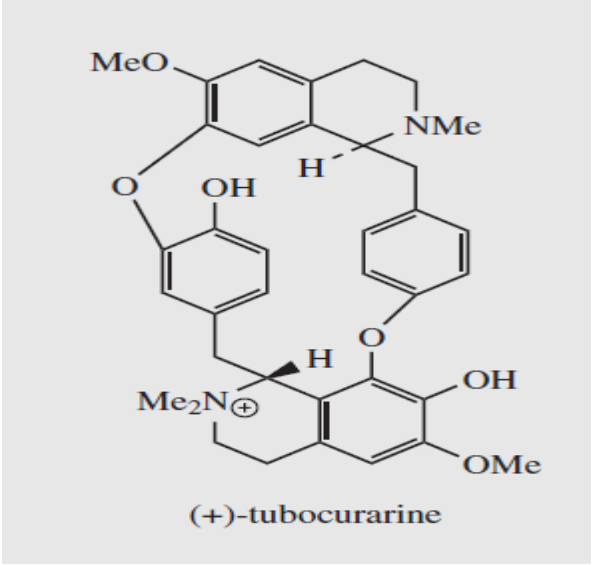
Write for literature to

FARBENFABRIKEN OF ELBERFELD CO.

40 Stone Street, New York,

SELLING AGENTS

Dimeric products of benzyltetrahydroisoquinoline alkaloids

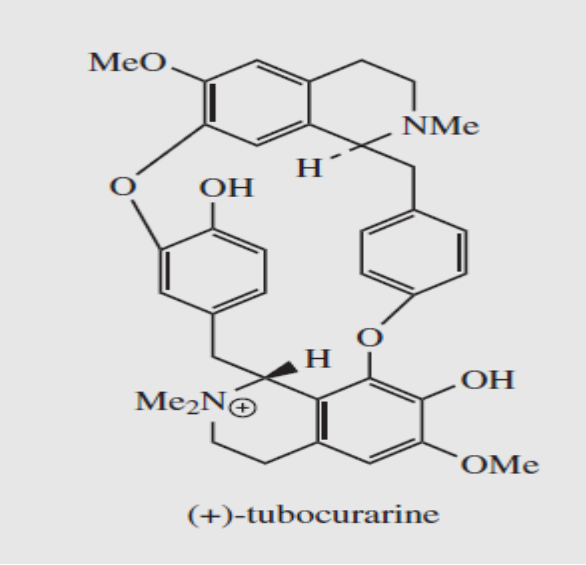


(+)-tubocurarine

Dimeric products of benzyltetrahydroisoquinoline alkaloids

- **D-tubocurarine** is a very interesting compound, although it was discovered long time before the final structure of it was found in the late 1960s . It is a **water-soluble** quaternary ammonium salt, and it is a **dimeric compound**, (possessing **two nitrogen** in its structure) .

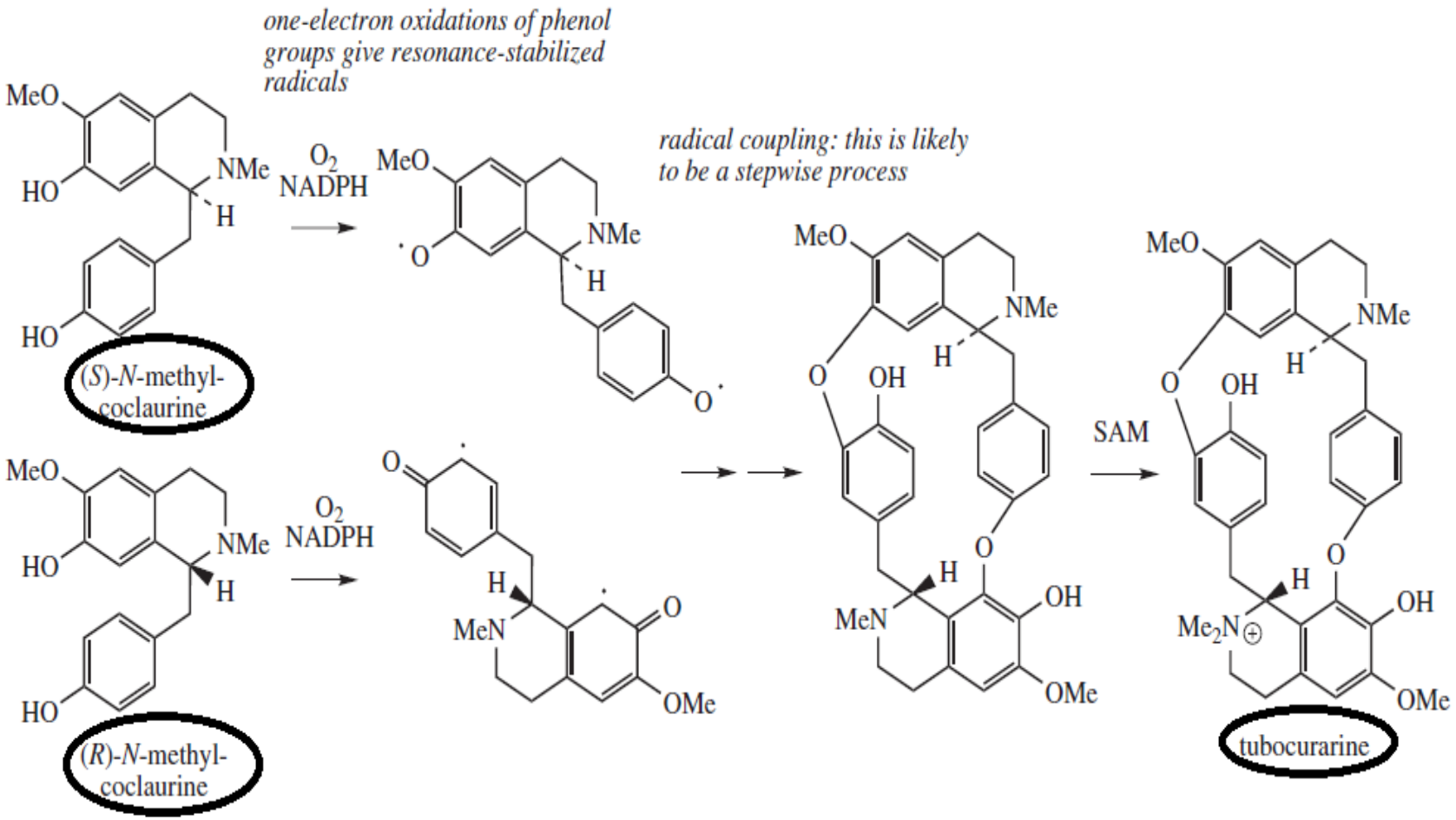
When we look at the structure of the D-tubocurarine we will recognize the two monomeric parts , we can see two groups of these (the benzyl group , the hydroxyl group and the tetrahydroisoquinoline group). Both monomeric parts are linked via ether bridges. The ether bridges are products of the oxidative coupling process .



(+)-tubocurarine

Dimeric products of benzyltetrahydroisoquinoline alkaloids

- D-tubocurarine is a dimmer of two N-methylcoclaurine one (S) one (R)
- it is a natural compound used widely as a **muscle relaxant** in many abdomen and thorax surgeries as well as in treatment of **Parkinson** disease , **multiple sclerosis** and in **tetanus** .
- Now there are many synthetic analogues which are currently used in different surgeries. These compounds can be ultra short acting (up to 10 minutes), short acting (10- 20 minutes), intermediate acting (up to 30 min) or long acting (up to two hours) depending on surgery .
- Upon toxicity the effect of these drugs can be antagonized by artificial respiration or Anti-acetylcholinesterase drugs like physostigmine and neostigmine.


one-electron oxidations of phenol groups give resonance-stabilized radicals
radical coupling: this is likely to be a stepwise process
MeO
HO
NMe
H
HO
(S)-N-methyl-coclaurine
O2
NADPH
MeO
O
NMe
H
O
MeO
HO
NMe
H
HO
(R)-N-methyl-coclaurine
O2
NADPH
O
H
MeN
O
OMe
MeO
NMe
H
O
OH
O
H
MeN
OH
OMe
SAM
MeO
NMe
H
O
OH
O
H
Me2N
OH
OMe
tubocurarine

D-tubocurarine

- D-tubocurarine is not the only compound that possesses the activities that we have mentioned , other similar minor alkaloids which are found in the same plant that contains d-tubocurarine are found to have these activities too .

- ***Note*** → There are two different terms which you shouldn't mix between: **Curare** and **d-tubocurarine**
- **Curare** is a collective term for the arrow poisons prepared by south American Indians and one of the compounds of these arrow poisons is d-tubocurarine , in addition to d-tubocurarine more than 30 different compounds were detected in the curare and they have the activities that we mentioned for the d-tubocurarine .

Curare

- Arrow poisons are prepared in Amazons by different tribes and each tribe was preparing its own arrow poisons based on the plants growing in their surroundings.
- Some of these tribes were using plants belonging to the family **Menispermaceae** , while other tribes which don't have Menispermaceae in their surroundings were using plants from the family **Loganiaceae** . Other tribes they have plants from the both families, so they mix them all together.
- So, basically, we have three different types of curare (curare from Menispermaceae, from Loganiaceae or from the two families) and all of them are used for the same purpose (for hunting or killing the animals) .

- In the case of Menispermaceae curare , the main tree which is used is the *Chondrodendron tomentosum* , the bark is scraped off , boiled with water and then they add some other plant materials to make the final product some sticky material so that it will stick to the arrows or darts . The main constituent (arrow poison) of this plant is d-tubocurarine .
- In the case of the Loganiaceae , the plants used are of the genus *Strychnos* ,the toxic ingredient in Strychnos is the toxipherons Not the strychnine . Toxipherons are Indole alkaloids not benzyl-tetrahydroisoquinoline alkaloids so we will talk about them later .
- In the case where there is a mixture of the two families , we will find the two poisons , d-tubocurarine and toxipherons .

Menispermaceae family with the main constituent d-tubocurarine :

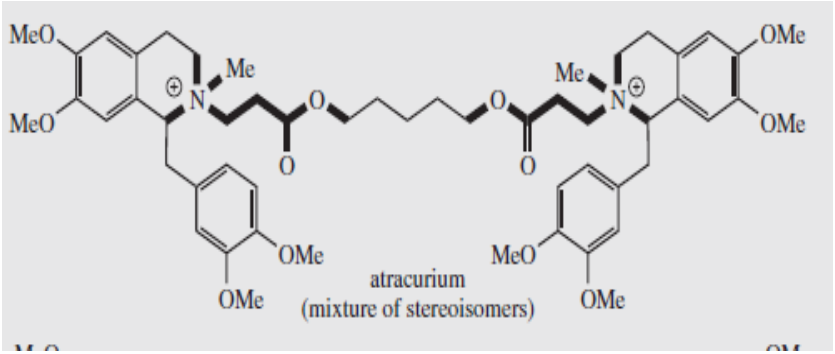
- * Curare is only effective if it enters the bloodstream, it is inactive when given orally.
- The potency of curare as an arrow poison is variable because of the variability of ingredients in it (e.g the extract which is obtained in summer will differ in its ingredients from the extract obtained in winter) and consequently the potency needs testing

- In medicine they are utilized in the paralysis and relaxation of the voluntary muscles , muscles of the respiration will mainly stop working .

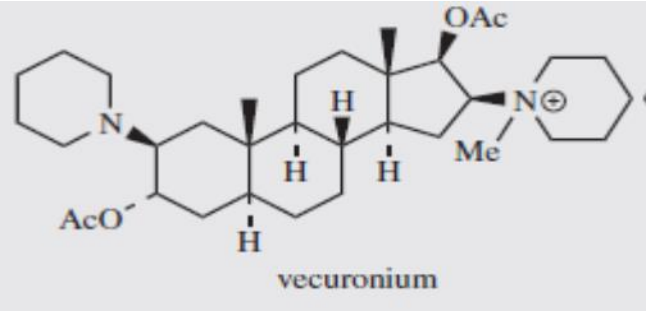
- We use them in Parkinson , tetanus , abdomen and tonsillectomy surgeries and the effect is counteracted by artificial respiration and Anti-acetylcholinesterase agents as we mentioned previously .

- Tubocurarine and the heterocyclic analogues are termed non-depolarizing or competitive muscle relaxants; their action may be reversed with anticholinesterase agents such as neostigmine that increase acetylcholine concentration at the neuromuscular junction by inhibiting its breakdown.

- Then synthesized analogues with heterocyclic structures like (**Atracurium**) it's like tubocurarine possessing benzyl tetrahydroisoquinoline, di-quaternary (base), atracurium is occurring as mixture of stereoisomers, later on separated into pure isomers and Cis is the one used, the two quaternary N here separated by 13 atoms
- So, they found that it's not obligatory that the distance in a physiological solution is ten atoms (14 angstroms) since 10 and 16 atoms show similar activity, also not necessary that the di-quaternary N to be separated by straight chain it may separated by a steroidal nucleus like in (**Vecuronium**) which is a **Mono-quaternary** ammonium salt where two N separated by steroidal nucleus.



atracurium
(mixture of stereoisomers)



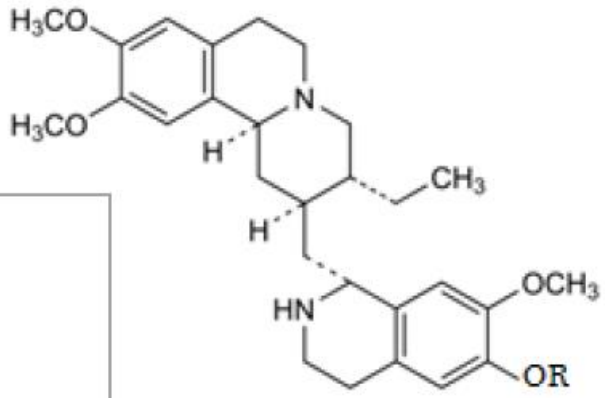
vecuronium

Radix Ipecacuanha
Ipecacuanha Root عرق الذهب

- We will talk about ipecac root and different constituents o ipecac root, definitely that ipecac syrup is very well known from your pharmacy practice, its obligatory part in poisoning antidote because it's emetic properties, also different expectorants contains ipecac extract, so it is a plant which has quit different utilization depending on the **doses** and depending on the **purification** of the major constituents.
- Ipecac extract **Major** constituents are **cephaeline** and **emetine.**
- Ipecac extract **Minor** constituents are **psychotrine** and **O-methylpsychotrine.**

- It is a South American plant, main countries produce it is Brazil, the major species of this plant is Cepahalis *ipecacuanha* the emetine to cephaeline ratio might be 2:1, whereas in *Cepahalis acuminate* ratio ranges from about 1:2 to 1:1.
- Emetine also used in amebic dysentery, as expectorant and antiviral.
- Ipecac extract: at high doses as emetic, at small doses as expectorant.
- Ipecac more recently is mixed with powdered opium to give **Dover's powder** where the ipecac content functioned as a diaphoretic (promote perspiration).

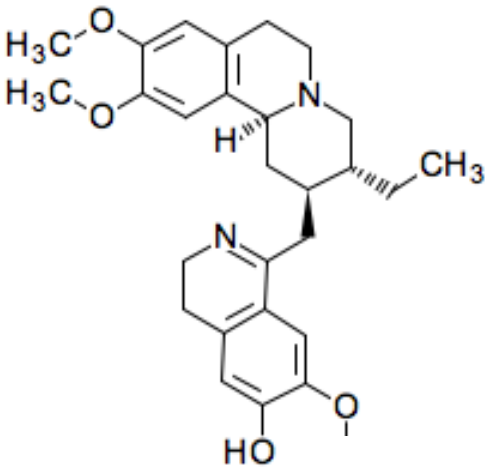
Ipecacuanha has a group of alkaloids { most importantly **emetine** and **cephaline**} .It was believed that emetine is responsible for vomiting , but later its found that emetine has very weak emetic property and the majority of vomiting effect comes from cephaline .



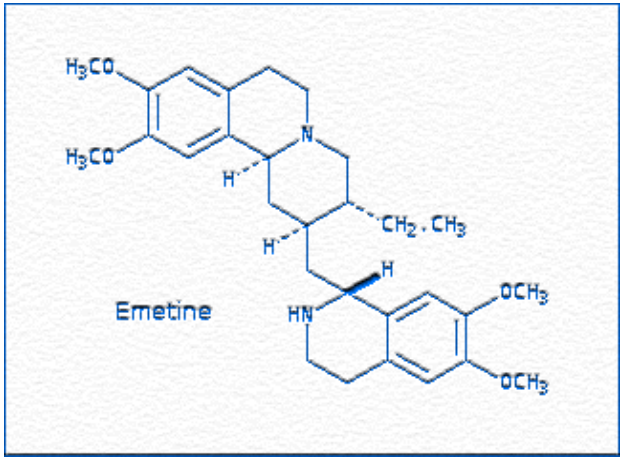
We have 2 isoquinoline molecules attached to each other by ethyl group.

R:CH3 => Emetine
R:H => Cephaline

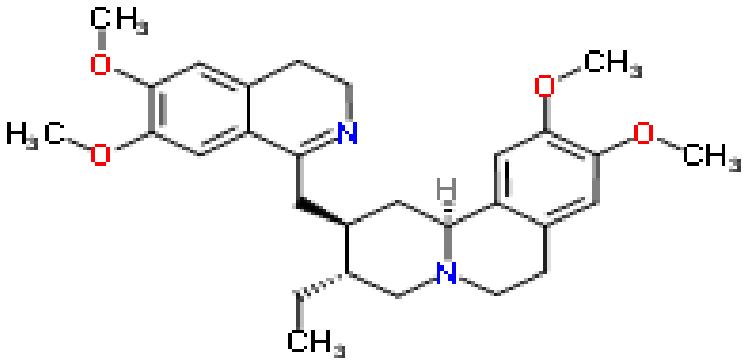
Emetine



C09612

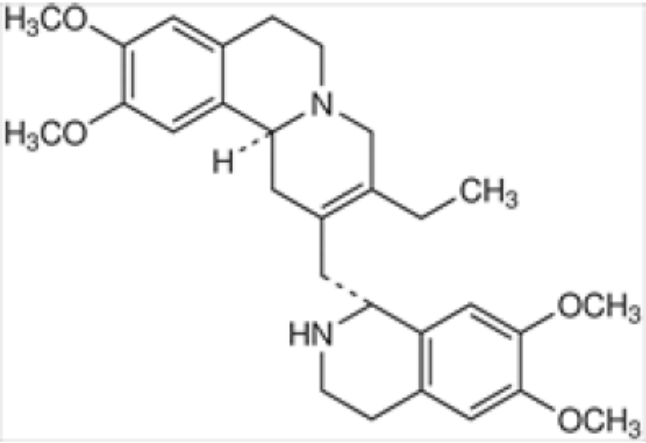


Psychotrine:



O-methylpsychotrine

(emetine) prevents the synthesis of proteins in microorganisms at the translocation stage and thus death, but it's too toxic for therapeutic use, instead we use the dehydro form .



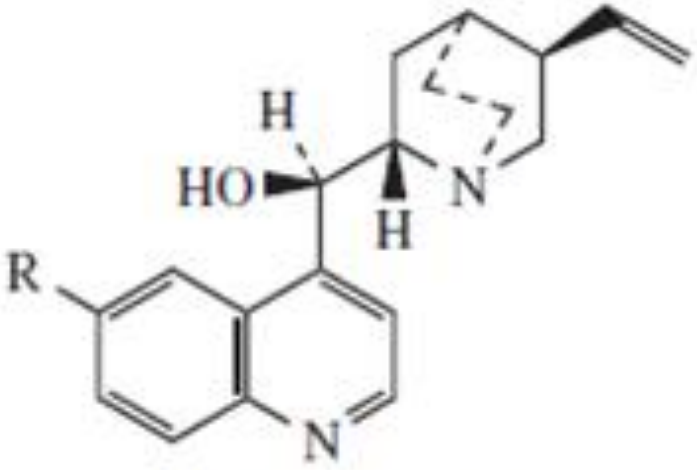
Dehydro emetine

completely synthetic compound and sometimes we can use emetine to produce it by removing two H's.

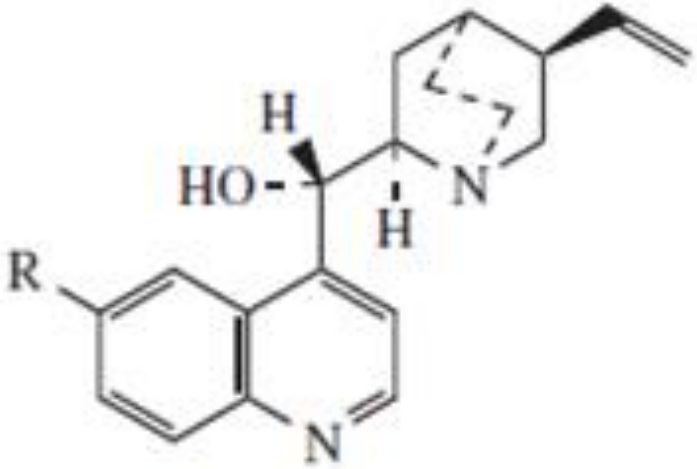
Quinoline alkaloids

- The **most** important **quinoline** alkaloids that found in plant tissue is **cinchona alkaloids** (family: **Rubiaceae**) which in turn has **diastereoisomers**:
- **1. Quinine**
- **2. Quinidine**
- **3. cinchonine**
- **4. cinchonidine**

Cinchona (Rubiaceae)



R = H, cinchonidine
R = OMe, quinine



R = H, cinchonine
R = OMe, quinidine

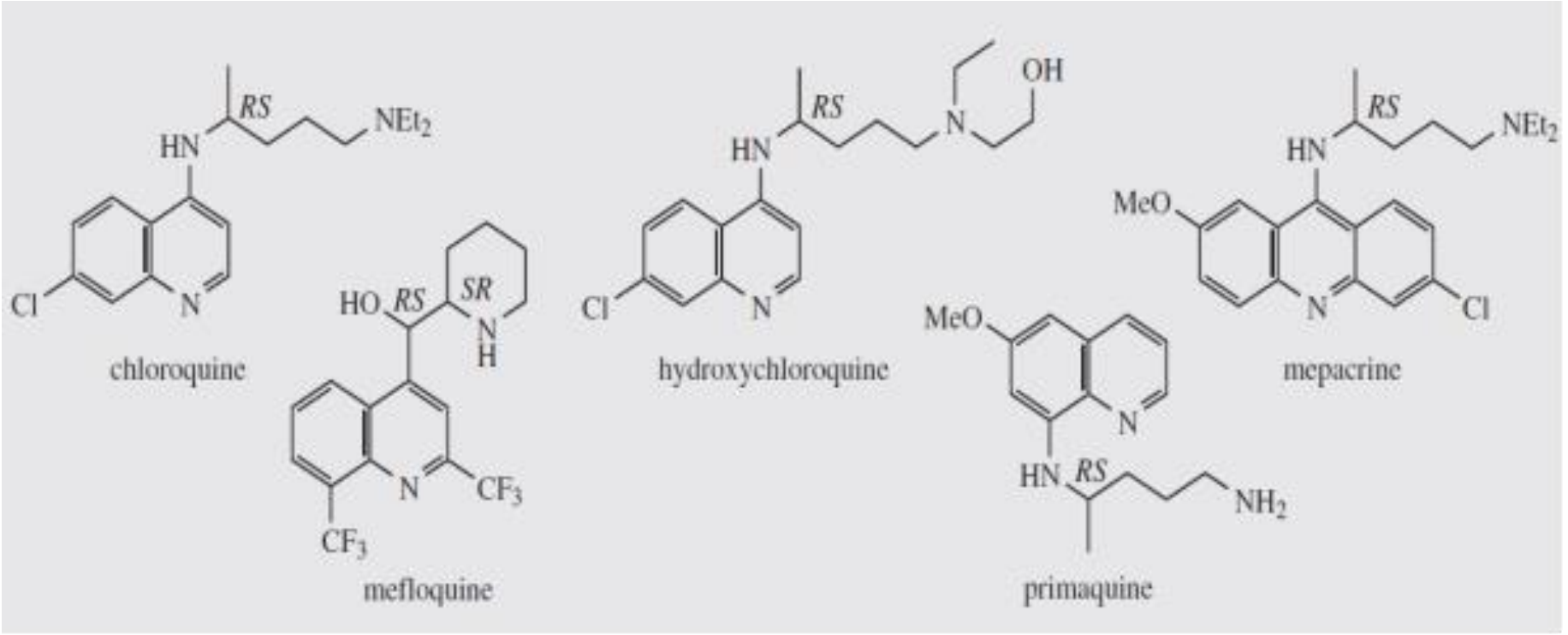
Cinchona-Red Cinchona Bark (قشر الكينا)

- *Cinchona succirubra* , ***Cinchona ledgeriana, Cinchona calisaya***
- Family: Rubiaceae.
- •**Medicinal Parts:** The medicinal part is the dried bark of **stem** and **roots** of 6- to 8-year-old trees.
- **Active constituents:** The bark contains alkaloids quinine; quinidine , cinchonine , cinchonidine and other alkaloids, quinamine, javanine.
- Tannin : cinchotannin.
- **Herbal Uses:**
- Quinine is **antimalarial.**
- Quinidine is **antiarrhythmic and cardiac tonic**, also used in psychic treatments. In large doses, it is sedative to CNS.
- **Quinine is toxic at over 3 g, quinidine at 1 g.**
- •Approved for:
- •**Loss of appetite**
- •Dyspeptic complaints.

- **Quinine** administered as free base or salts, continues to be used for treatment of multidrug-resistant malaria.
- Quinine also has a skeletal muscle relaxant effect with a mild curare-like action. It thus finds use in the prevention and treatment of nocturnal leg cramps, a painful condition affecting many individuals, especially the elderly.

- Until recently, **quinidine** was used to treat cardiac arrhymias. It inhibits fibrillation, the uncoordinated contraction of muscle fibres in the heart. However, it is rapidly absorbed by the gastrointestinal tract and overdose can be hazardous, leading to diastolic arrest. This has effectively decreased it's use.
- Quinidine, Cinchonine, and Cinchonidine also have antimalarial properties, but these alkaloids are not as effective as quinine. The cardiac effect makes quinidine unsuitable as an antimalarial. However, mixtures of total *Cinchona* alkaloids, even though low in quinine content, are acceptable antimalarial agents. This mixture, termed **Totaquine**, has served as a substitute for quinine during shortages.

- When this source was cut off by Japan in the Second World War, a range of synthetic antimalarial drugs was hastily produced as alternatives to quinine. Many of these compounds were based on the quinine structure. They took the quinine and substituted it with an amino group , a wide range of compounds was produced, chloroquine, primaquine, and mefloquine.
- **Primaquine** is exceptional in having an 8-aminoquinoline structure, whereas **chloroquine** and **mefloquine** retain the 4-substituted quinoline as in quinine.


RS
NEt2
HN
Cl
N
chloroquine
HO
RS
SR
N
H
N
CF3
CF3
mefloquine
OH
RS
HN
N
Cl
N
hydroxychloroquine
MeO
RS
NEt2
HN
N
Cl
mepacrine
MeO
N
HN
RS
NH2
primaquine

- Long time use of quinines cause hearing impairment, particularly high-frequency loss. Although some studies suggest that this high-frequency hearing impairment is reversible, it has not been conclusively established whether such impairment is temporary or permanent .