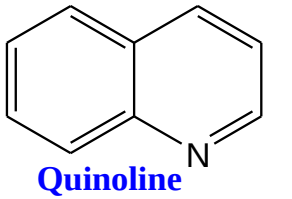
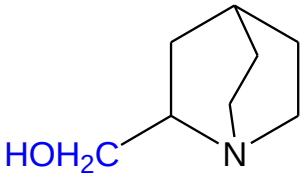
QUINOLINE ALKALOIDS

Cinchona alkaloids

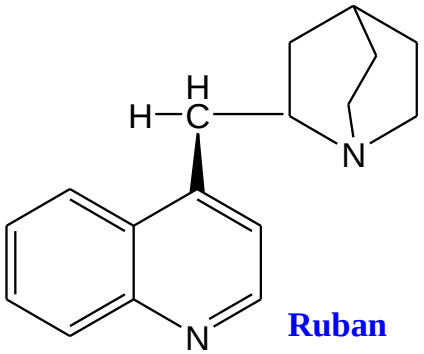
- The basic skeleton is ruban-9-Ol (derived from the parent compound ruban, named after Fam. Rubiaceae).
- Ruban nucleus is a combined skeleton formed from a quinoline ring attached through a methylene group to a quinuclidine ring (a bicyclic ring contains N).
- In Rubanol, the methylene group is oxidized to a secondary alcoholic group and the carbon atom becomes asymmetric.



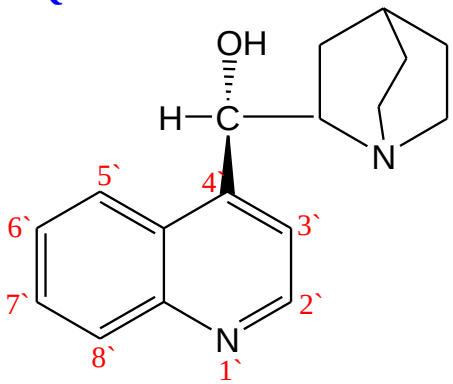
Quinoline



Quinuclidine

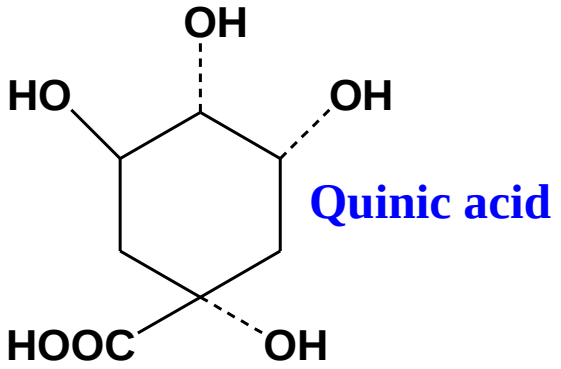


Ruban



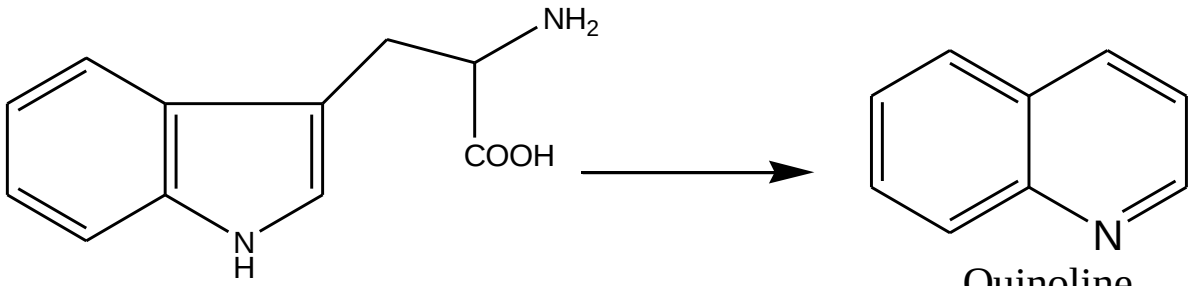
Ruban-9-ol

The alkaloids of Cinchona present in the parenchymatous tissues of bark in combined with special organic acids quinic acid, cinchotanic acid and quinoic acid.



Quinic acid

Biosynthetically from tryptophane amino acid

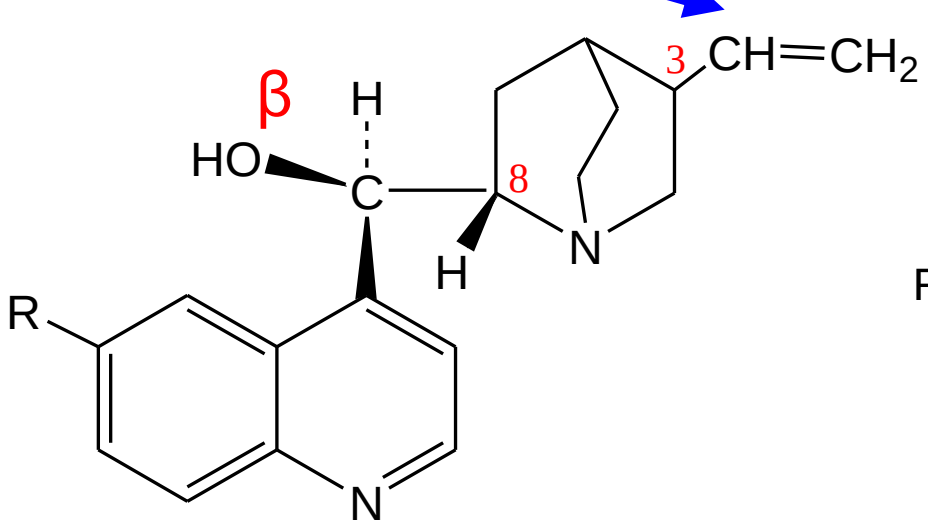


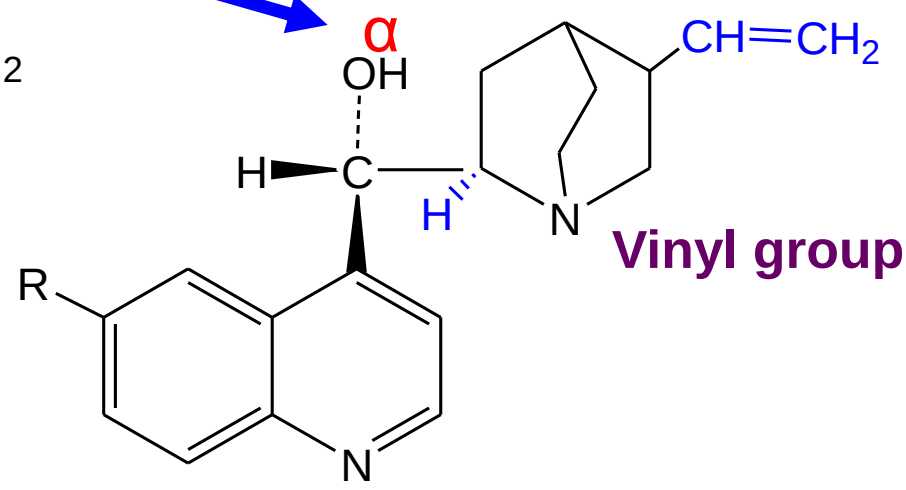
Tryptophane

Quinoline

SAR

SAR





Vinyl group

R = OCH_3: (-) **Quinine**

R = H: (-) **Cinchonidine**

R = OCH_3: (+) **Quinidine**

R = H: (+) **Cinchonine**

- Quinine and quinidine have opposite configurations at two centers.
- Cinchonidine and cinchonine are demethoxy analogues

4 pairs of steroismoers:
(-)-quinine and its dihydroform, (+)-quinidine
(+)-cinchonine and its dihydroform, (-)-cinchonidine

Physical properties

Properties	Qunine	Quinidine	Cinchonine	Cinchonidine
Solubility in ether	soluble	soluble	insoluble	soluble
Solubility in water (bi So4)	soluble	soluble	soluble	soluble
Mono So4	insoluble	soluble	Soluble	soluble
Monotartarate	Insoluble in water	Soluble in water	Soluble in water	Insoluble in water
Optical activity	*(l)*	(*d*)	(*d*)	*(l)*

Pharmacological action and uses of Cinchona alkaloid

1- Quinine, quinidine used as anti-malarial drugs.

2- Quinidine used in treatment of cardiac arrhythmia particularly in auricular fibrillations.

3- In much smaller amounts, quinine is an ingredient of tonic drinks, acting as a bettering agent.

4- **Cinchonine & cinchonidine Anti-inflammatory in rheumatoid.**

Toxicity

Cinchonism can occur from therapeutic doses of quinine, either from one or several large doses, or from small doses over a longer period of time, not from the amounts used in tonic drinks.

Quinidine can also cause Cinchonism.

Symptoms of mild Cinchonism (which may occur from standard therapeutic doses of quinine) include flushed and sweaty skin, ringing of the ears (tinnitus), blurred vision, impaired hearing, confusion, reversible high-frequency hearing loss, headache, abdominal pain, rashes, photosensitivity. vertigo, dizziness, nausea and vomiting, and diarrhea

Test for identity: (qualitative colour test).

1- Quinine and quinidine produce strong blue fluorescence when dissolved in oxygenated acids (H_2SO_4).

2- Thalleioquine Test:-

Quinine acid salts + drops Br_2 water + ammonia $\longrightarrow$ deep green colour is produced (Thalleioquine).

The test positive with quinine and quinidine, but negative with cinchonine, cinchonidine

All the alkaloids decolorize $KMnO_4$ solution and Br_2 solution due to the presence of $-CH=CH_2$ attached to C_3

3- Erythroquine test.

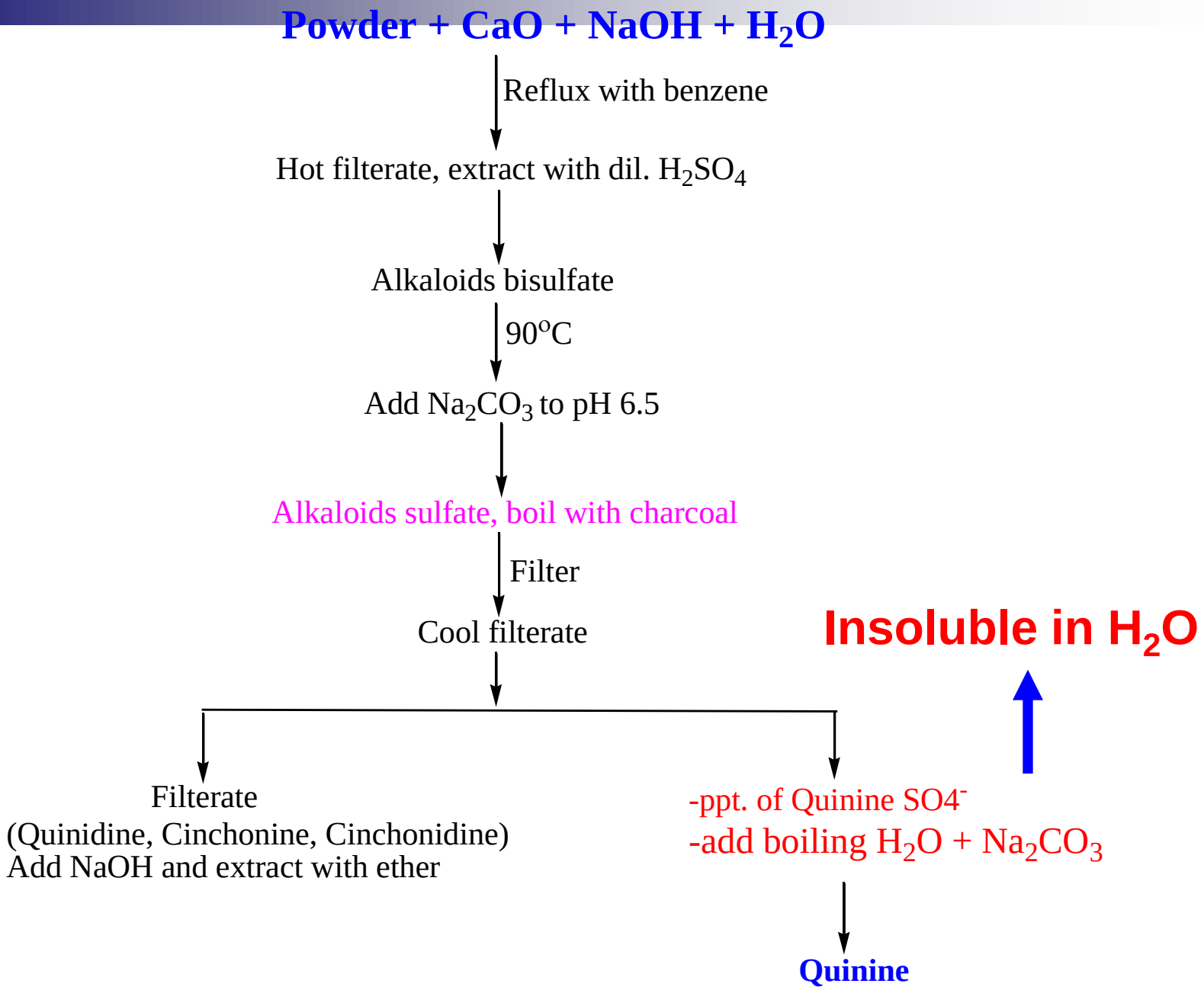
Quinine + dil HOAC + drop Br_2 water + drop of K_4-ferrocyanide + drop $NH_4OH \longrightarrow$ red solution $\longrightarrow$ shake with 1 ml $CHCl_3$ it becomes red.

4- Herpathite test:

Boiling salts of quinine + glacial acetic acid + 5 drops of conc. H_2SO_4 + iodine in alcohol $\longrightarrow$ crystals of **Iodosulphate** of quinine formed called **herpathite** which have metallic luster.

Assay of Cinchona alkaloid in the bark.

- Assay for total Cinchona alkaloids carried out gravimetric.


Powder + CaO + NaOH + H2O
Reflux with benzene
Hot filterate, extract with dil. H2SO4
Alkaloids bisulfate
90°C
Add Na2CO3 to pH 6.5
Alkaloids sulfate, boil with charcoal
Filter
Cool filterate
Insoluble in H2O
Filterate
(Quinidine, Cinchonine, Cinchonidine)
Add NaOH and extract with ether
-ppt. of Quinine SO4-
-add boiling H2O + Na2CO3
Quinine

Filterate

(Quinidine, Cinchonine, Cinchonidine)
Add NaOH and extract with ether

Insoluble in Ether

Aqueous (Cinchonine)

-Evaporate to dryness
-Extract with alcohol
-Decolourise with charcoal
and leave to crystallize

Cinchonine

Ether (Quinidine, Cinchonidine)

Add dil. acid

-Neutralize acid solution
-Add Na K tartarate

ppt. (Cinchonidine tart.)

-Add HCl

Cinchonidine HCl

Add NH_4OH

Cinchonidine

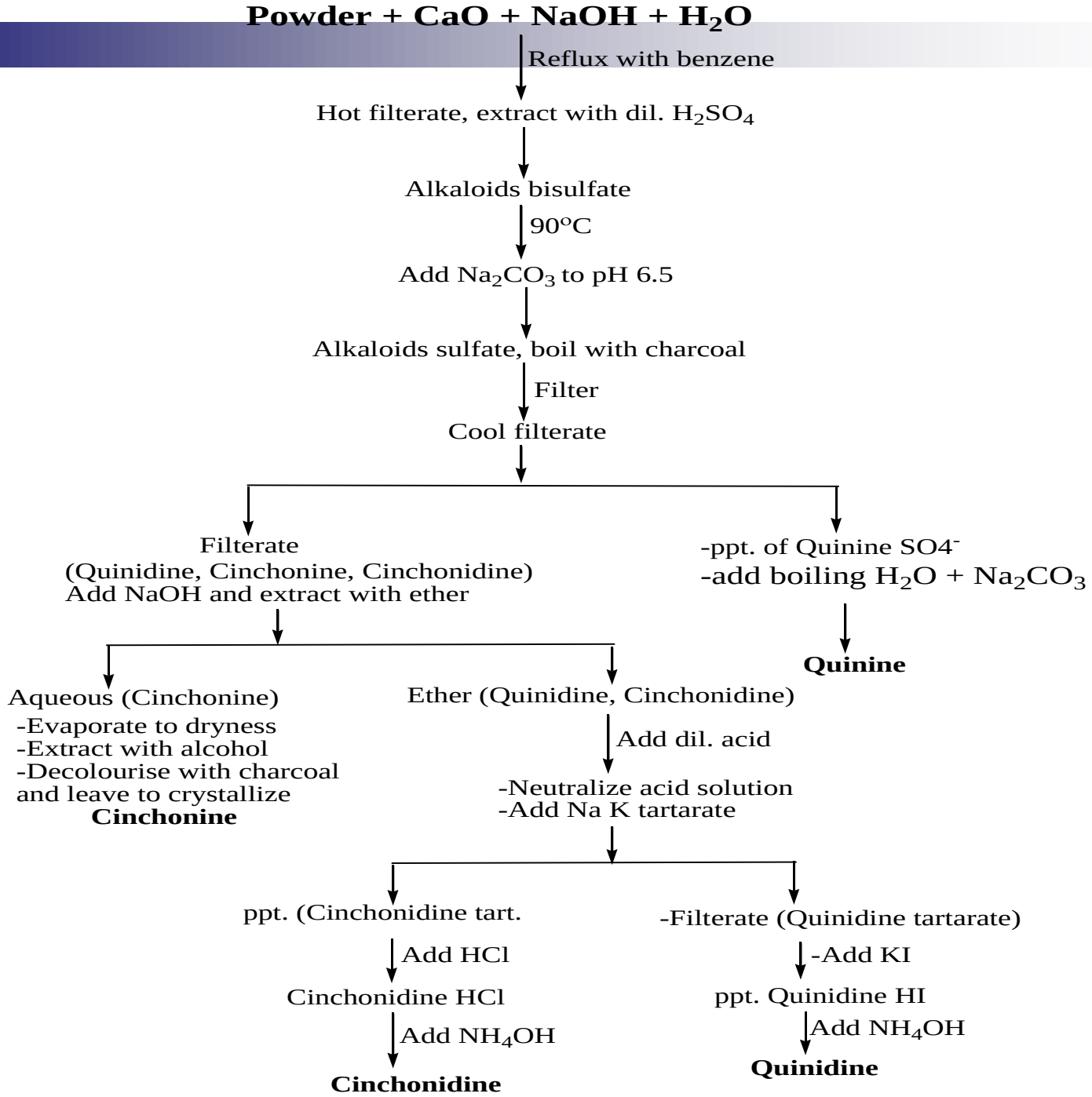
-Filterate (Quinidine tartarate)

-Add KI

ppt. Quinidine HI

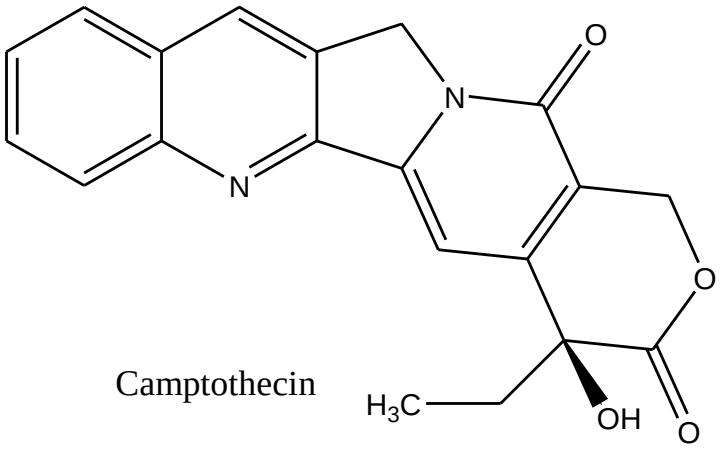
Add NH_4OH

Quinidine


Powder + CaO + NaOH + H_2O
Reflux with benzene
Hot filterate, extract with dil. H_2SO_4
Alkaloids bisulfate
90°C
Add Na_2CO_3 to pH 6.5
Alkaloids sulfate, boil with charcoal
Filter
Cool filterate
Filterate
(Quinidine, Cinchonine, Cinchonidine)
Add NaOH and extract with ether
-ppt. of Quinine $SO4^-$
-add boiling H_2O + Na_2CO_3
Quinine
Aqueous (Cinchonine)
-Evaporate to dryness
-Extract with alcohol
-Decolourise with charcoal
and leave to crystallize
Cinchonine
Ether (Quinidine, Cinchonidine)
Add dil. acid
-Neutralize acid solution
-Add Na K tartarate
ppt. (Cinchonidine tart.
Add HCl
Cinchonidine HCl
Add NH_4OH
Cinchonidine
-Filterate (Quinidine tartarate)
-Add KI
ppt. Quinidine HI
Add NH_4OH
Quinidine

Camptothecin

- Camptothecin is obtained from the Chinese tree *Camptotheca acuminata* (Nyssaceae).



Camptothecin

Uses

1. Camptothecin showed broad-spectrum anticancer activity.
2. Camptothecin acts by inhibition of the enzyme topoisomerase, which is involved in DNA replication and reassembly, by binding to and stabilizing a covalent DNA–topoisomerase complex.
3. Camptothecin has also been shown to have potentially useful activity against pathogenic protozoa such as *Trypanosoma brucei* and *Leishmani donovani*, which cause sleeping sickness and leishmaniasis respectively.

ISOQUINOLINE GROUP

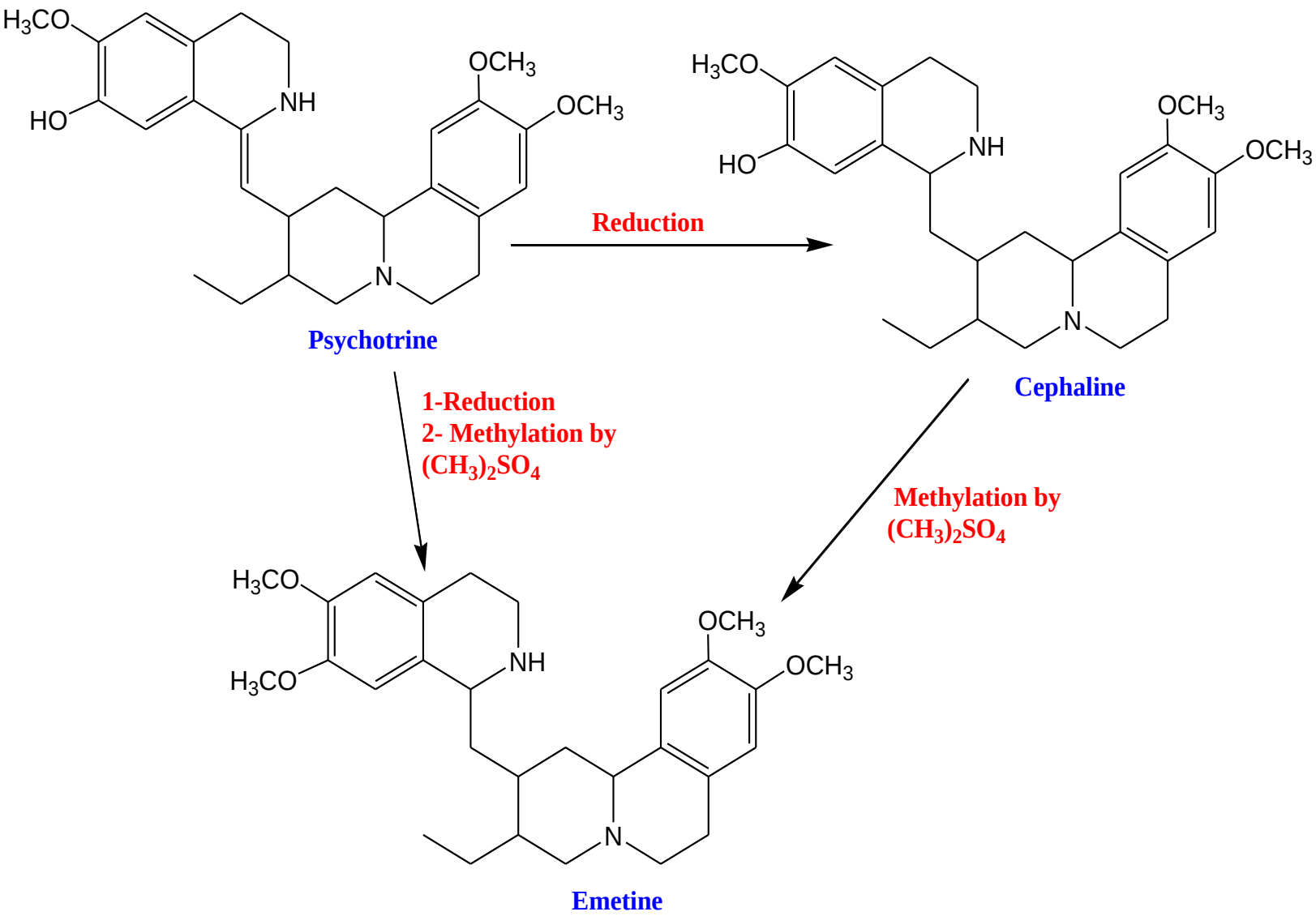
A-Ipecacuanha alkaloids

Cephalis Ipecacuanaha **(Rio or Brazilian),**
Cephalis acuminata **(Cartegena ipeca) Fam. Rubiaceae.**

B- Curare contains (tubocurarine type).

C- Opium capsules contains (papaverine type).

A-Ipecacuanha alkaloids



Physical properties

	Emetine	**Cephaeline**	**Psychotrine**
State	Amorphous	needles	Yellow prism
Ether	Soluble	Soluble	**In**soluble
NaOH	**In**soluble	Soluble	Soluble

1- Froehd's reagent gives with;

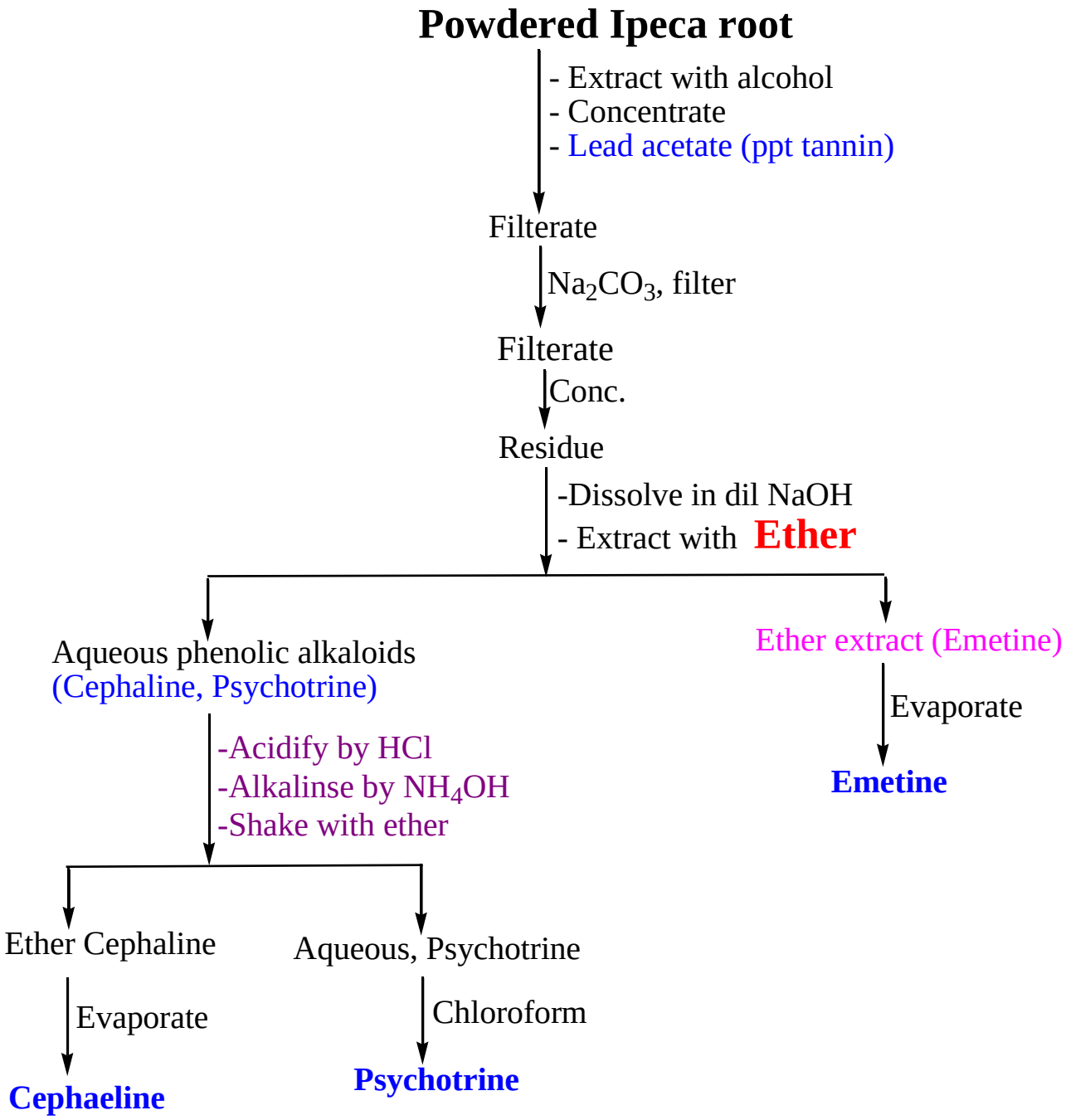
A- Emetine dirty green which disappear after period.

B- Cephaeline → greenish yellow → dull greenish blue.

C- Psychotrine → pale green colour.

2- Cephaeline or Psychotrine + *P*. dinitrobenzene + NaOH → purple colour.

3- Psychotrine + H_2SO_4 + HNO_3 → cherry red Colour.


Powdered Ipeca root
- Extract with alcohol
- Concentrate
- Lead acetate (ppt tannin)
Filterate
Na_2CO_3, filter
Filterate
Conc.
Residue
-Dissolve in dil NaOH
- Extract with Ether
Aqueous phenolic alkaloids
(Cephaline, Psychotrine)
Ether extract (Emetine)
Evaporate
Emetine
-Acidify by HCl
-Alkalinse by NH_4OH
-Shake with ether
Ether Cephaline
Aqueous, Psychotrine
Evaporate
Chloroform
Cephaeline
Psychotrine

Uses

- Ipeca tinctures used as expectorant and emetic.
- Emetine is used :In severe amoebic dysentery and Hepatic amabiases.
- Emetine is more expectorant and less emetic than cephaline.
- Ipecac alkaloids are diaphoretic and used in combination with opium (Dover's powder).
- Emetine & psychotrine showed antiviral activity.

Drug combination:

- Emetine + oxytetracycline in intestinal amabiasis. Where oxytetracyclineis useful as luminal amebicides.
- Emetine + chloroquine in amebic liver abscess.

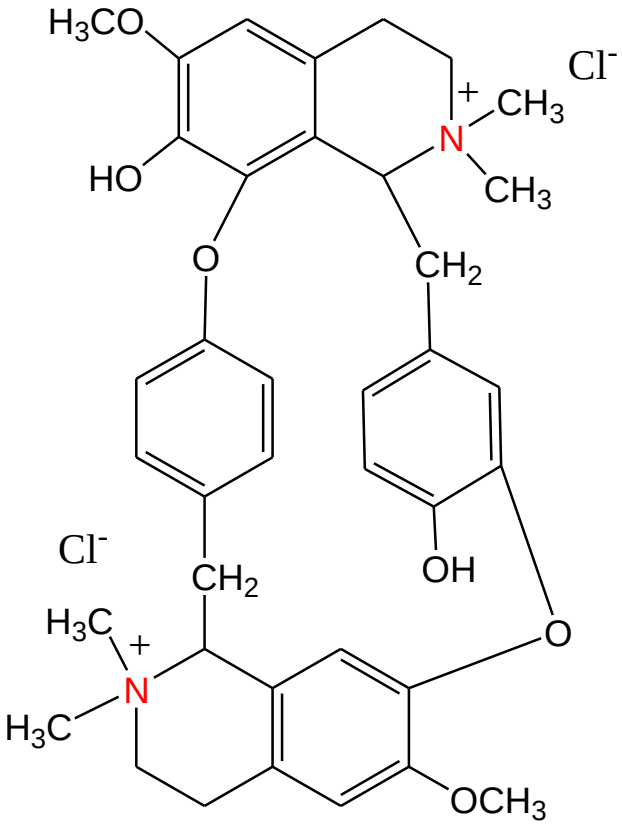
Contra-indications;

- Significant heart diseases where emetine is a myocardial toxin and Polyneuritis.

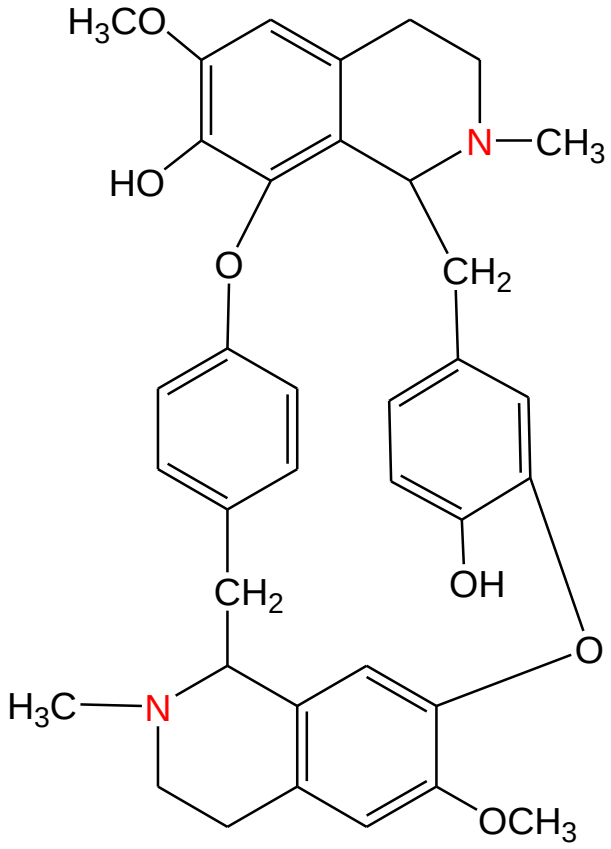
B- BIS-BENZYLISOQUINOLINE ALKALOIDS

Curare alkaloids

Curare alkaloids; *Strychnos toxifera* Fam. Loganaceae



d- Tubocurarine

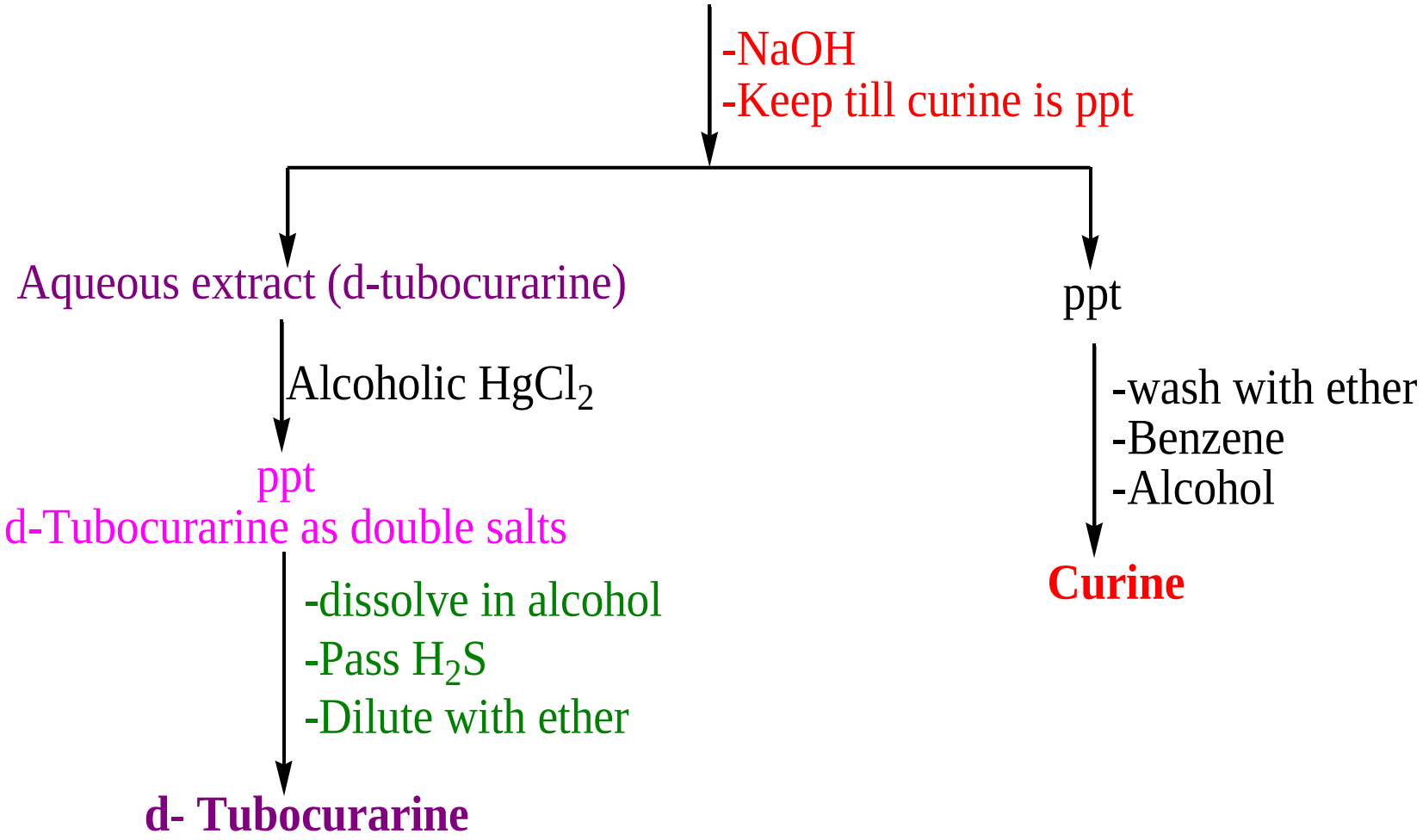


Curine

Structures:

- Curare Alkaloids: Biosynthetically derived from Tyrosine amino acid.
- Dimeric alkaloids.They are e.g. of Bis-benzyltetrahydroisoquinoline alkaloids.
- Curare contains several alkaloids the most important are d-tubocurarine (major) and curine (minor).
- D-Tubocurarine is a yellowish white powder, quaternary alkaloid, soluble in H2O.
- Curine is tertiary alkaloid insoluble in H2O.

Aqueous extract of bark and stem of Strychnous and Chondroendrom



Uses

1- d (+) Tubocurarine chloride is mainly used by I.M or I.V routes as a skeletal muscle relaxant in light surgical operations.

2- Anti convalescent in marital diseases.

3- As diagnostic agent in myasthenia gravis.

4- It is an adjunct to shock therapy in neuropsychiatry.

5- Used to control convulsions of strychnine poisoning and tetanus

Test of identity

1- Aqueous solution of d. tubocurarine HCl + $FeCl_3$ $\rightarrow$ faint green colour.

2- Aqueous solution of d. tubocurine HCl + Na_2CO_3 solution$\rightarrow$ Yellow brown ppt.

Quantitative estimation (Head-drop Crossover test, biological):

- This depends on the paralytic effect of d-tubocurarine on the voluntary muscle of frog or rabbit.