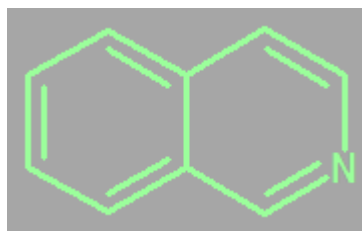


Alkaloids Derived from Phenylalanine and Tyrosine

Isoquinoline Alkaloids



(Part III)

Crude Opium

- ❑ Milky exudate obtained by incising the unripe capsules of *Papaver somniferum* (Papaveraceae)
- ❑ The active principles are represented by 10 to 20% alkaloids, more than 25 alkaloids of different types have been obtained
- ❑ The most important type is the morphinane type e.g. morphine, codeine, Thebaine
- ❑ Opium alkaloids occur naturally combined with specific acid (meconic acid). It occurs only in opium

Chemical test for meconic acid:

- ❑ by directly adding ferric chloride to the aqueous extract 
 red color



OPIUM POPPY
Papaver somniferum

Classification

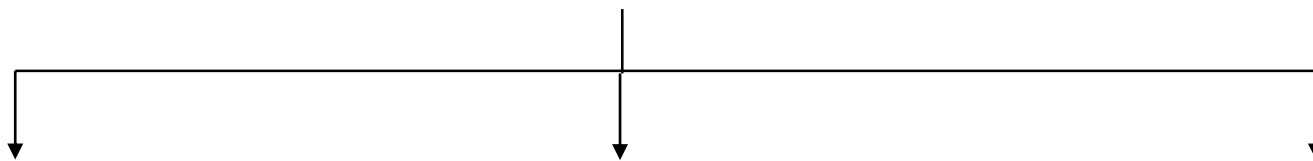
Natural opiates: are alkaloids contained in the latex of opium as morphine, codeine, and thebaine.

Semi-synthetic opioids: created from the natural opiates, such as heroin, oxycodone, and hydrocodone are derived from morphine, codeine, and thebaine.

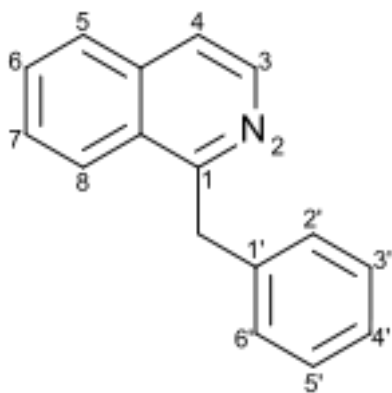
Fully synthetic opioids: such as pethidine, methadone, tramadol.

Endogenous opioid peptides, produced naturally in the body, such as endorphins, endomorphins,

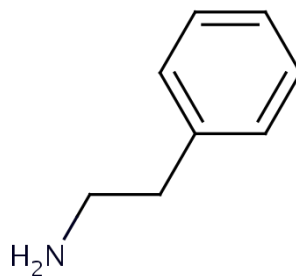
Opium alkaloids are subclassified into 3 groups:



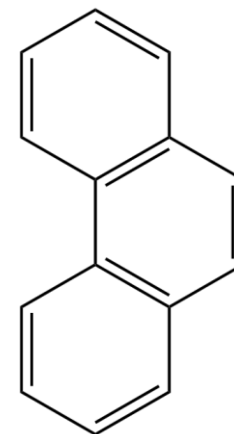
**Benzylisoquinoline
alk.**



**Phenylethylamine
alk.**



Phenanthrene alk.



Benzyl Isoquinoline

Papaverine

Properties:

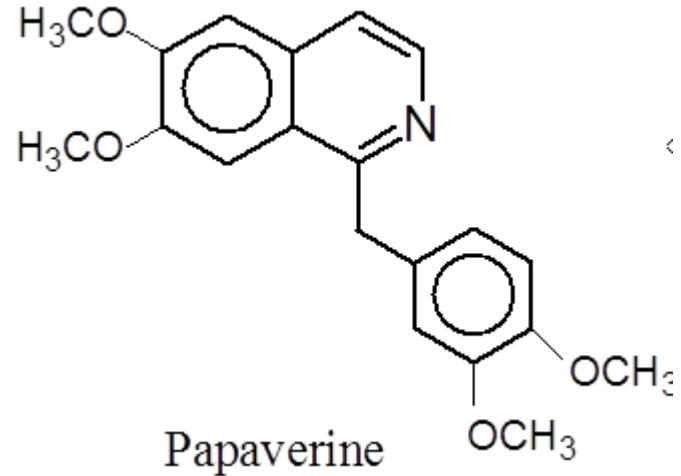
It is a weak base and is optically inactive.

Tests for identification

▪ Warren's test (specific for papaverine):

Papaverine + crushed crystal of KMnO_4

+ Marqui's reagent \rightarrow green color \rightarrow blue.

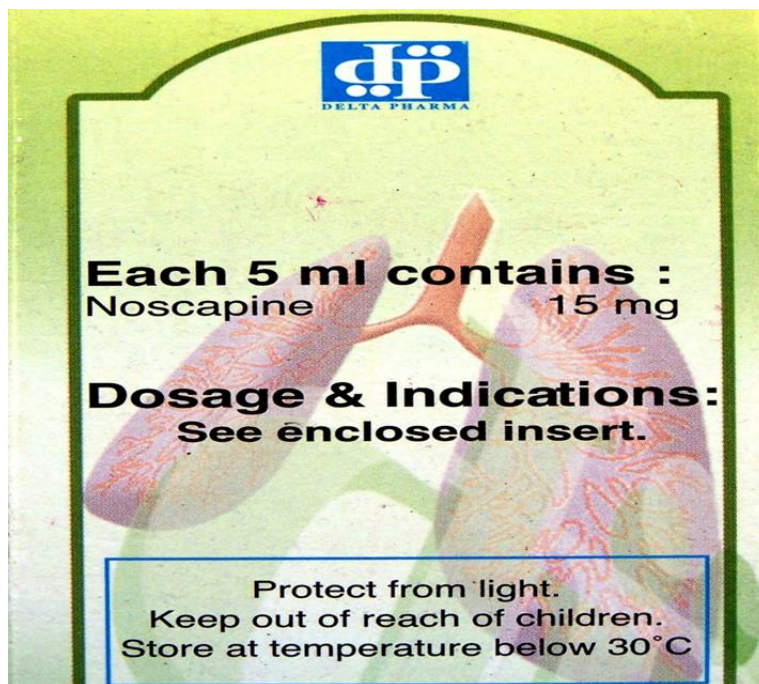
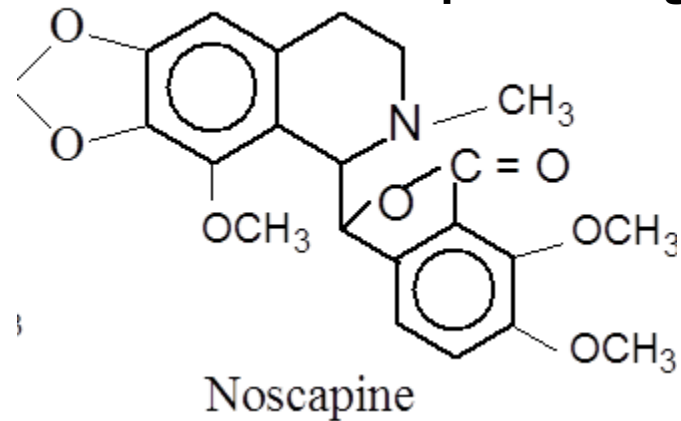


Uses:

Papaverine possesses **smooth muscle relaxant** activity. It is used as **antispasmodic** for **GIT spasms**, clots and in **bronchial asthma** in a dose up to 600 mg of papaverine HCl daily.

Noscapine

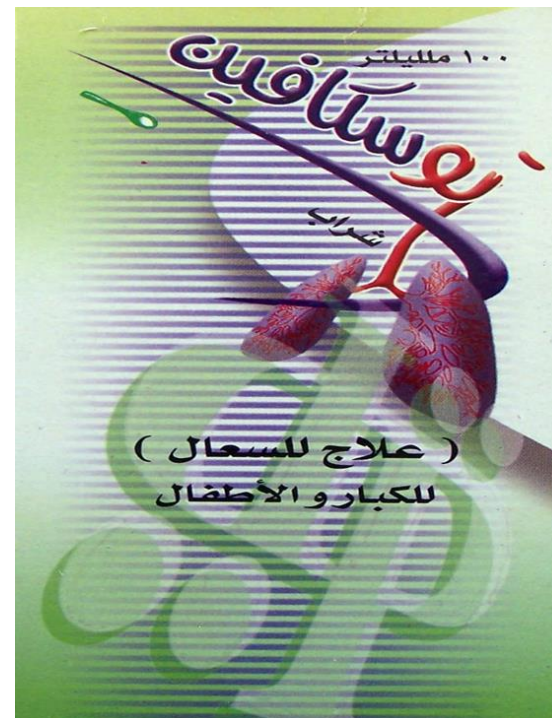
Used as antitussive medicine without pain killing effect



Each 5 ml contains :
Noscapine 15 mg

Dosage & Indications:
See enclosed insert.

Protect from light.
Keep out of reach of children.
Store at temperature below 30°C



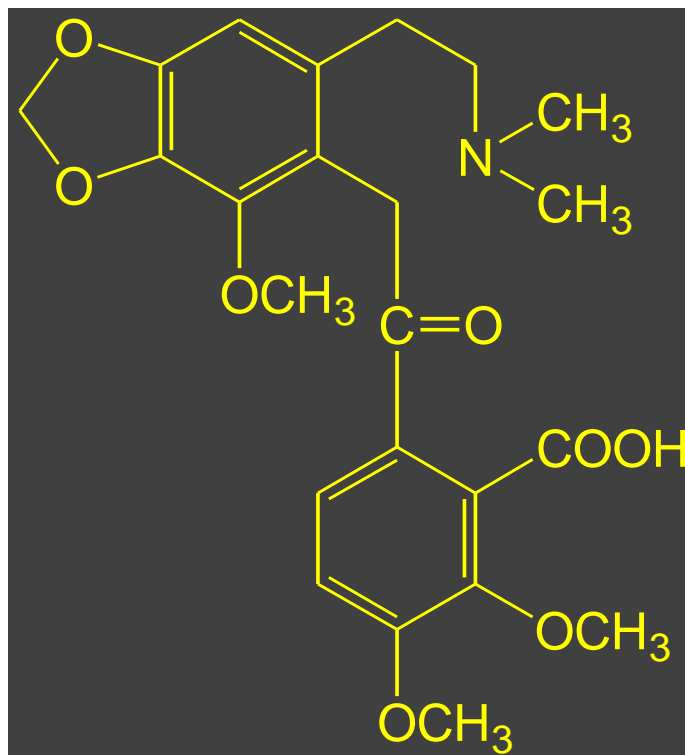
١٠٠ مليلتر
نوسكافين
شراب
(علاج للسعال)
للکبار و الأطفال

Phenyl alkylamines

Narceine

Properties:

It is a tertiary Alkaloids. Narceine is an amphoteric alkaloid since it contain a carboxylic group.



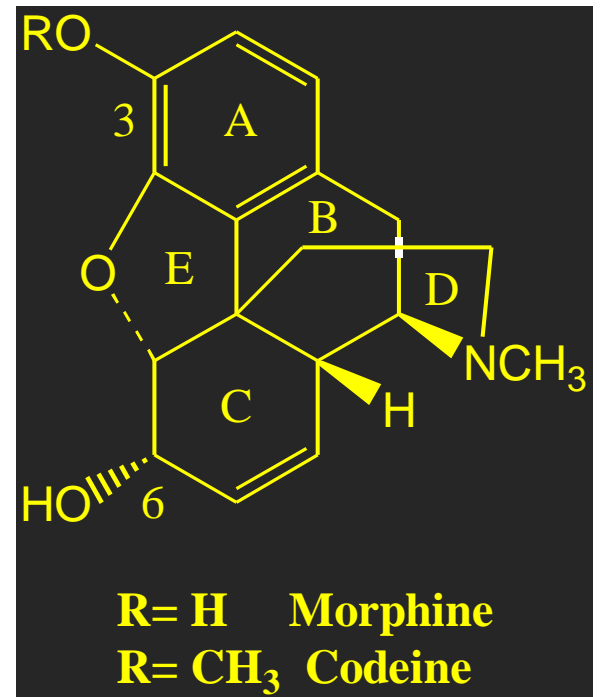
Phenanthrenen Group

Morphine

Properties:

Morphine is levorotatory, insoluble in water, sparingly soluble in ethanol (1:250) and chloroform (1:1500), practically insoluble in ether and benzene.

It contains 2 OH groups, one is a phenolic at C-3 (gives a soluble phenate with alkali) and the other is a 2ry alcoholic at C-6.



Tests for Identification:

Tests due to phenolic properties:

- 1- Morphine gives a blue color with FeCl_3 .
- 2- Nitrous acid test: solution of morphine in dilute HCl + NaNO_2 + $\text{NaOH} \rightarrow$ red color.
- 3- Morphine + dil H_2SO_4 + $\text{HI} \rightarrow \text{I}_2$ give violet colour when dissolve in CHCl_3

Tests with alkaloidal color reagents:

- 1- Liebermann' s reagent \rightarrow black color.
- 2- Mandalin's reagent \rightarrow bluish-gray color.
- 3- Marquis' reagent \rightarrow violet color.
- 4- $\text{HNO}_3 \rightarrow$ red colour convert to yellow on heating.

USES:

Morphine act as a narcotic analgesic (reduce pain & induce sleep) in a dose of 5-20 mg of morphine hydrochloride, sulfate or tartrate, administered orally or parentally, every 4 hours.

Used before and after surgical operations and to terminally ill cancer patients.

Suppress peristaltic movement so stops diarrhea.

Adverse Effects:

Two major problems are associated to morphine use:

Addiction and Tolerance.

Codeine

Properties:

- It is soluble in H₂O, boiling H₂O, ethanol, CHCl₃ and ether, (c.f. morphine).
- Codeine is non Phenolic.

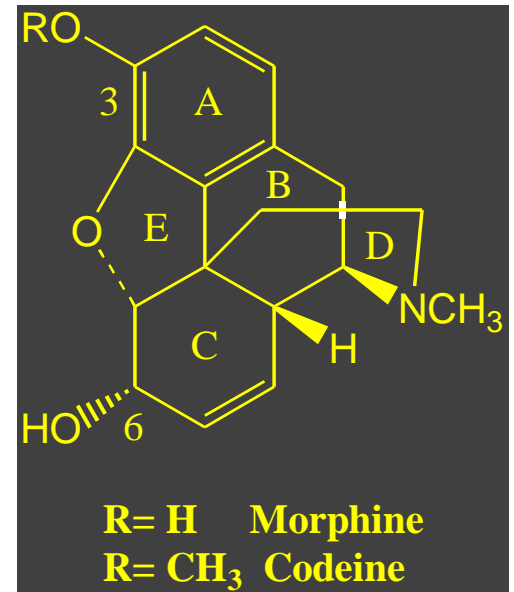
Test:

- Codeine + concentrated H₂SO₄ + FeCl₃, warm in water bath → bluish violet color ≠ HNO₃ → Red color.

Uses:

It has less narcotic analgesic than morphine.

It is mainly used as antitussive.

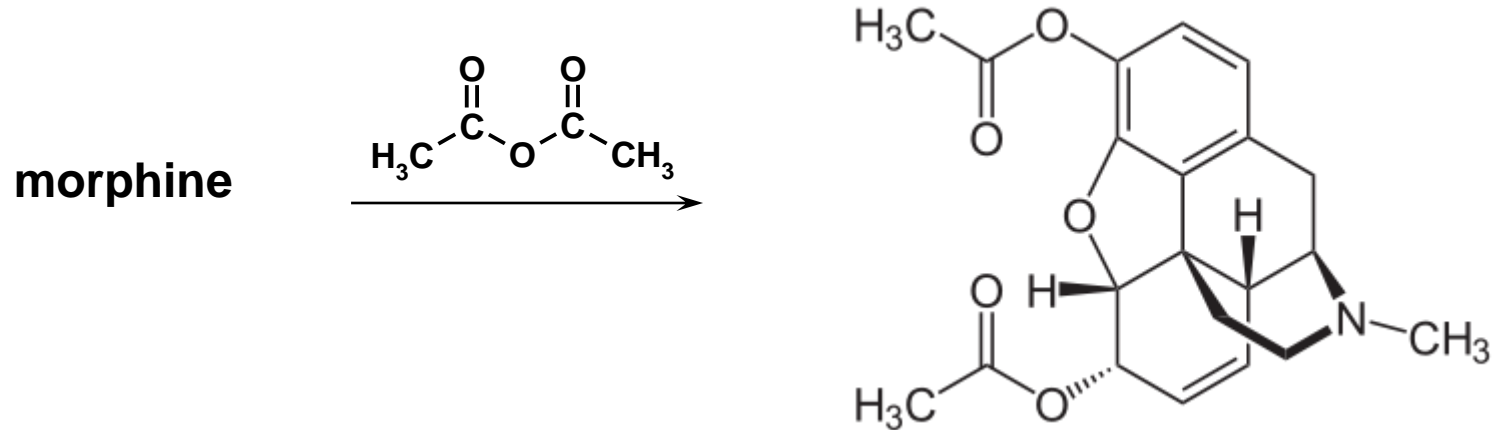


SEMI-SYNTHETIC DERIVATIVES OF MORPHINE

Heroin

It is the diacetyl derivative of morphine. It has no any medical applications but it is one of the most dangerous abused substance.

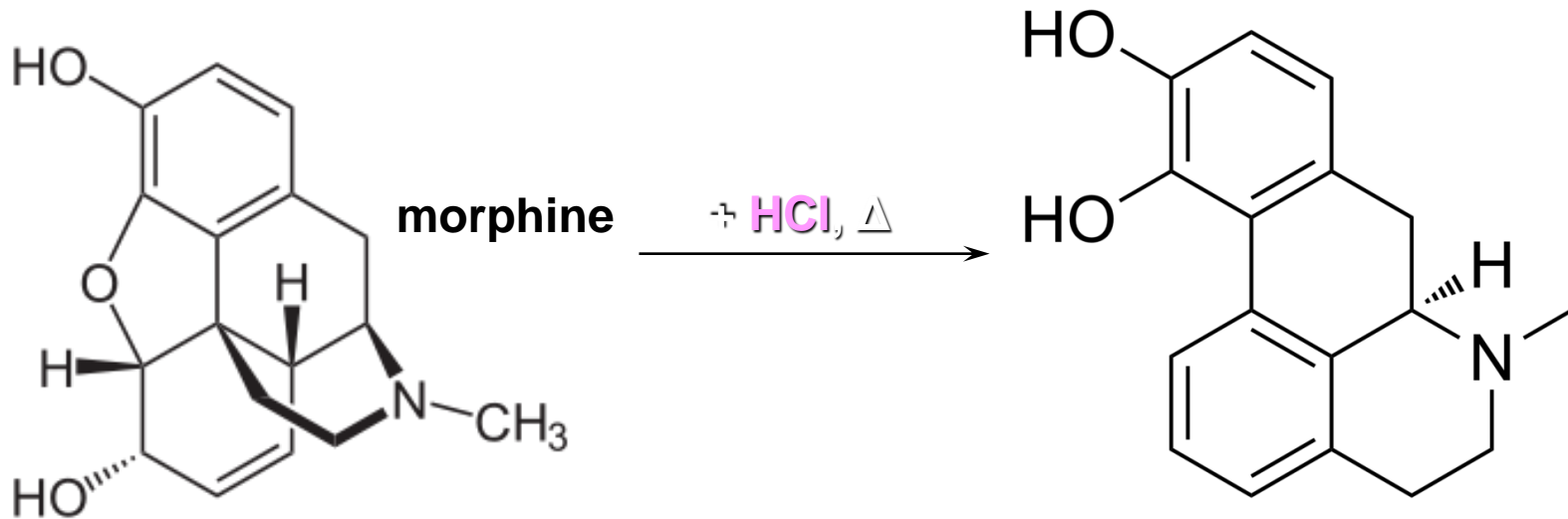
Morphine is easily acetylated to diacetylmorphine using acetic anhydride.



Heroin is more potent than morphine (it takes less for the same effect), lasts longer, and is more addicting.

Apomorphine

Obtained by heating morphine with conc. HCl in sealed vials. During this reaction rearrangement and elimination of water takes place. Apomorphine is used in the treatment of Parkinson's disease and erectile dysfunction.

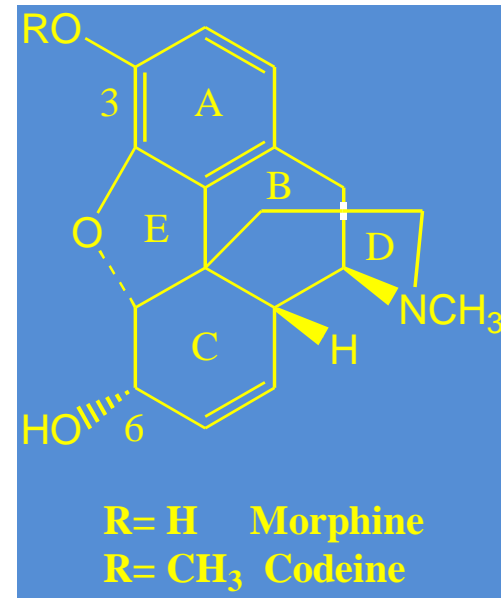
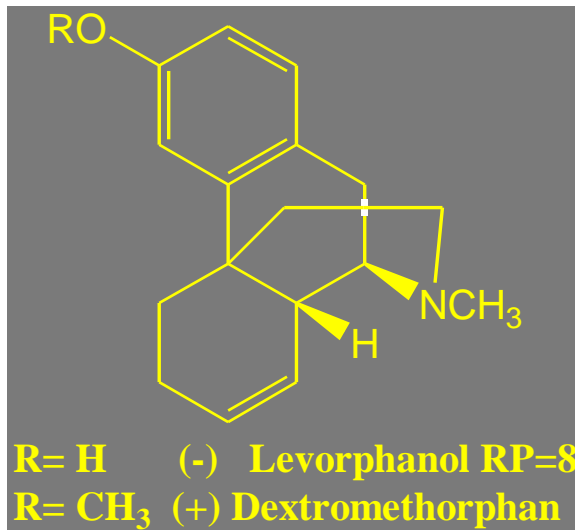


Ether bridge opening (ring E):

Resulted in group of compounds called morphinans. Synthetic morphinans are racemic compounds.

Only the levo isomers have analgesic activity. **Levorphanol** is 8 times as active as morphine.

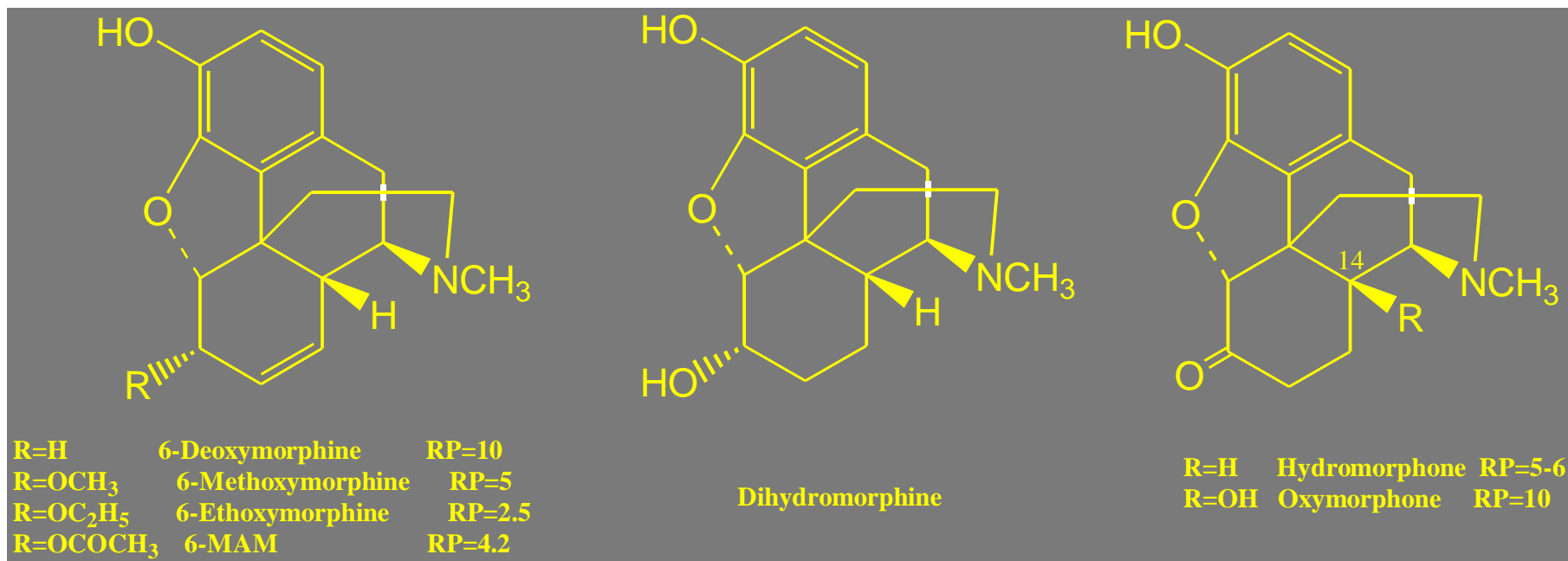
The dextro isomers as **dextromethorphan** lack the CNS and analgesic effects, however, they are used as cough suppressants.



The C-6 Hydroxyl group and ring c modifications:

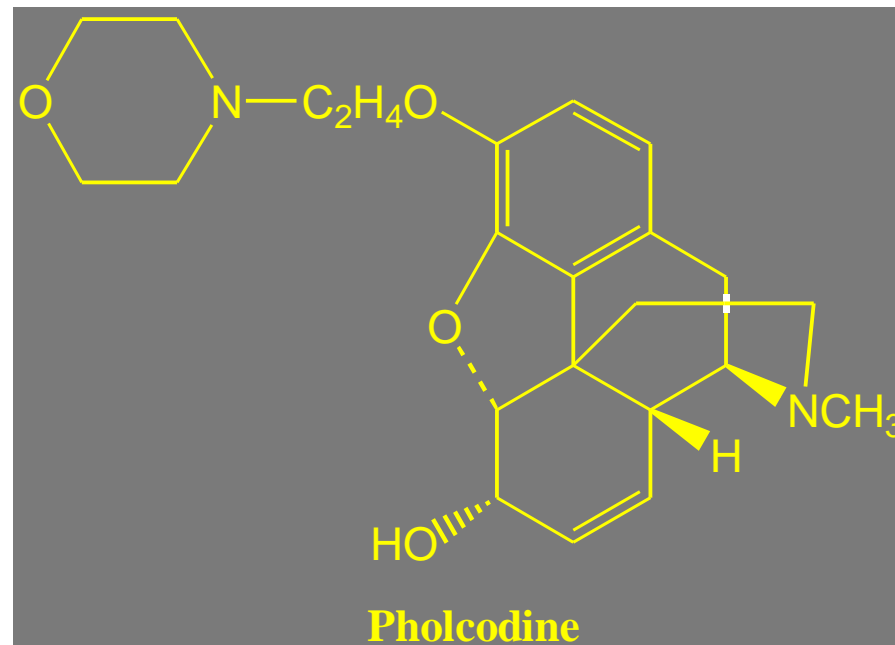
Removal or derivitization of the alcoholic hydroxyl group at C-6 increase lipophilicity and consequently the analgesic activity.

Reduction of the 7,8 double bond, oxidation of C-6 hydroxyl and addition of OH group at C-14 all increase the activity.



The C-3 Hydroxyl group:

Etherification of this phenolic OH decrease the analgesic activity and the compounds are used mainly as antitussive e.g. Codeine and Pholcodine.




Melrosum[®] with codeine
 In catarrhs of the respiratory organs. Soothes irritative and spasmodic cough.

الموسم الكوديني
 البلسم الشافي

Formula:

Codein. phosphoric.	0.1 g
Mel	45.0 g
Tinctura Grindellae	0.2 ml
Tinctura Pimpinellae	0.2 ml
Tinctura Primulae	1.0 ml
Tinctura Rosae	1.0 ml
Tinctura Thymi	1.2 ml
Corrigentia	ad 100.0 ml

Melrosum[®]
 with codeine
 100 ml



NATTERMANN
 RHÔNE-POULENC GROUP

Syrup

CODAPHED


Composition:
 Each teaspoonful (5mL) contains :

Ephedrine HCl	7.5mg
Chlorpheniramine Maleate	1.0mg
Codeine Phosphate	4.0mg

Dosage:
 Adults: 2 teaspoonfuls
 Children 6-12 years: 1-2 teaspoonfuls
 Children 1-6 years: 1/2-1 teaspoonful
 Infants over 6 months: 1/2 teaspoonful

Dose to be repeated 3-4 times daily or as directed by the physician.

Keep all medicines out of the reach of children.
 Store at room temperature not exceeding 25°C.




NOSCAPHEN

SYRUP

For Rapid & Effective Control of Cough

120 ml



PHARCO Pharmaceuticals
 ALEXANDRIA

NÉO-CODION[®]

COMPOSITION
 Codeine camphosulfonate 0.1722 g
 Excipients s.q. 100 ml.

BOUCHARA RECORDATI


88, rue Marjolin
 92300 Levallois-Perret - FRANCE

Syrup

CODAPHED

120mL

Antitussive
 Bronchodilator



Produced by: **Julphar**
 Gulf Pharmaceutical Industries,
 Ras Al Khaimah, U.A.E.

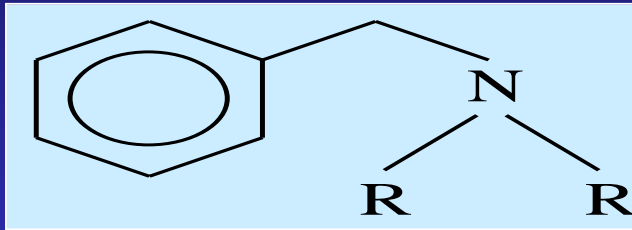
Phenylalkylamine Alkaloids

Alkaloids Derived from phenylalanine

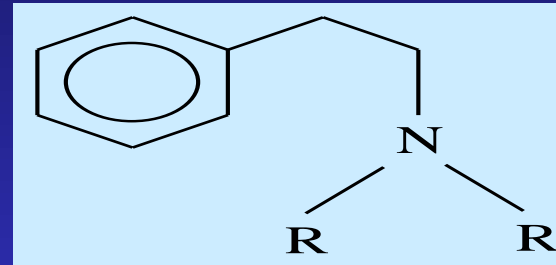
Alkaloids with Exocyclic Nitrogen

Phenylalkylamine group

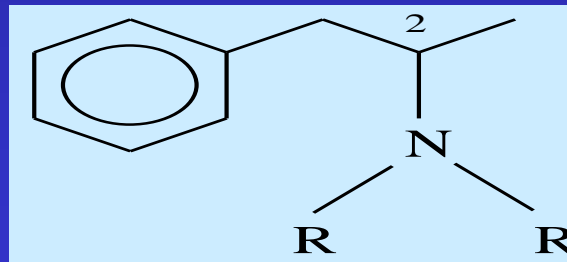
1.1. Benzylamine type



1.2. Phenylethylamine type

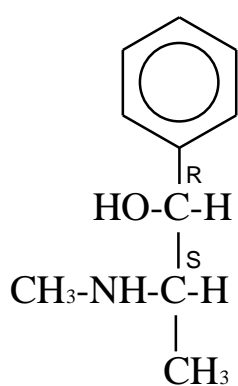


1.3. 2-Aminophenylpropan type

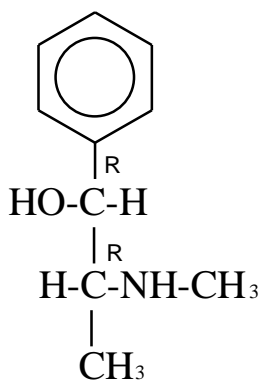


1- Ephedra Alkaloids

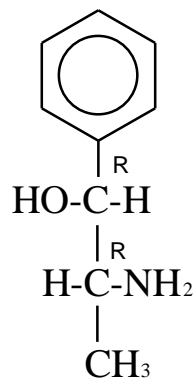
- ❑ Various Ephedra species, e.g. *E. sinica* (Ephedraceae)
- ❑ Ephedra used as remedy for Asthma in Chinese medicine
- ❑ Contains 2% alkaloids e.g. ephedrine, Pseudoephedrine, norpseudoephedrine.



L-Ephedrine

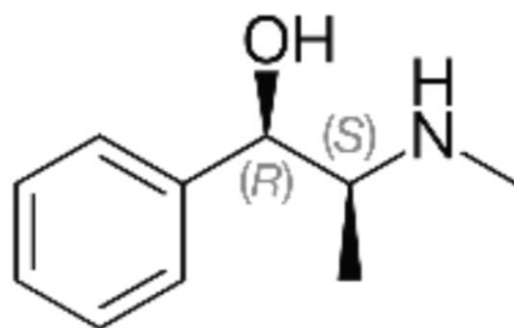


D-Pseudoephedrine

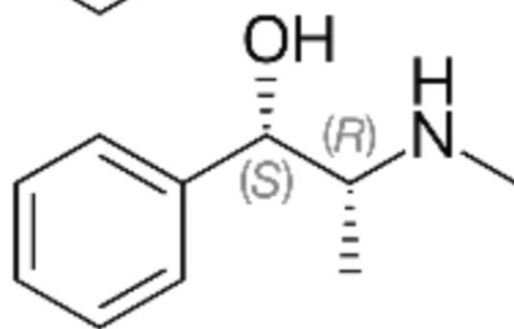


D-Norpseudoephedrine

- (-)-Ephedrine is the major Alkaloid in *Ephedra*.
- Ephedrine is a phenylalkylamine with N atom in the side chain



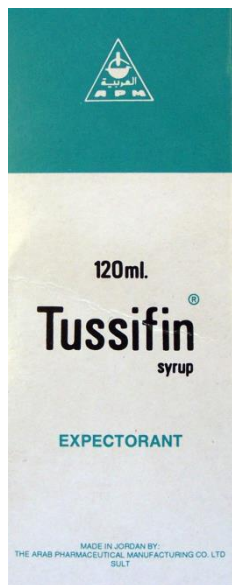
Ephedrine



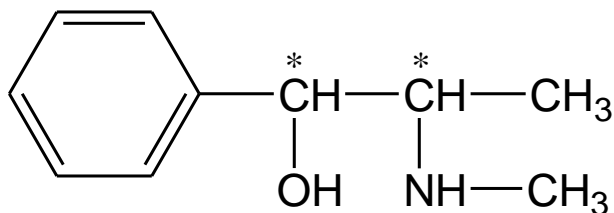
Pseudo ephedrine



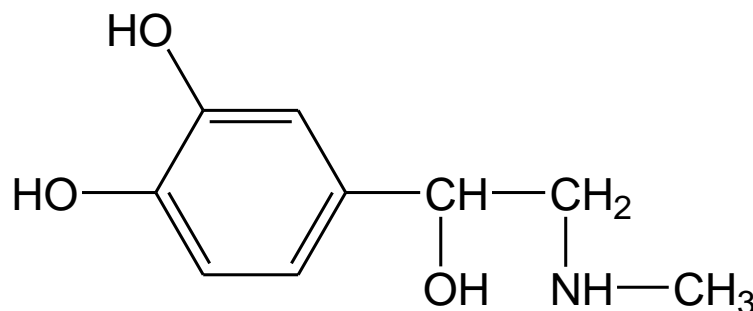
E. sinica



- Ephedrine is similar to adrenaline in structures.
- Advantages of Ephedrine over adrenaline:
 - 1- Orally active.
 - 2- Prolonged action



Ephedrine



Adrenaline

Pharmacology: ephedrine is an indirect sympathomimetic, close to adrenaline

Uses: in asthma, allergic drugs, bronchodilator, nasal congestion and in cough mixtures

Chen's test:

Ephedrine HCl in water + 0.1 ml CuSO_4 + 1ml NaOH → Violet colour, shake with Ether →

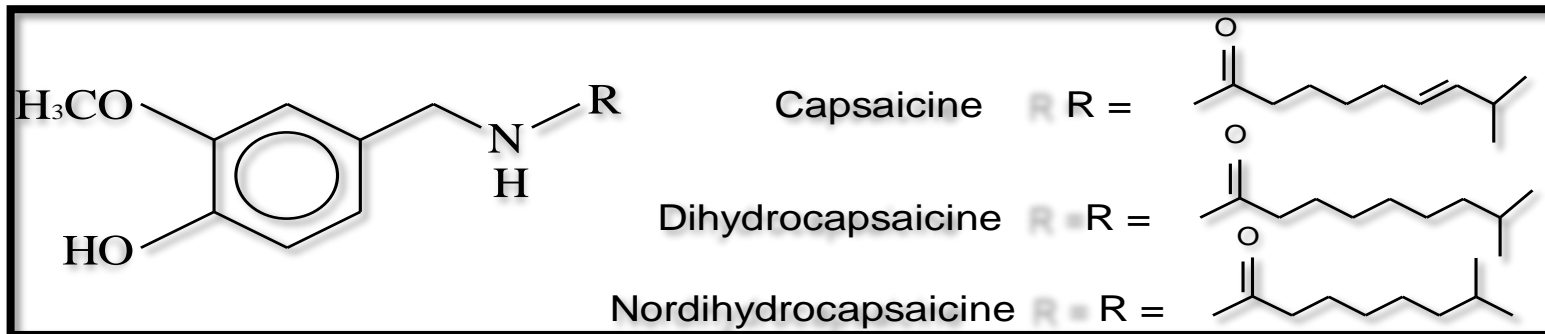
Ether layer → purple

Aqueous layer → blue



2- Capsicum

- Ripe fruit of *Capsicum annum* (Solanaceae)
- Contains 1.5% Capsainoids (amides of vanillylamines with saturated or unsaturated C₈-C₁₃ fatty acids)



Uses: as carminative, counterirritant in the form of tincture or plaster in the treatment of rheumatism and neuralgic pains

Test: 1- solution of capsaicine + FeCl₃ \longrightarrow green color
2- Capsaicine + H₂SO₄ + small amount of sugar
 \longrightarrow violet color after period of 1 h



Capsicum annum



Capsicum frutescence



3- Khat

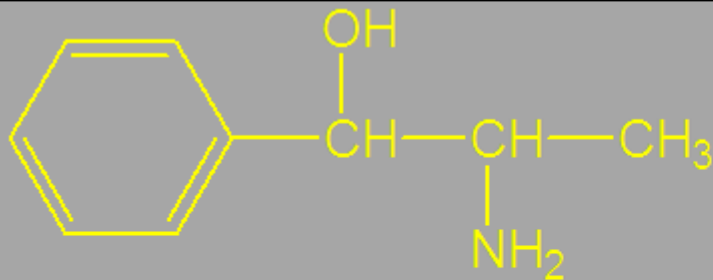
□ Leaves of *Catha edulis* (Celastraceae)

□ in fresh leaves \longrightarrow cathinone, in the dried \longrightarrow cathine

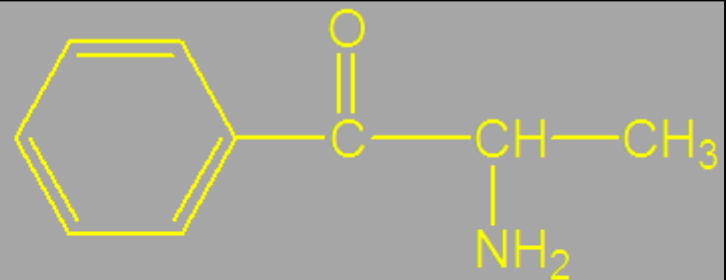
Pharmacology:

□ It causes anorexia, hyperthermia, respiratory stimulation, mydriasis, arrhythmia and hypertension.

□ It induces the release of catecholamines.



Cathine



Cathinone

Alkaloids Derived from Phenylalanine and Tyrosine

Tropolone Alkaloids

Colchicum Alkaloids

□ Dried, ripe seed and corm of *Colchicum autumnale* (Liliaceae)

□ Up to 1.2 %, the chief constituent is colchicine

□ **Colchicine** possesses a tropolone structure and being non- basic or weak- basic in character, soluble in H₂O, aq. alcohols and CHCl₃, occurs as pale yellow needles.

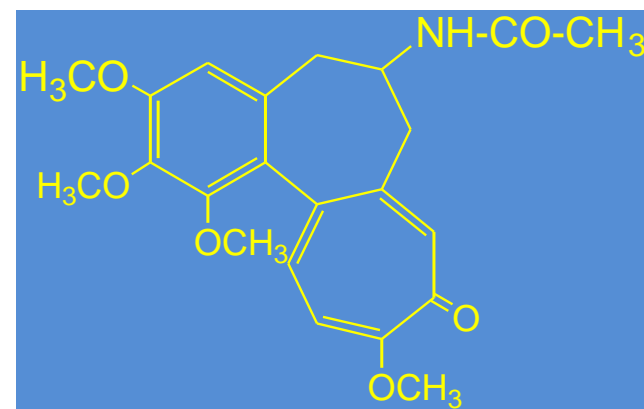
Tests for colchicine:

- 1- with few drops of mineral acids, gives yellow color
- 2- with conc HNO₃, dirty violet color is produced, which changes through brown to yellow.

Pharmacology:

□ Colchicine possesses an anti-mitotic and anti-inflammatory activity.

□ It is useful for treating of the acute attack of gout.

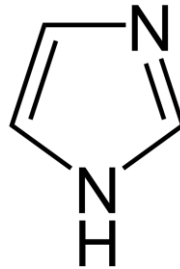




Colchicum autumnale L.
Image processed by Thomas Schoepke
www.plant-pictures.de

Alkaloids Derived from histidine

Imidazole Alkaloids



Imidazole Alkaloids

Pilocarpus Alkaloids

- Source: Jaborandi leaves (*Pilocarpus jaborandi*).
- Constituents: (+)-Pilocarpine.

- Properties:

- 1- Oily liquid miscible with water.
- 2- Non-volatile liquid alkaloid.
- 3- Lactone function.



- Test:

Helche's test:

Alkaloid + Dil acid + $K_2CrO_7 \rightarrow$ violet colour

- Uses:

1- Miotic.

2- Diaphoretic.

3- Hair preparations.

Effects/Uses:

- Pilocarpine is a cholinergic agent causing constriction of the pupil (Antagonistic to Atropine).
- Pilocarpine salts are valuable in ophthalmic practice and are used in eye drops as miotics and for the treatment of glaucoma.
- Pilocarpine gives relief for dryness of the mouth that results in patients undergoing radiotherapy for mouth and throat cancers.

Chemical tests:

1- Helch's test ($\text{H}_2\text{SO}_4 + \text{H}_2\text{O}_2 + \text{KCr}_2\text{O}_7$)
gives violet color

2- Ekkert's test (Na-nitroprusside + NaOH)
leave for a period in HCl-solution, it gives red color

