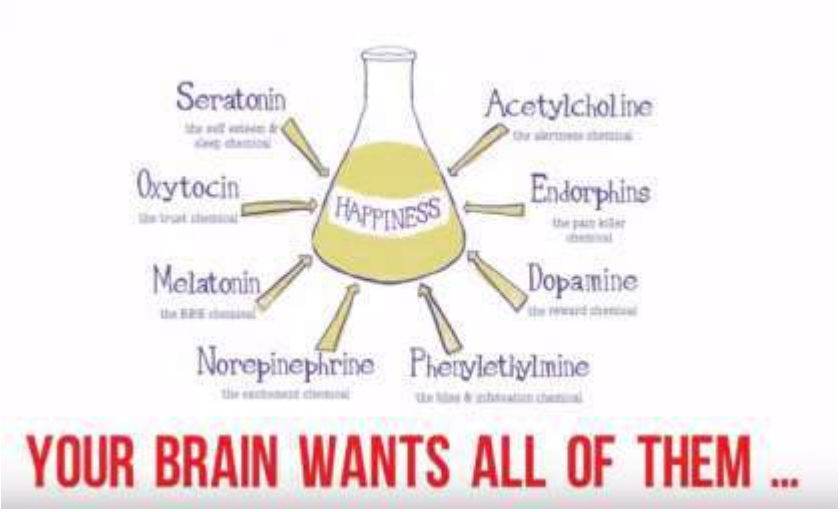
Phytochemistry 3

Dr. Mazen A. El-Sakka

2022

1



1

Definition

- Alkaloids are **natural** compounds, with **nitrogen** in structure, which in **minimum** **dose** give pharmacological properties.

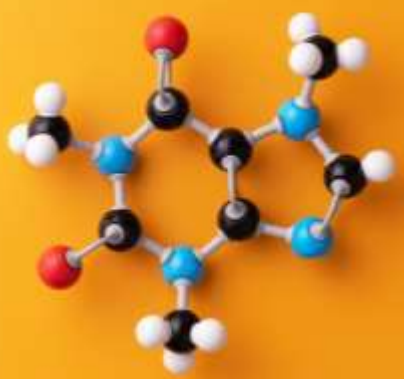
2

2

Classification of Alkaloids

3

3



According to Chemical Structure

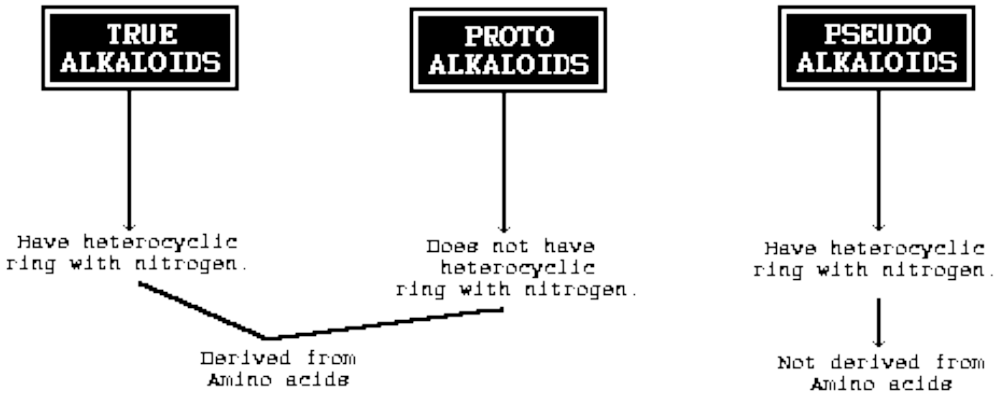
Non-heterocyclic or atypical alkaloids that are sometimes called ''protoalkaloids' or biological amines.

Heterocyclic or atypical alkaloids that are sub-classified into different groups according to their ring structure.

4

4

According to Hegnauer's classification

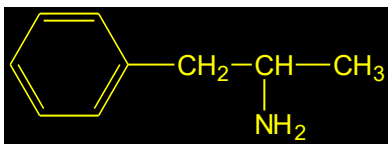


5

5

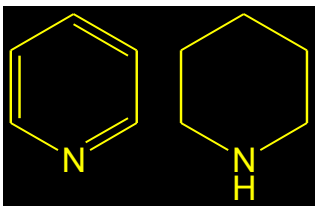
- **Phenylalkylamines:**

  e.g. Ephedrine



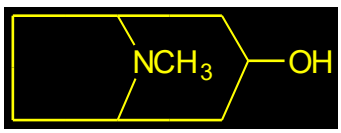
- **Pyridine and piperidine**

  e.g. lobeline, nicotine



- **Tropane**

  e.g. Atropine.



6

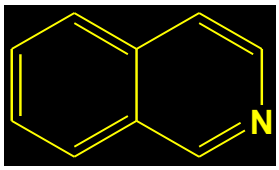
6

- **Quinoline**

  e.g.quinine and quinidine

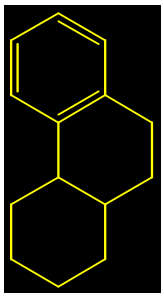
- **Isoquinoline**

  e.g. papaverine



- **Phenantheren**

  e.g. Morphine

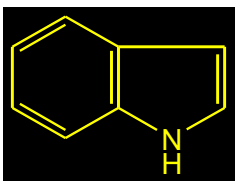


7

7

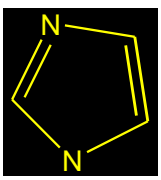
- **Indole**

  e.g.ergometrine



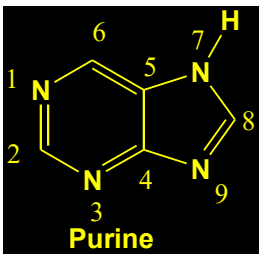
- **Imidazole**

  e.g. pilocarpine



- **Purine**

  e.g. caffeine

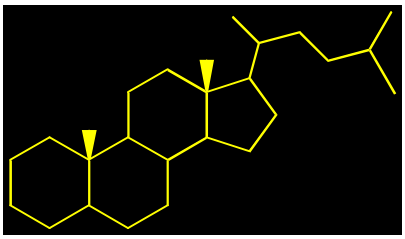


8

8

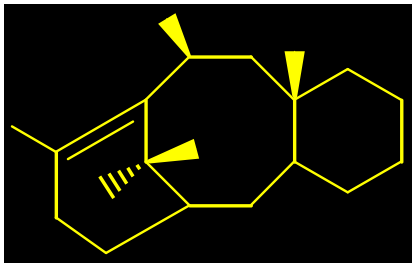
- **Steroidal**

  e.g. Solanum and *Veratrum* alkaloids



- **Terpenoid**

  e.g. Taxol



9

Biogenesis Classification

Robinson Classification

1. Ornithine & Lysine alkaloids
2. Carboline & Purine alkaloids
3. Phenylalanine alkaloids
4. Tryptophan alkaloids
5. Pseudoalkaloids

Robinson J. Classification

1. Ornithine alkaloids
2. Lysine alkaloids
3. Phenylalanine alkaloids
4. Tryptophan alkaloids
5. **Carboline alkaloids**
6. **Purine alkaloids**
7. **Histidine alkaloids**
8. **Alline alkaloids**
9. Pseudoalkaloids

10

Nomenclature

- Chemical rules stated that their trivial names should end by ***"ine"***
  - Atrop**ine**
  - Coca**ine**
  - Emet**ine**
  - Pelleriер**ine**
  - Hygr**ine**

11

11

Prefixes & Suffixes

- Prefixes:
  - **"Nor"** -designates N-emethylation or Ndemethoxylation, e.g .norpseudoephedrine and normicotine.
  - **"Apo"** -designates dehydration e.g . apomorphine.
  - **"Iso"-**, pseudo-, neo-, and epi-" indicate different types of isomers.
- Suffixes:
  - **"dine"** designates isomerism as in the case of the Cinchona alkaloids, **quinidine** and **cinchonidine** are optical isomers of quinine and cinchonine respectively.
  - **"ine"** indicates a lower pharmacological activity e.g .ergotamine is less potent than ergometrine.

12

12

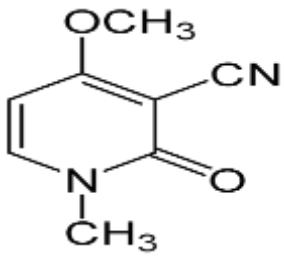
Basicity

- In plants, alkaloids occur as free bases, salts or N-oxides (N O).
- ***Factors that may influence the degree of basicity***
  - The structure of the molecule such as the **degree of unsaturation** of the heterocyclic ring .
  - **Unsaturation increase the basicity** e.g .Piperidine alkaloids are more basic than pyridine alkaloids.
- The **presence and position of other substituents and functional groups**:
  - The electron releasing groups, such as **alkyl groups, increase the basicity**.
  - The electron withdrawal groups, such as the **carbonyl groups, decrease the basicity .**

13

13

Alkaloids may, therefore, be **neutral or slightly acidic**, as the electron availability on the amino nitrogen atom decreases .An example of acidic alkaloid is **Ricinine.**

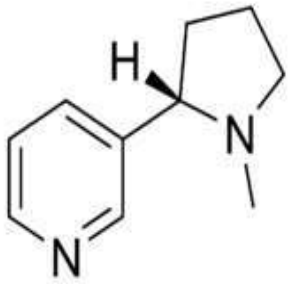


Some alkaloids are **amphoteric** due to the presence of acidic groups in their molecule such as **Morphine.**

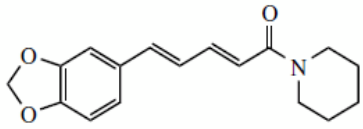
14

14

Most alkaloids contain oxygen in their molecules .Few alkaloids are oxygen-free such as **nicotine** and **coniine**



Very weak bases form unstable salts, Such as caffeine, piperine



piperine

15

15

Physical Properties

Condition

volatile e.g .nicotine and coniine, or

Non-volatile e.g . pilocarpine and hyoscine

Color

- Colchicines and berberine are **yellow**.
- Canadine is **orange**.
- The salts of sanguinarine are **copper-red**.

Solubility

- Alkaloids soluble in alcohol & organic solvents and insoluble in water
- Exceptions:
  - Bases soluble in water :caffeine, ephedrine, codeine, colchicines, pilocaepine and quaternary ammonium bases.
  - Bases insoluble or sparingly soluble in certain organic solvents :morphine and psychotrine ether, therobromine and theophylline in benzene.
  - Salts are usually soluble in water and, insoluble or sparingly soluble in organic solvents.

Optical activity

- L-ephedrine is 3.5 times more active than d-ephedrine and,
- L-ephedrine is 3.4times more active than d-ergotamine.

- d-Tubocuranie is more active than the corresponding 1-from.
- Both quinine)1-from (and its d-isomer quinidine are active.
- The racemic dl-atropine is physiologically active.

16

16

Chemical Properties:

I- Nitrogen:

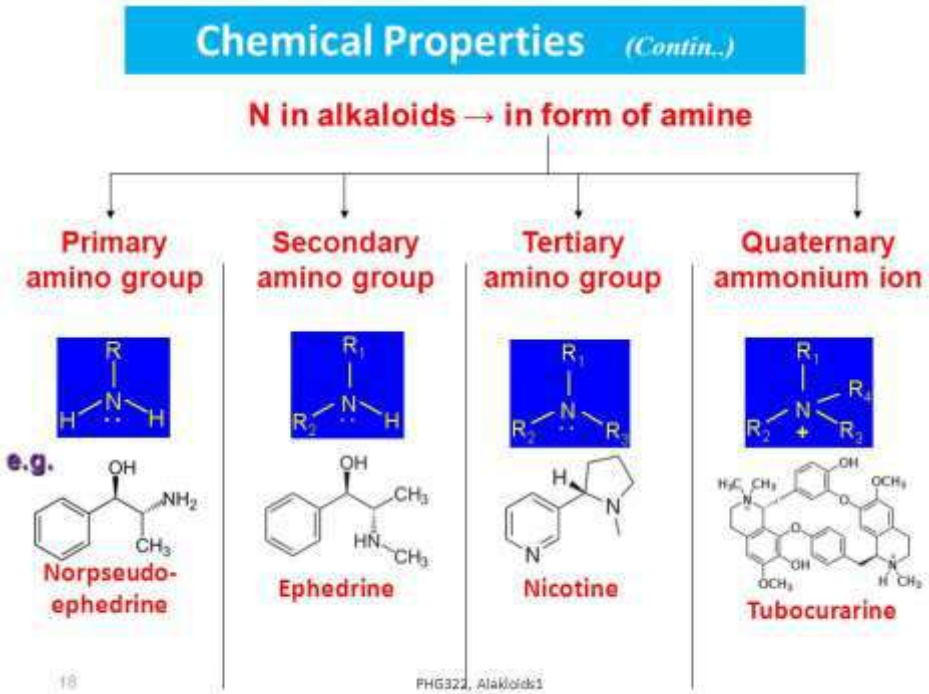
- Primary amines $R\text{-}NH_2$ e.g. Norephedrine
- Secondary amines $R_2\text{-}NH$ e.g. Ephedrine
- Tertiary amines $R_3\text{-}N$ e.g. Atropine
- Quaternary ammonium salts $R_4\text{-}N$ e.g *d*-Tubocurarine

II- Basicity:

- $R_2\text{-}NH > R\text{-}NH_2 > R_3\text{-}N$
- Saturated hexacyclic amines is more basic than aromatic amines.

17

17



18

18

Chemical Properties

Salt formation

- Acid/base – Weak/strong
- Amphoteric alkaloids containing phenolic or carboxylic group

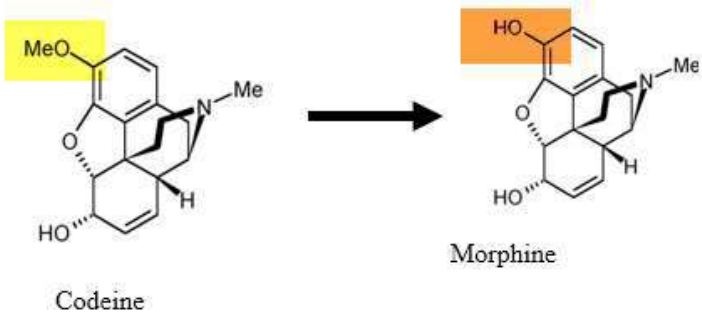
Stability

- Effect of heat
  - Alkaloids are decomposed by heat; expect caffeine that sublimes without decomposition.
  - Most tertiary amine alkaloids are easily transformed to the N-oxides when exposed to light and oxygen at elevated temperature.
- Effect of acid
- Effect of alkali

19

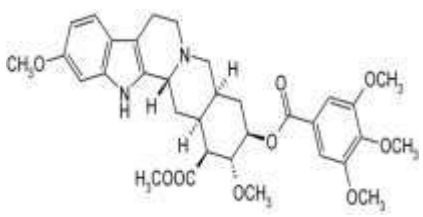
Effect of Acids

- **Dehydration:**
  - **morphine lead to apomorphine**
  - **Atropine to Apoatropine**
- **Demethylation:**
  - **Codeine to morphine**
- **Hydrolysis:**
  - **Reserpine, Solanine**

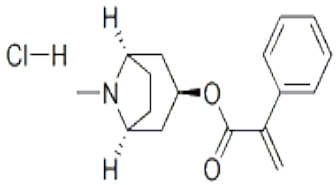


Codeine

Morphine



Reserpine

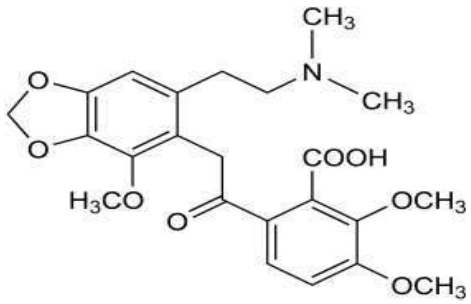


Apoatropine

20

Effect of Alkali

- Weak alkalis liberate most alkaloids from their salts (NH_3)
  - from salts with alkaloids containing a carboxylic group e.g .**narceine**, when treated with NaHCO3,
- Strong alkalis :such as aqueous NaOH and KOH
- Hot alkalis :heating with alkalis results in :hydrolysis ester alkaloids
  - pilocarpine is transformed to pilocarpic acid.



Narceine

21

Tests for detection and identification

Precipitation reactions

- production of amorphous or crystalline precipitates of various colors, in which the precipitating reagent is added to extract.
- The reagents used contain heavy metals such as Hg, Pt, Bi and from double salts with most alkaloids.

Color Reactions

- Addition of color reagents to the solid free bases not to their salts to produce characteristic-colored solutions *(The reagents contain concentrated acid and an oxidizing agent)*.
  - Van-Urk's test for ergot alkaloids, these give a blue colour
  - Vitalis' test for tropan alkaloids, these give a violet color

22

- **Classification of Alkaloidal precipitating agents:**

1- Reagents that form double salts:

a- Mayer's Reagent: Potassium Mercuric Iodide.

b- Dragendorff's Reagents: Potassium Iodobismethate.

2- Reagents Containing Halogens:

a- Wagner's Reagent: Iodine/ Potassium Iodide.

3-Organic Acids:

a- Hager's Reagent: Picric Acid

b- Tannic Acid.

4- Oxygenated High Molecular Weight Acids:

a- Phosphomolybdic acid

b- Phosphotungestic acid

c- Silicotungestic Acid

23

Extraction, Purification and Isolation of Alkaloids from Powdered plants

- **Extraction and purification**

Method I:

The powder is treated with **alkalis** to liberates the free bases that can then be extracted with water immiscible organic solvents.

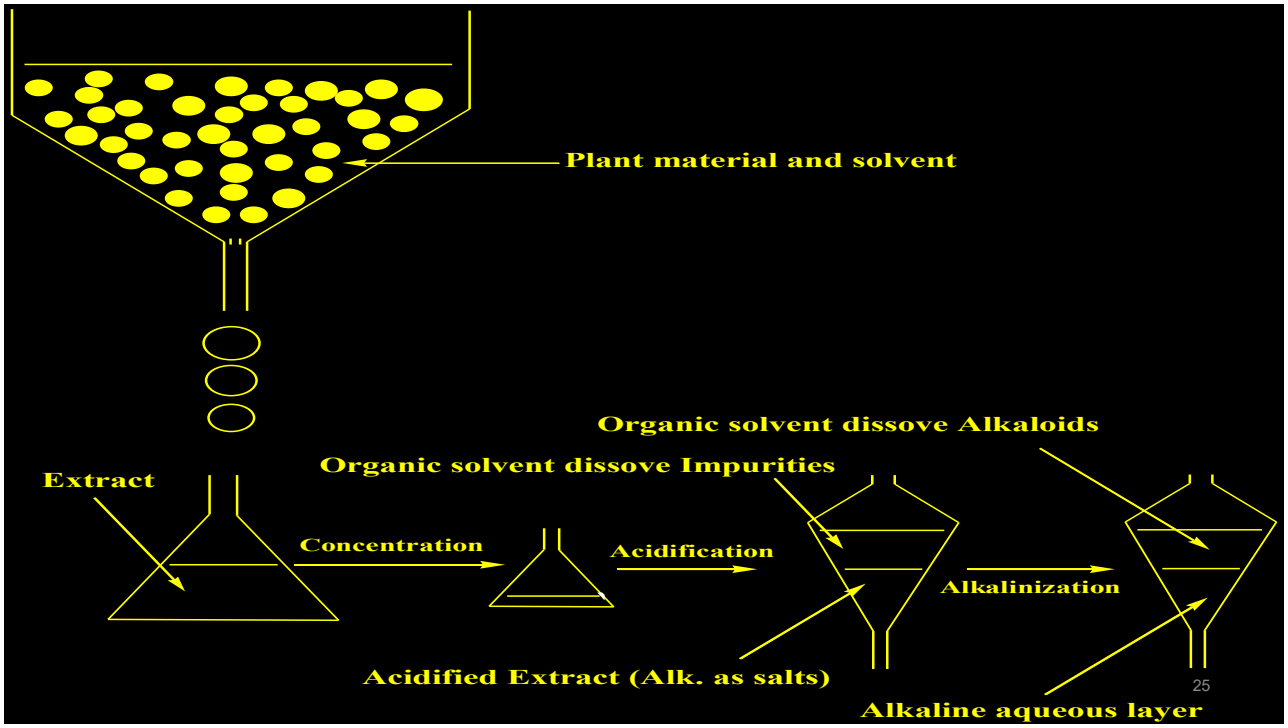
Method II:

The powdered material is extracted with water or aqueous alcohol containing dilute **acid**. Alkaloids are extracted as their salts together with accompanying soluble impurities.

Method III:

The powder is extracted with **water soluble organic solvents** such as MeOH or EtOH which are good solvents for both salts and free bases.

24



25

- **Extraction of the free bases:**
- **$CHCl_3$:**

  Strong solvent can extract most of the alkaloids.

  Extracts contain more impurities.

  Carcinogenic.
- **Ether:**

  Gives cleaner Extract but have some disadvantages:

  1- High volatility

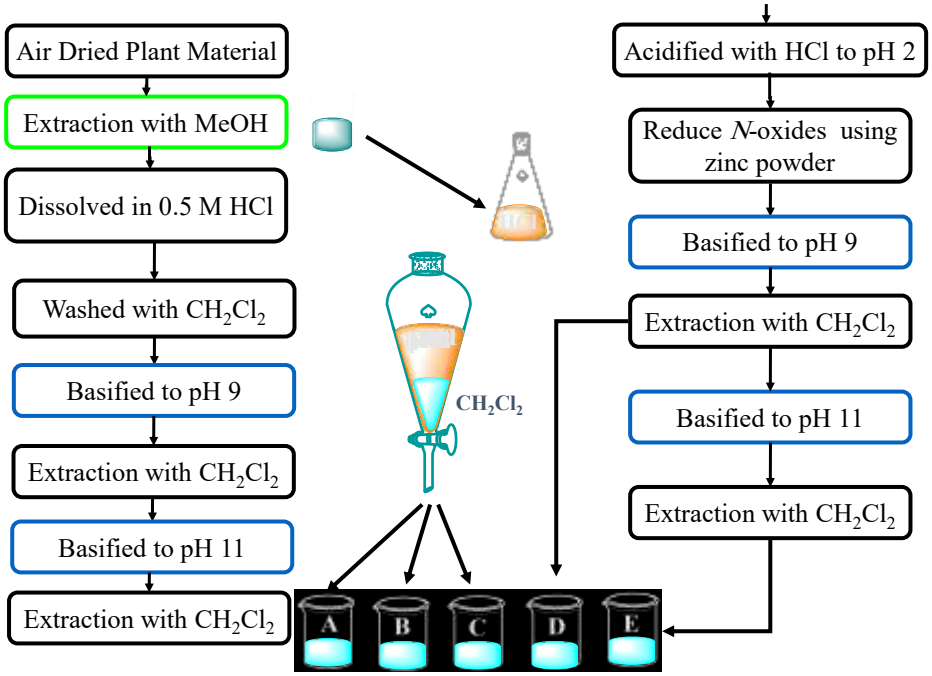
  2- Peroxide formation

  3- High water miscibility

26

26

Crude Alkaloid Fractionation



27

27

Crude Alkaloids Fractions

Dried plant Weigh (g)	MeOH fraction (g)	Fractions (mg)				
		A	B	C	D	E
		HCl	pH9	pH11	pH9	pH11
						
6161.6	628.4	2815.5	984.2	211.1	357.6	197.7
Dragendorff reagent test		-ve	++ve	+ve	+ve	+ve

- Fraction A: no alkaloids present
- Alkaloids are presents in all other fractions
- Fraction B is the alkaloids rich fraction
- Fraction B applied for chromatographic process

28

28

➢Purification of the Crude Alkaloidal Fractions:

- **Repeated Acid-Base procedures:**

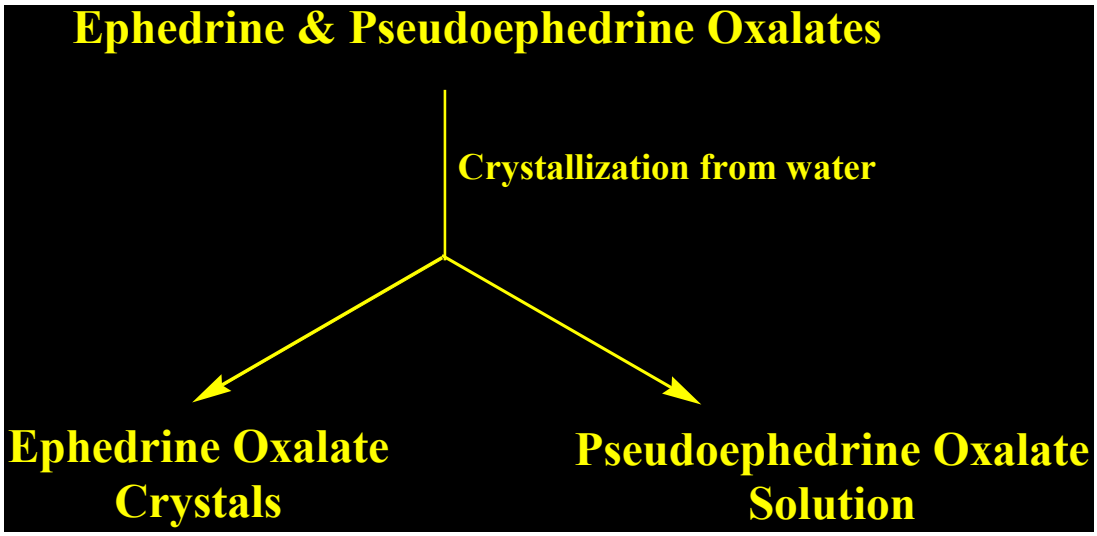
  Render extract **Acidic**, extract with **organic solvent** (dissolve non alkaloidal impurities), **Alkalinize** and extract again with **organic solvents** (Dissolve Alkaloids).
- Precipitation with alkaloidal precipitating agent.
- Convert to crystalline salts.

29

29

➢Separation of Alkaloidal Mixtures:

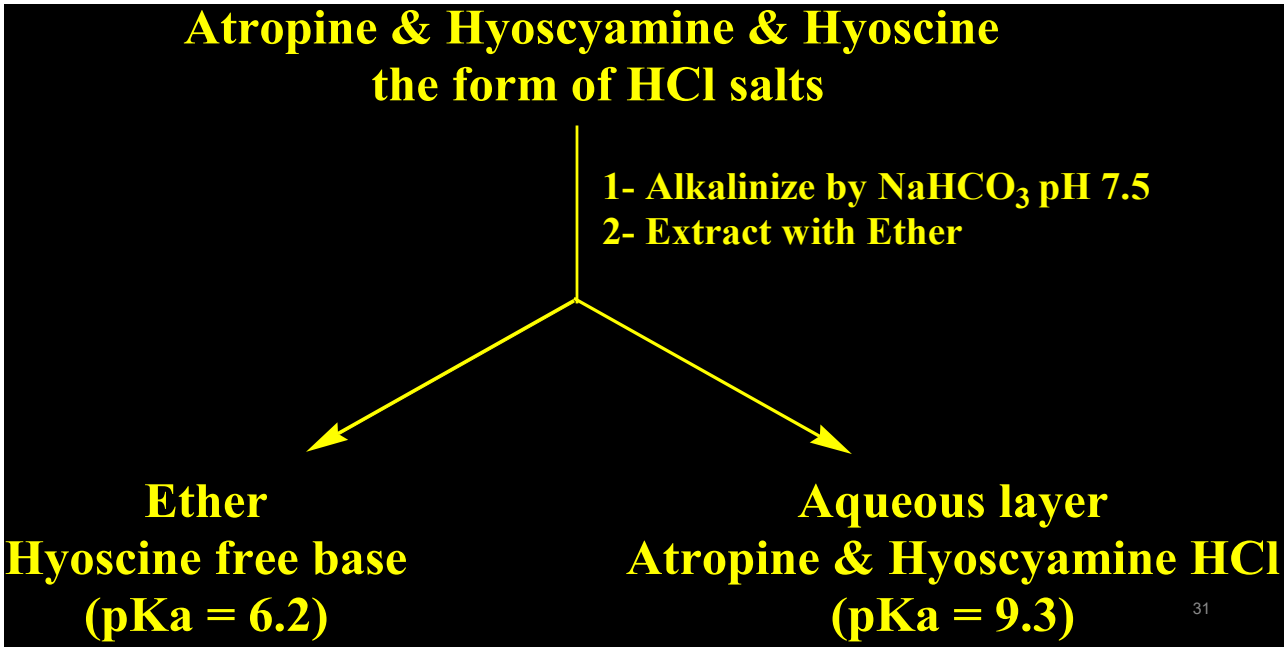
- **Fractional Crystallization:**



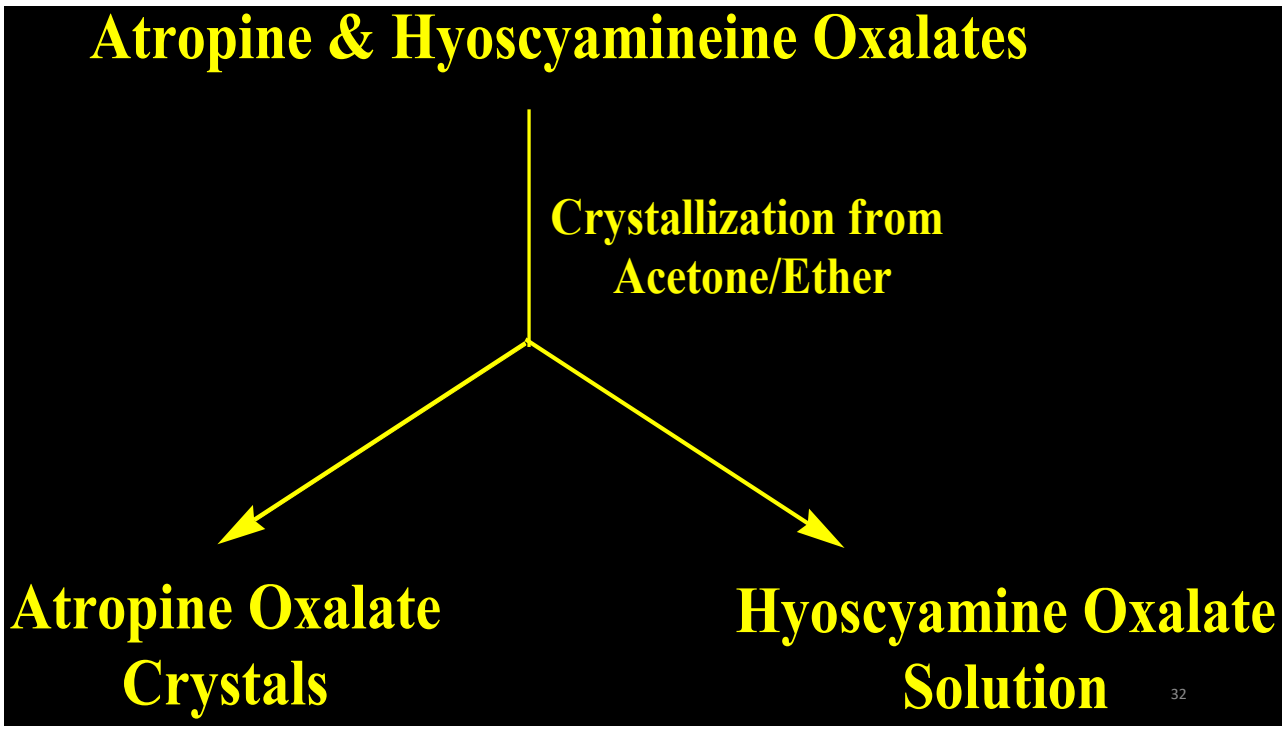
30

30

- **Fractional Liberation:**



31



32

33

Identification of Alkaloids:

- Melting point
- Color test
- Optical Rotation
- Microcrystal test
- HPLC, GC, GC-MS
- UV, IR, NMR, MS.

33

Quantitative Determination of Alkaloids:

- **Volumetric methods**
- **Gravimetric methods**
- **Colorimetric Method**
- **Spectrophotometric Methods**
- **Polarimetric Method**
- **Fluorometric Method**
- **Chromatographic Methods**

34

34

Pharmacological Properties

They can varieties from tonic to cancer

1. Aanalgesics and narcotics e.g .morphine and codeine
2. CNS stimulants e.g . caffeine and strychnine.
3. Mydriatics e.g .atropine.
4. Anti-asthmatics e.g . ephedrine.
5. Antitussive e.g .codeine.
6. Expectorants e.g . lobeline.

7. Anti-hypertensives e.g . reserpine.

8. Smooth muscle relaxants e.g . atropine and papaverine

9. Skeletal muscle relaxants e.g .d-tubocurarine.

10 Anthelmintics e.g .pelletierine and arecoline.

11. Antiparasitics e.g .quinine and emetine.

12. Anticancers e.g .vincristine, vinblastine and colchicine

35

35

1. Ornithine Alkaloids – Tropan Nucleus

36

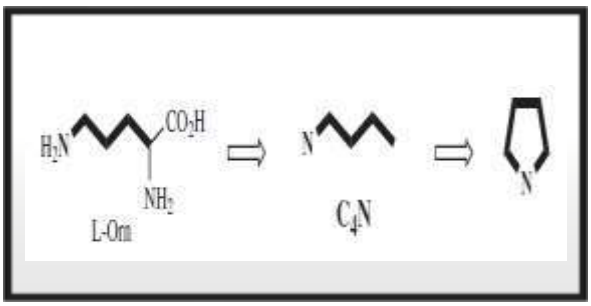
36

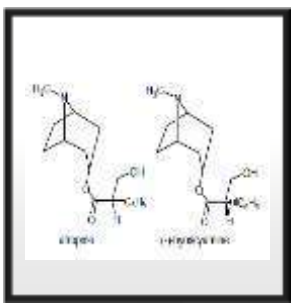
Chemistry

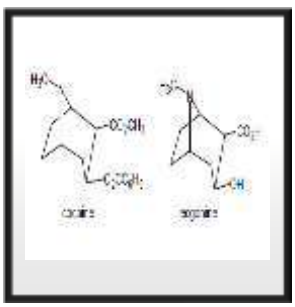
- L-Ornithine is a **non-protein amino acid** forming part of the urea cycle in **animals**, where it is produced from **L-arginine** in a reaction catalyzed by the enzyme arginase.
- **In plants** it is formed mainly from **L-glutamate.**
- Ornithine contains both δ -and α-amino groups, and it is the nitrogen from the **former group** which is incorporated into alkaloid structures along with the carbon chain, except for the carboxyl group .
- Ornithine **supplies a C_4N building block** to the alkaloid, principally **as a pyrrolidine ring system**, as part of the **tropane alkaloids**.

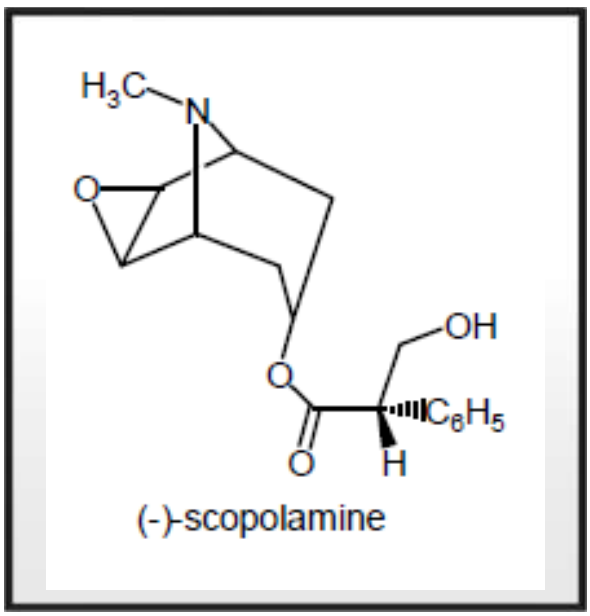
37

37









38

38

Structure of Tropane Alkaloids

39

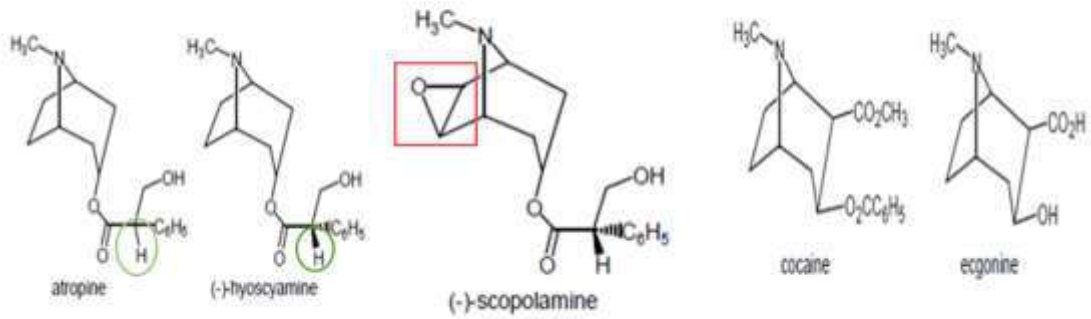
39

Properties
- Alcohol-

- **Tropanols**
  - These alcohols **depending on the orientation of the OH in 3 position.**
  - These can be tropan **3α-ol** and tropan **3β-ol**.
  - Tropan **3α-ol** are essentially specific to **Solanaceae** family.
  - Tropan **3β-ol** are essentially specific to **Erythroxylaceae** family.
  - In the absence of other substituents, the **Tropanols are optically inactive.**
  - The tropanols are often **hydroxylated at C6 or/and C7**.
  - The tropanols are often **epoxidized at C6 and C7**.

40

40

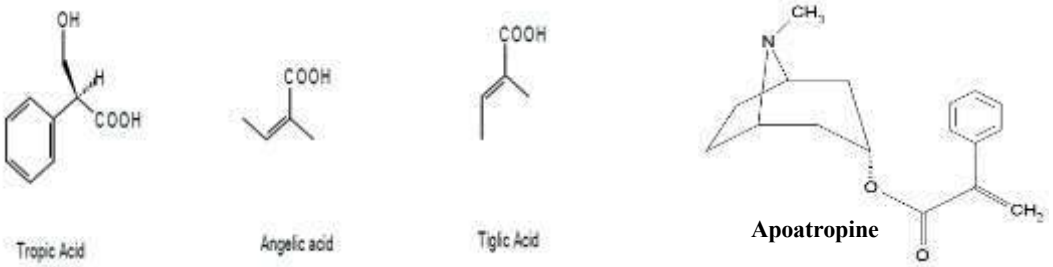


41

41

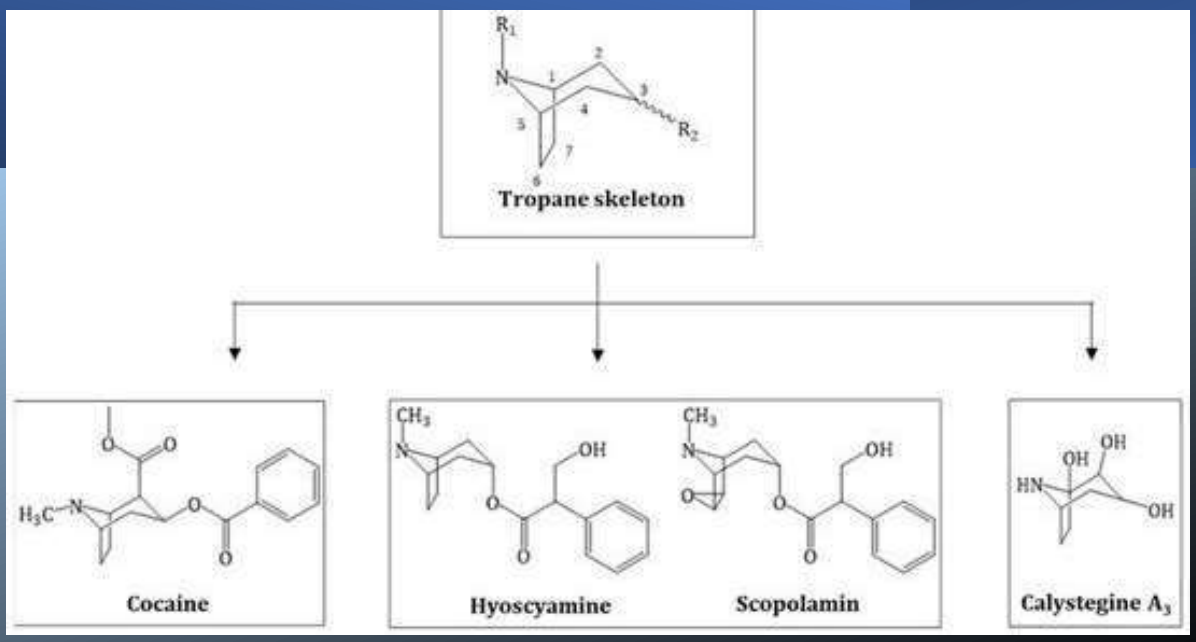
Properties: Acid & Base

Acid (aliphatic or aromatic) **Base** (Alkaloids)



42

42



43

43

Biosynthesis

44

44

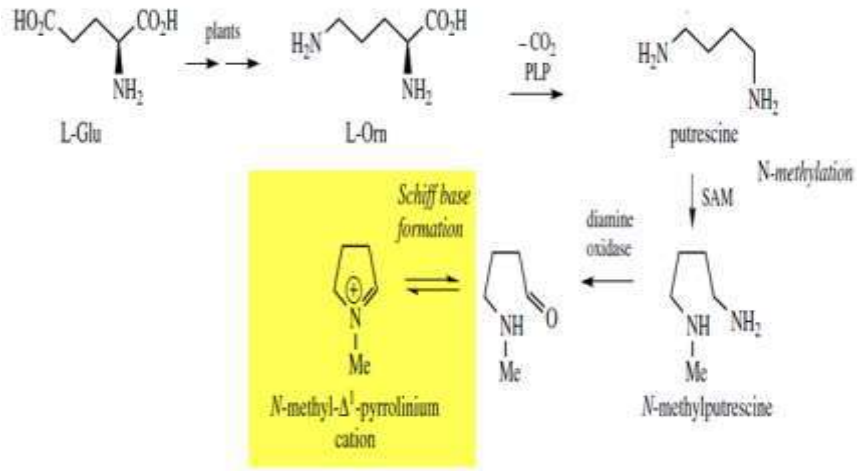
Pyrrolidine & Tropane Alkaloids

- **Simple pyrrolidine-containing alkaloid structures are exemplified by hygrine and cuscohygrine**;
- the pyrrolidine ring system is formed initially as a Δ1-pyrrolinium cation.
- Biosynthesis of tropane alkaloids **started** when Pyridoxal 5'-phosphate (PLP) dependent decarboxylation of ornithine gives putrescine, which is then methylated to **N-methyl-**putrescine (SAM reaction).
- *SAM reaction is a biological methylator. ... SAM's biochemical role is to transfer a methyl group to another molecule.*
- **Oxidative deamination** of N-methyl-putrescine by the action of a **diamine oxidase gives the aldehyde**, and **Schiff base** in formation produces the **N-methyl-Δ1-pyrrolinium cation**.

45

45

Biosynthesis



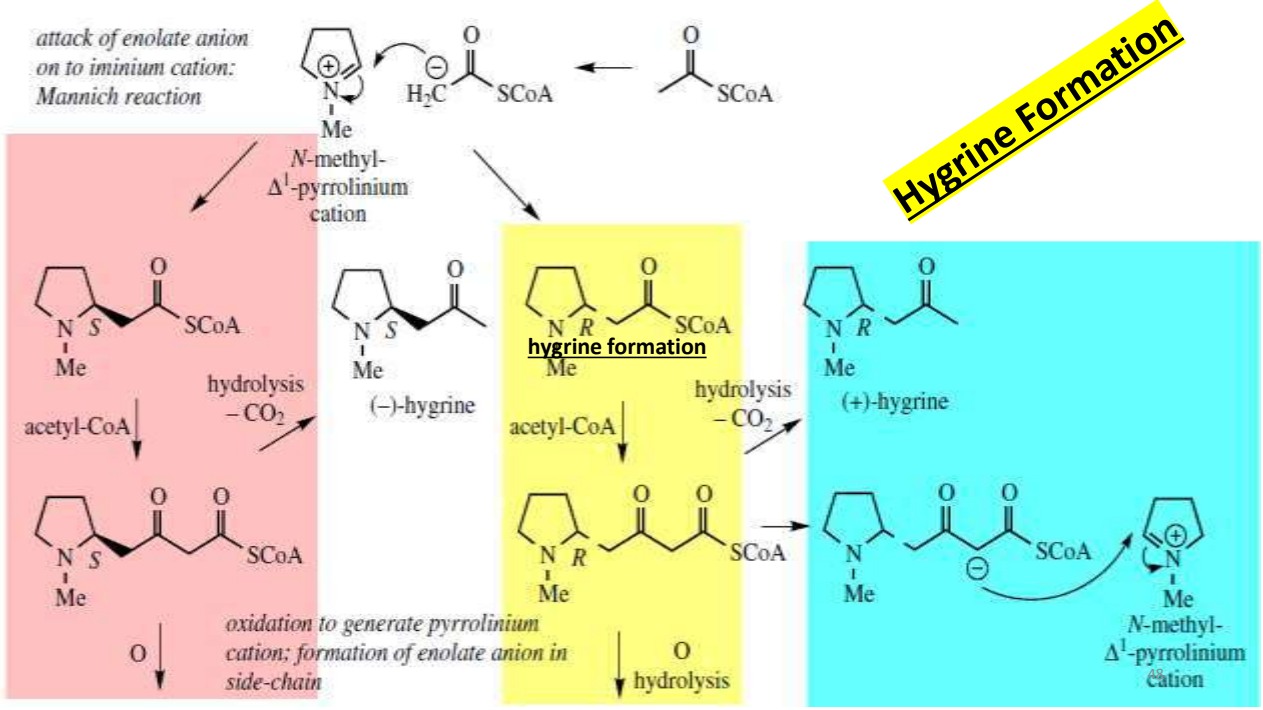
46

46

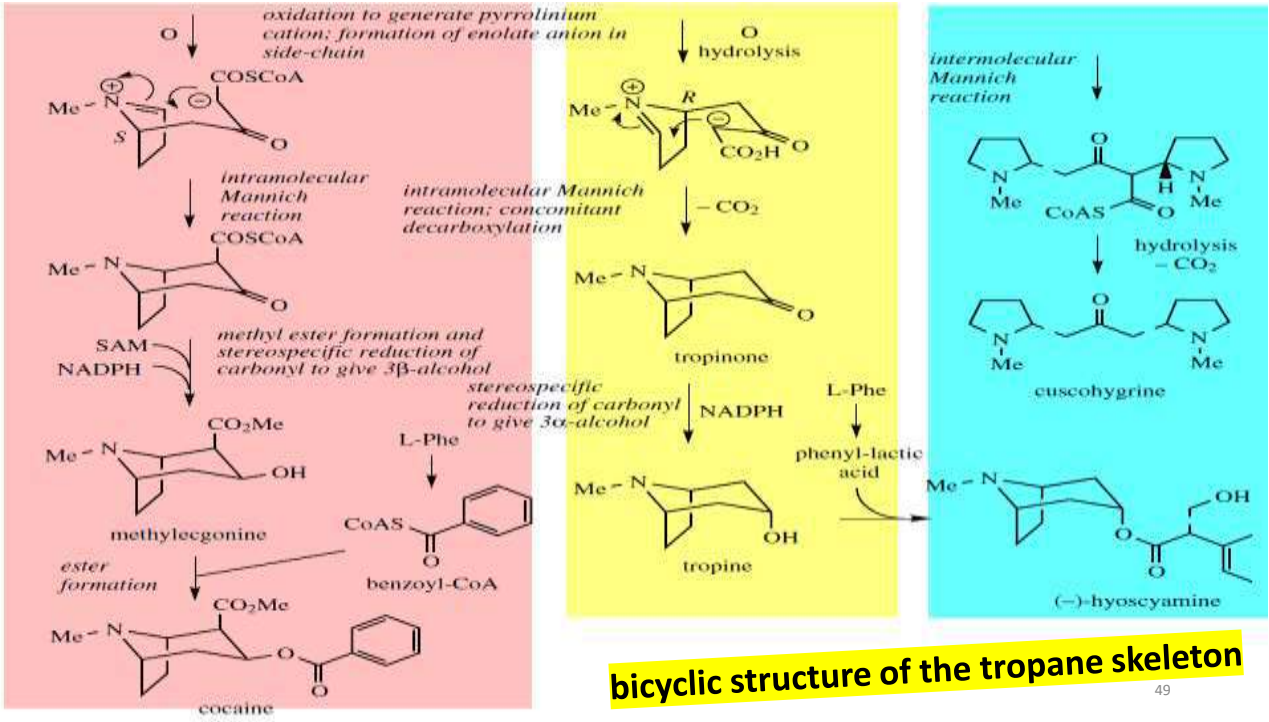
- The **extra carbon atoms required** for **hygrine formation** are derived **from acetate** via acetyl-CoA, and the sequence appears to involve stepwise addition of two acetyl-CoA units.
  - In the **first** step, the enolate anion from acetyl-CoA acts as nucleophile towards the pyrrolinium ion in a **Mannich-like reaction**;
  - The **second** addition is then a **Claisen condensation** extending the side-chain, and the product is the **2-substituted pyrrolidine**;
- The **bicyclic structure of the tropane skeleton** in hyoscyamine and cocaine is achieved by a **repeat of the Mannich-like reaction** just observed
- **This requires** an oxidation step to generate **a new Δ1-pyrrolinium cation**, and removal of a proton α to the carbonyl.

47

47

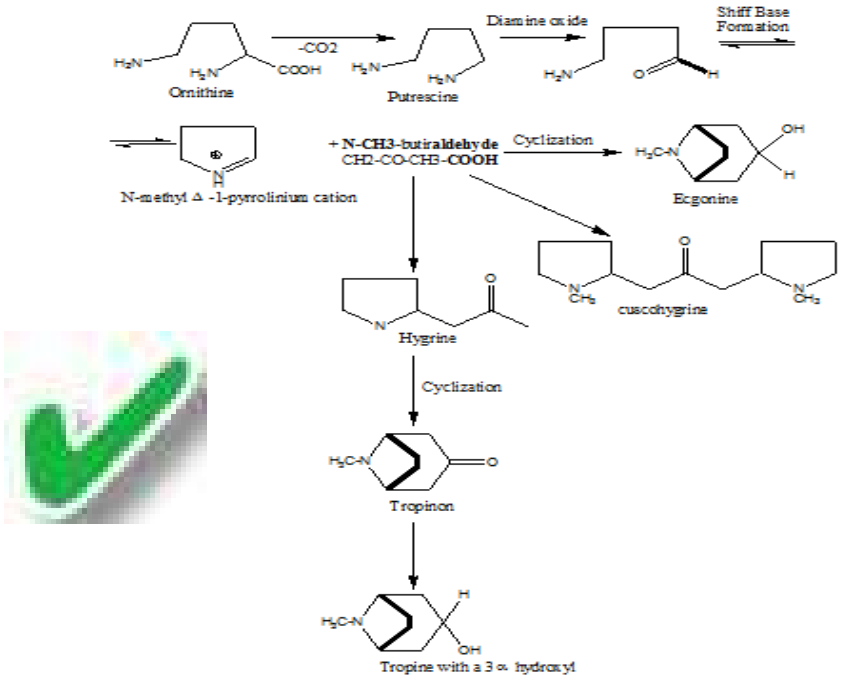


48


oxidation to generate pyrrolinium cation; formation of enolate anion in side-chain
hydrolysis
intermolecular Mannich reaction
intramolecular Mannich reaction
intramolecular Mannich reaction; concomitant decarboxylation
– CO2
tropinone
hydrolysis – CO2
cuscohygrine
methyl ester formation and stereospecific reduction of carbonyl to give 3β-alcohol
SAM
NADPH
stereospecific reduction of carbonyl to give 3α-alcohol
NADPH
L-Phe
phenyl-lactic acid
methylecgonine
tropine
(–)-hyoscyamine
ester formation
benzoyl-CoA
cocaine
bicyclic structure of the tropane skeleton

49

49


Ornithine
-CO2
Putrescine
Diamine oxide
Shiff Base Formation
N-methyl Δ -1-pyrrolinium cation
+ N-CH3-butiraldehyde
CH2-CO-CH3-COOH
Cyclization
Ecgonine
Hygrine
cuscohygrine
Cyclization
Tropinon
Tropine with a 3 α hydroxyl

50

50

Drugs Containing Ornithine Alkaloids-Tropane nucleus =Solanaceae Family=

51

51






52

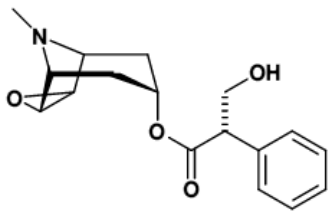
52

Parts used

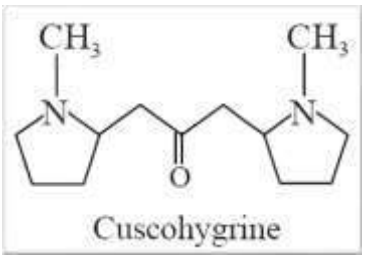
Atropa belladonnae	Hyocyamus aureus/niger	Datura stramonium
• Folium • Semen • Radix	• Folium • Semen • Radix	• Folium • Semen • Radix

53

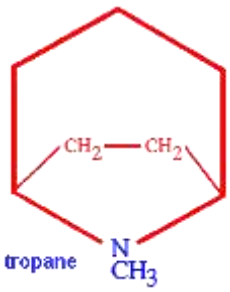
53

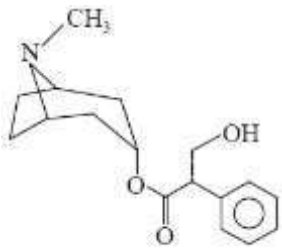


Scopolamine



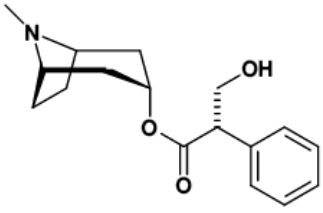
Cuscohygrine





Hyoscyamine

Hygrine



Atropine

54

54

To Remember

Anticholinergic

- An **anticholinergic** agent is a substance that **blocks the neurotransmitter acetylcholine** in the central and the peripheral nervous system.
- **Anticholinergics inhibit parasympathetic nerve impulses** by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells.

Acetylcholine

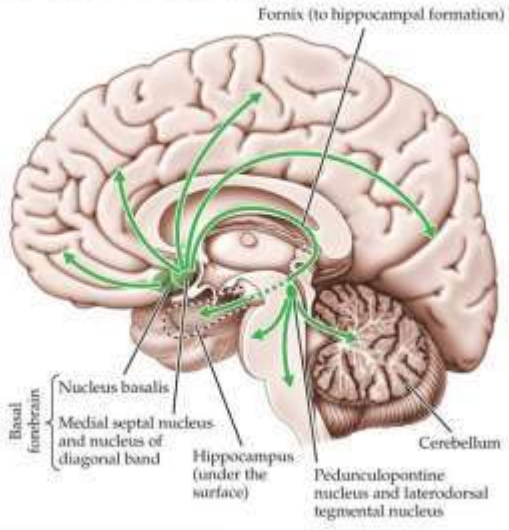
- **Acetylcholine**, the first neurotransmitter discovered
- In the autonomic nervous system, acetylcholine (**ACh**) is the neurotransmitter in the preganglionic **sympathetic** and **parasympathetic** neurons.
- **When activated, it causes the contraction of skeletal muscles and activates glandular functions in the endocrine system.**

55

55

Cholinergic Pathways in the Brain

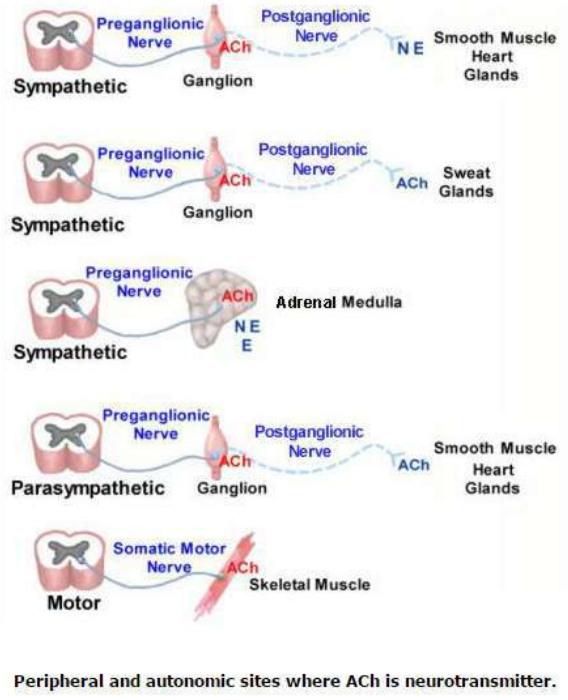
Cholinergic nerve cell bodies and projections contain ACh.



BIOLOGICAL PSYCHOLOGY 7e, Figure 4.3

56

56



Peripheral and autonomic sites where ACh is neurotransmitter.

57

57

How anticholinergics work?

- Anticholinergics **block acetylcholine** from binding to its receptors on certain nerve cells.
- They **inhibit** **parasympathetic nerve impulses**.
- These nerve impulses are responsible for **involuntarily muscle movements** in the gastrointestinal tract, **lungs**, **urinary tract**, and other parts of the body.
- The nerve impulses help control functions such as **salivation**, **digestion**, **urination**, and mucus **secretion**.

58

58

Effect

Atropa belladonnae	Hyocyamus aureus/niger	Datura stramonium
• **Anti-cholinergic**-parasympatholytic, spasmolytic, positive, dromotropic and chronotropic effect. • Relaxation of organs with smooth muscles.	• **Anti-cholinergic**-parasympatholytic, spasmolytic, positive, dromotropic and chronotropic effect. • Relaxation of organs with smooth muscles.	• **Anti-cholinergic**-parasympatholytic, spasmolytic, positive, dromotropic and chronotropic effect. • Relaxation of organs with smooth muscles.

59

59

Effect

Atropa belladonnae	Hyocyamus aureus/niger	Datura stramonium
• **Blocking** the action of **acetylcholine at muscarinic receptors**. • Competitive **antagonist of the muscarinic acetylcholine receptors.**	• **Produce** a parasympatholytic or anticholinergic effect by **competitive inhibition of acetylcholine**. • Exert peripheral actions on the autonomic nervous system and **on smooth muscle, as well as the central nervous system.** • **Relieve muscular tremors of central nervous origin**.	• **Blocking** the action of acetylcholine at muscarinic receptors. • Competitive **antagonist** of the muscarinic acetylcholine receptors. • **Antiepileptic** • **Hallucinogenic** • **Narcotic**

Muscarinic receptors producing, or mediating the effects (as a slowed heart rate, increased secretion by exocrine glands, and increased activity of smooth muscle

60

60

Indication

Atropa belladonnae	Hyocyamus aureus/niger	Datura stramonium
• Mydriatic • Mild sedation	• *Spasm* and *pain* • Sedative (stomach pain). • Nervous depression • Sharp, dry, nervous cough • Hypnotic • Diuretic	• spasm of bronchitis in asthma • Sedative, hypnotic and narcotic. • Antihistaminic • Helps in curing of motion sickness, nausea and dizziness.

61

61

Contraindication

Atropa belladonnae	Hyocyamus aureus/niger	Datura stramonium
• Glaucoma	• Tachycardiac arrhythmias, prostatic adenoma, angle-closure glaucoma, acute pulmonary edema • Pregnancy and lactating women	• Glaucoma, suspicion of glaucoma, paralytic ileus, pyloric stenosis, enlarged prostate, tachycardia, arrhythmias, acute pulmonary edema.

62

62

Side Effects & Overdose

Atropa belladonnae	Hyocyamus aureus/niger	Datura stramonium
• Ventricular **fibrillation**, supraventricular or ventricular **tachycardia**, giddiness, nausea, **blurred vision**, loss of balance, dilated pupils, **photophobia**, **confusion**, **hallucinations** and **excitation.** • In overdoses, atropine is **poisonous** .	• Dry mouth, red skin, constipation, overheating, reduced sweating, vision disturbances, increased heart rate, urination problems, drowsiness, restlessness, hallucinations, delirium, manic episodes, and death.	• Poisoning & narcotic • Datura increases the heart beat and may lead to cardiac arrest. • Dilated pupils. • Amnesia • Blurred vision, nausea, giddiness, confusion, rapid pulse & hyperthermia

63

63

Emergency

Atropa belladonnae	Hyocyamus aureus/niger	Datura stramonium
• Injections of atropine are used in the treatment of bradycardia & cases of cardiac arrest.	• Not used	• Not used

64

64

Drugs Containing Ornithine Alkaloids- Tropane nucleus =Erythroxylaceae Family=

65

Erythroxylum coca

66

Erythroxylum coca
History

- The Coca leaf has been cultivated, at the first time, by Indian peoples **to avoid starvation**.
- In **1855** the cocaine alkaloid "**erythroxyline**", was first isolated.
- In **1860**, Albert Niemann, a Ph.D .student at the University of Göttingen in Germany, who then developed an improved **purification process of cocaine.**
- In **1879** cocaine began to be used to **treat morphine addiction**.
- In **1884** cocaine was introduced into clinical use as a **local anesthetic** in Germany.

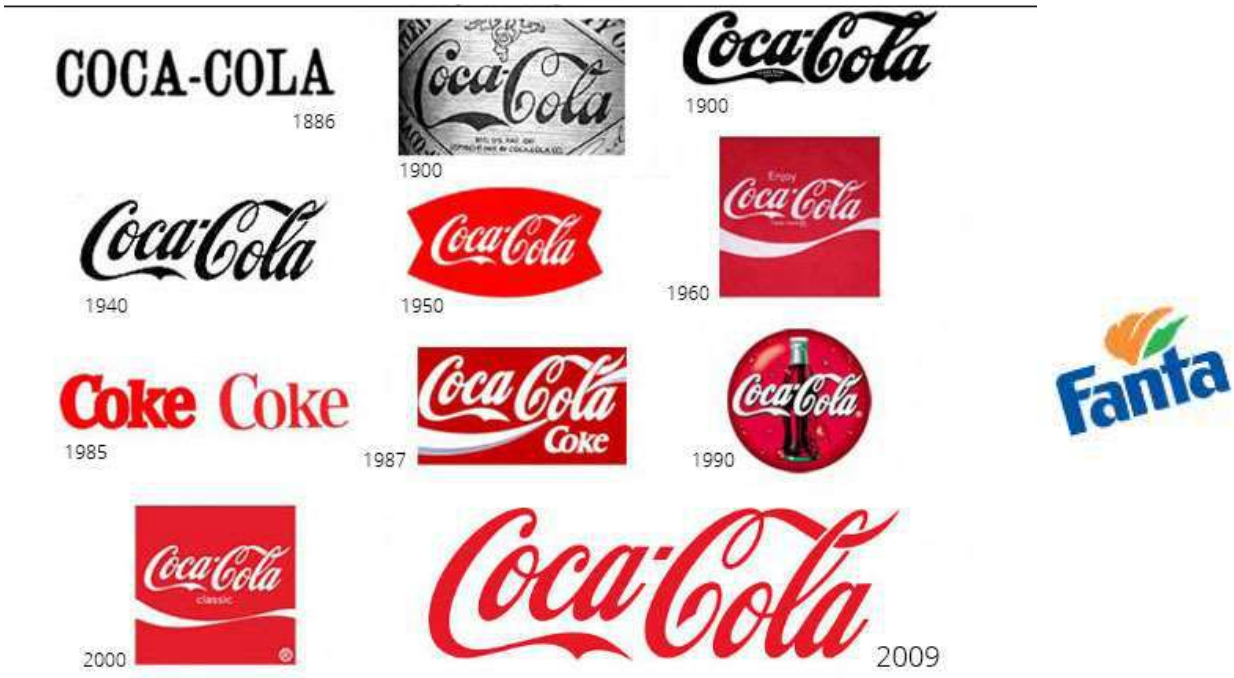
67

67

- In **1886** **John Pemberton** introduced in Atlanta, **a beverage consisting of coca leaf extracts, African kola nuts, and sweet carbonated syrup** . The product was named **Coca-Cola**.
- Coca-Cola was **sold in bottles** for the first time on **March 12, 1894**
- The first synthesis and **elucidation of the structure of the cocaine** molecule was by Richard Willstätter in **1898**
- Originally intended as **a patent medicine** when it was invented in the **late 19th century** by John Pemberton
- **Patterns of coca consumption** changed dramatically **in the 20th century**.
- In **1923**, Richard Willstatter was able to **synthesize** a mixture of D-cocaine, L-cocaine, D-pseudococaine, and L-pseudococaine.
- A registered trademark of The Coca-Cola Company in the United States **since March 27, 1944.**
- In **1955, first can of coca-cola.**

68

68


COCA-COLA
1886
1900
1900
1940
1950
1960
Coke Coke
1985
1987
1990
Fanta
2000
2009

69

69


70
Addiction Terms & Definitions

70

- **Abuse** means using a drug, alcohol or other substance in a way not intended by its manufacturers. They divide the misuse of substances into two categories: substance abuse and substance dependency.
- **Addicted** refers to the state of being compelled to use a habit-forming drug, substance or to perform an activity even when you have tried to quit or have the desire to quit.
- **Addict-** An addict is someone who is physiologically or psychologically dependent upon a potentially harmful drug or substance or form of compulsive behavior.
- **Addiction** is a chronic, progressive but treatable disorder in which someone becomes dependent on a substance or behavior that's psychologically or physically dangerous and habit-forming. **Addiction** is a brain disease able to relapse.
- **Addictive substances** are chemicals or materials that can create physical and/or psychological dependencies.
- **Blackout**—a blackout is a period of amnesia or memory loss, typically caused by chronic, high-dose substance abuse. The person later cannot remember the blackout period. Blackouts are most often caused by sedative-hypnotics such as alcohol and the benzodiazepines.
- **Bipolar disorder** is a mental disorder characterized by drastic and unusual mood shifts. It used to be called manic depression.
- **Controlled substance-**a "controlled substance" is a drug or substance of which the use, sale, or distribution is regulated by a state government entity. These controlled substances are listed specifically or by classification on the governmental level in the controlled substances act (CSA).

71

- **Crack**—cocaine (cocaine hydrochloride) that has been chemically modified so that it will become a gas vapor when heated at relatively low temperatures. Also called "rock" cocaine.
- **Drug abuse-**refers to the use of illicit drugs or to the inappropriate use of a legal drug or substance, such as alcohol, nicotine, prescription drugs, or inhalants.
- **Drug craving**, according to the United Nations International Drug Control Programme and the World Health Organization, "is the desire for the previously experienced effects of a psychoactive drug.
- **Drug addiction-**is defined as the continued compulsive use of drugs despite adverse health or social consequences.
- **Ecstasy**—slang term for methylenedioxymethamphetamine (mdma).
- **Euphoria** is a state of extreme happiness, usually accompanied by overwhelming emotion.
- **Hallucinogens**—a broad group of drugs that cause distortions of sensory perception.
- **Neuroleptic medication**—a drug used to treat psychosis, especially schizophrenia.
- **Paranoia**—a type of delusion, or false idea, that is unchanged by reasoned argument or proof to the contrary.

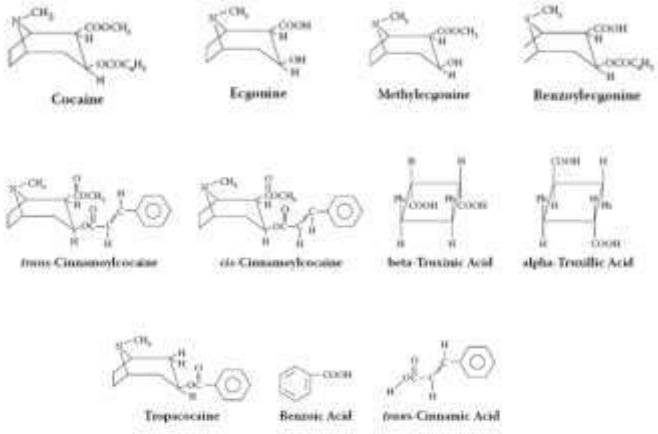
72

- **Physical dependence**: take place when a drug has been used habitually and the **body** has become dependent on its effects .The person must then continue to use the drug ***in order to feel normal***, or its absence will trigger the ***symptoms of withdrawal***.
- **Psychological dependency**: take place when a drug has been used habitually and the **mind** has become emotionally dependent on its effects, either to elicit pleasure or relieve pain, and does not feel capable of functioning without it .Its absence produces intense **cravings**, which are often brought on or magnified by stress.
- **Psychosis**—a mental disorder that is characterized by distinct distortions of a person's mental capacity, ability to recognize reality, and relationships to others to such a degree that it interferes with that person's ability to function in everyday life.
- **Relapse**—a breakdown or setback in a person's attempt to change or modify any particular behavior.
- **Stigma**—a negative association attached to some activity or condition. A cause of shame or embarrassment.
- **Tolerance**- Tolerance occurs when the body needs increasingly larger doses to get the same effect from a substance or a behavior.
- **Withdrawal** is a general term describing the physical and psychological symptoms that may occur when a person suddenly stops using an addictive drug.

73

Phytochemicals

- Coca contains several alkaloids 0.75 -2%, tropane alkaloids from cis serial as ecgonine respectively pseudotropine ester and tropococaine.
- The main alkaloid is Cocaine.



74

What is Cocaine?

- Cocaine is a **POWERFULLY ADDICTIVE STIMULANT DRUG** made from the leaves of the coca plant.
- Although health care providers can use it for valid medical purposes, such as local anesthesia for some surgeries, recreational cocaine use is illegal.
- Popular nicknames for cocaine include:
  - **Blow (shock, disappointment)**
  - **Coke (Coca)**
  - **Crack (Crash)**
  - **Rock (shock)**
  - **Snow (Ice)**

75

75

Mechanism of Action

76

76

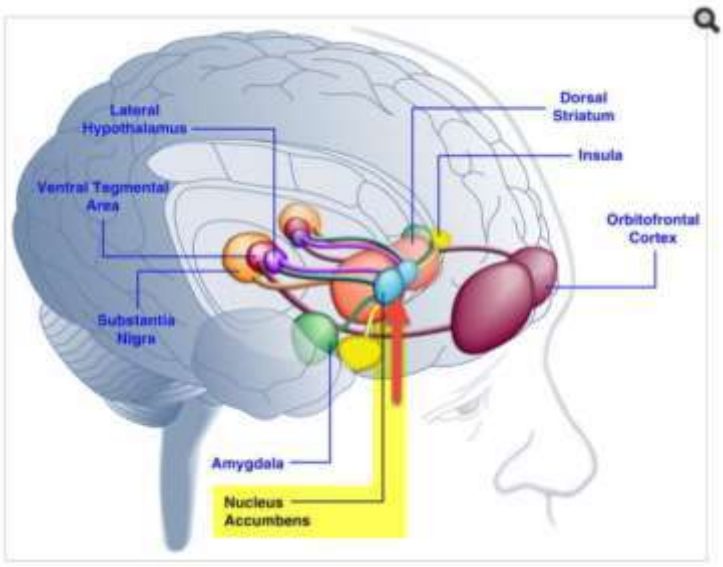
To remember

- **Dopamine:** A brain chemical, classified as a neurotransmitter, found in regions of the brain (**Nucleus accumbens**) that **REGULATE** movement, emotion, motivation, and pleasure.
- **Gamma-aminobutyric acid (GABA):** The main **INHIBITORY** neurotransmitter in the central nervous system. GABA provides the needed **counterbalance** to the actions of other systems, particularly the excitatory neurotransmitter glutamate.
- **Glutamate:** An **EXCITATORY** neurotransmitter found throughout the brain that **influences the reward system** and is involved in learning and memory, among other functions.

Nucleus accumbens: A brain region involved in motivation and reward. Nearly **all drugs of abuse** directly or indirectly **increase dopamine in the nucleus accumbens, contributing to their addictive properties**.

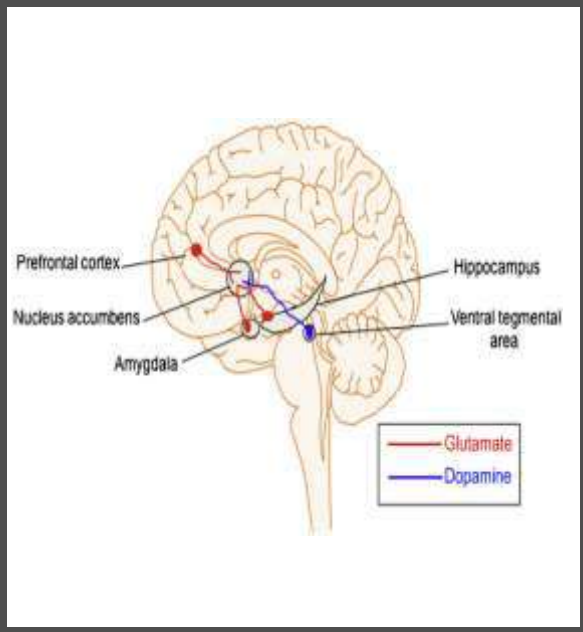
77

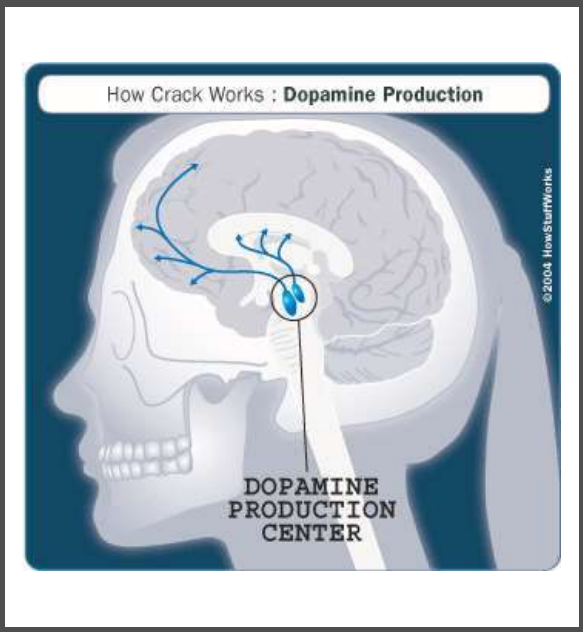
77



78

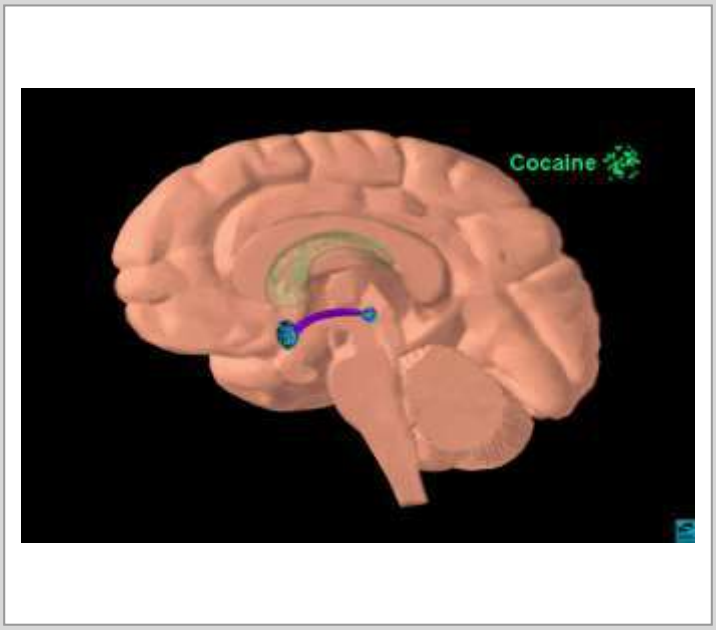
78


Prefrontal cortex
Hippocampus
Nucleus accumbens
Ventral tegmental area
Amygdala
Glutamate
Dopamine

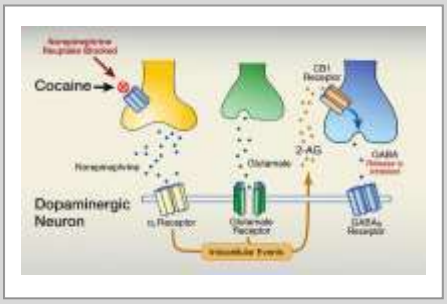

How Crack Works : Dopamine Production
©2004 HowStuffWorks
DOPAMINE PRODUCTION CENTER

79

79

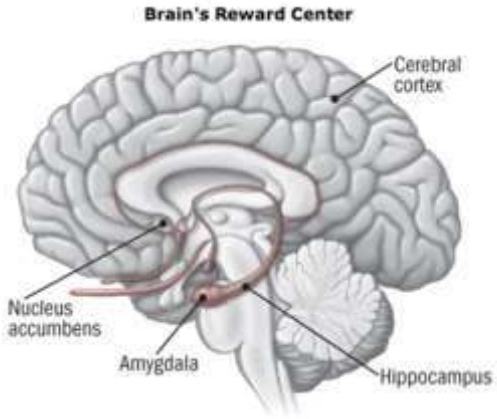

Cocaine

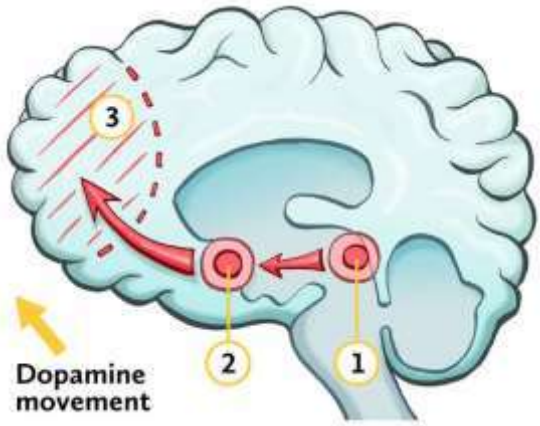

THC


Cocaine
Dopaminergic Neuron
2-AG

80

80





81

81

Effect of Cocaine HCl

- Cocaine Hydrochloride acts as a local anesthetic ***(Anesthetic: An agent that causes insensitivity to pain)*** and stimulates the central nervous system.
- In high doses, the drug causes paralysis of motor neuron fibers.
- Non narcotic.

BUT

- Powder of cocaine hydrochloride **salt** is **narcotic**, can be snorted or dissolved in water and then injected.

82

82

Crack Cocaine

- Crack cocaine is the **freebase** form of cocaine that can be **smoked**.
- Crack cocaine is a **highly addictive** and **powerful stimulant** that is derived from powdered cocaine using a simple conversion process.
- Crack users may experience acute respiratory problems, including coughing, shortness of breath, and lung trauma and bleeding .
- Crack cocaine smoking also can cause aggressive and **paranoid behavior**.

83

83

Effect of Cocaine Base

- Cocaine is a powerfully **addictive stimulant** that **directly** affects the **brain**.
- Cocaine's effects appear almost immediately **after a single dose** and disappear within a few minutes to an hour.
- Taken in small amounts, cocaine usually makes the user feel euphoric, energetic, talkative, and mentally alert, especially to the sensations of sight, sound, and touch.
- It can also temporarily decrease the need for food and sleep.

84

84

Effect of Cocaine Base

- The duration of cocaine's euphoric effects depend upon the route of administration.
- The **faster absorbed** drug, the more intense the resulting high, but also the **shorter** the **duration**.
- The high from snorting is relatively slow to arrive, but it may last from 15 to 30 minutes; in contrast, the effects from smoking are more immediate but may last only 5 to 10 minutes.
- All routes of administration are commonly used for cocaine:
  - **Snorting,**
  - **Smoking, and**
  - **Injecting**
- The **LD_{50}** of cocaine when administered to mice is **95.1 mg/kg**.
- There is **no specific antidote** for cocaine overdose.

85

85

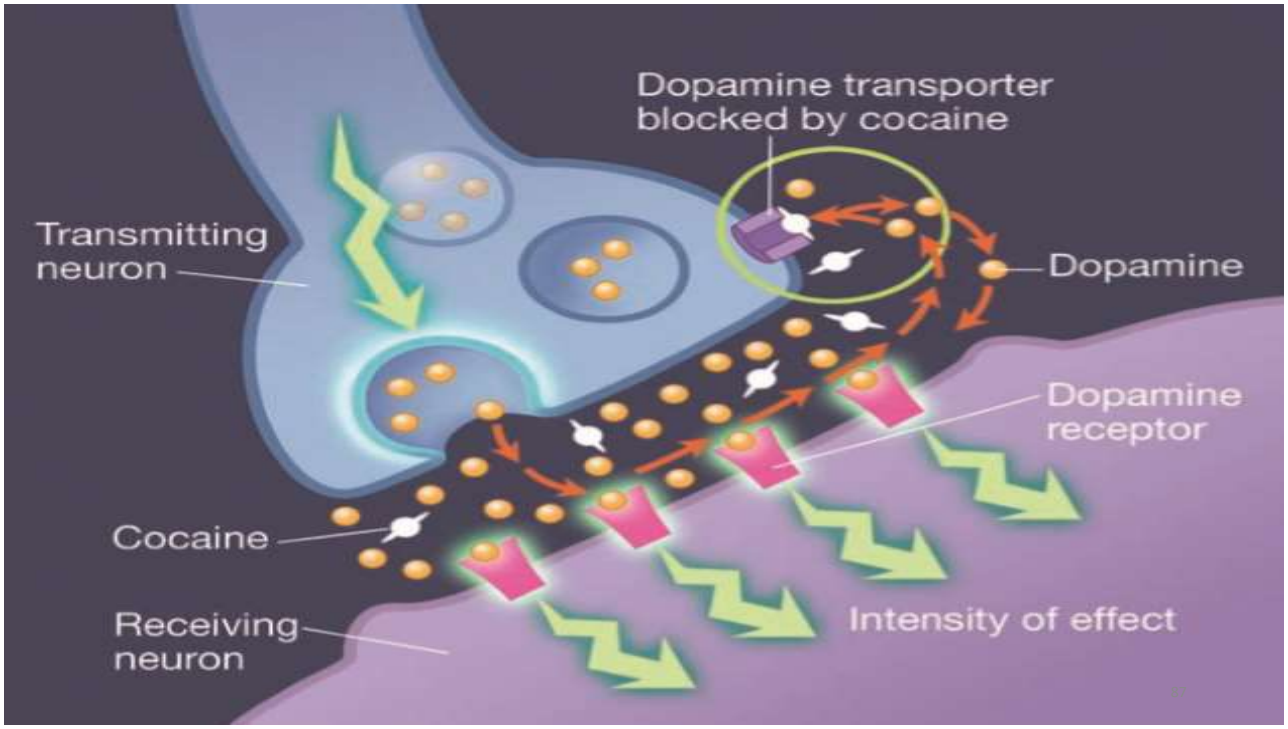
How Does Cocaine Affect the Brain?

Cocaine is a strong central nervous system stimulant that increases levels of dopamine, associated with pleasure and movement, in the brain's reward circuit.

***Normally**, dopamine is released by a neuron in response to a pleasurable signal (e.g., the smell of good food), and then recycled back into the cell that released it, thus shutting off the signal between neurons.*

Cocaine acts by preventing the dopamine from being recycled, causing excessive amounts of the neurotransmitter to build up, amplifying the message to and response of the receiving neuron, and ultimately disrupting normal communication.

86



87

Short-Term Effects

- Short-term health effects of cocaine include:
  - **extreme happiness and energy**
  - **mental alertness**
  - **hypersensitivity to sight, sound, and touch**
  - **irritability**
  - ***paranoia*—extreme and unreasonable distrust of others**
- Some addicts find that cocaine helps them perform simple physical and mental tasks more quickly, although others experience the opposite effect.
- Large amounts of cocaine can lead to bizarre (Curious), changeable, and violent behavior.

88

88

Short-Term Effects

- Cocaine's effects **appear almost immediately and disappear within a few minutes to an hour**.
- How long the effects last and how intense they are **depend on the method of use**.
- **Injecting** or **smoking** cocaine produces a quicker and stronger but shorter-lasting **high than snorting**.
- The high from **snorting** cocaine may last 15 to 30 minutes.
- The high from **smoking** may last 5 to 10 minutes.

89

89

Long-Term Effects

- Some long-term health effects of cocaine depend on the method of use and include the following:
  - ***snorting:*** loss of smell, nosebleeds, frequent runny nose, and problems with swallowing
  - ***smoking:*** cough, asthma, respiratory distress, and higher risk of infections like pneumonia
  - ***consuming by mouth:*** severe bowel decay from reduced blood flow
  - ***needle injection:*** higher risk for contracting HIV, hepatitis C, and other bloodborne diseases, skin or soft tissue infections, as well as scarring or collapsed veins

90

Death from overdose can occur on the first use of cocaine or unexpectedly thereafter

91

91

Withdrawal symptoms

- Withdrawal symptoms include:
  - Depression
  - Fatigue/headach
  - Increased appetite
  - Unpleasant dreams and insomnia
  - Slowed thinking

92

92

"Adverse Effects" of Cocaine

1. Constricts blood vessels
2. Dilates pupils
3. Increases body temperature, heart rate, and blood pressure.
4. Headaches
5. Gastrointestinal complications
6. Loss of the sense of smell; nosebleeds; problems with swallowing; hoarseness; and a chronically runny nose.
7. Ingesting cocaine can cause severe bowel gangrene as a result of reduced blood flow.
8. Injecting cocaine can bring about severe allergic reactions and increased risk for contracting HIV/AIDS and other blood-borne diseases & hepatitis.
9. **Severe paranoia**
10. **Heart attack or stroke, which may cause sudden death**
11. **Respiratory arrest.**

93

Identification-Types of Drug Screening

- **Scott test:** It is best known for the cobalt thiocyanate test (*in* ***HCl medium and extraction with chloroform***), in which blue color is indicate the presence of cocaine.
- **Saliva test**– Cocaine is detectable in saliva after 5 to 10 minutes of taking the drug. It may be detected in saliva till 2 to 4 days.
- **Urine test**– Detectable after 2 to 5 hours of use, till a period of 3 to 4 days.
- **Blood testing** is more specific. The drug is detected after 5 to 6 hours till around 5 to 7 days or even more.
- **Hair test:** The drug starts showing in hair after 5 to 7 days till around 80 to 90 days.

94

94

Behavioral therapy may be used to treat Cocaine Addiction

95

96

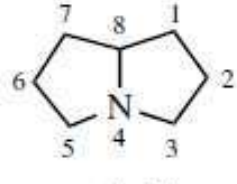
Strategies for Managing Difficult Behavior

97

98

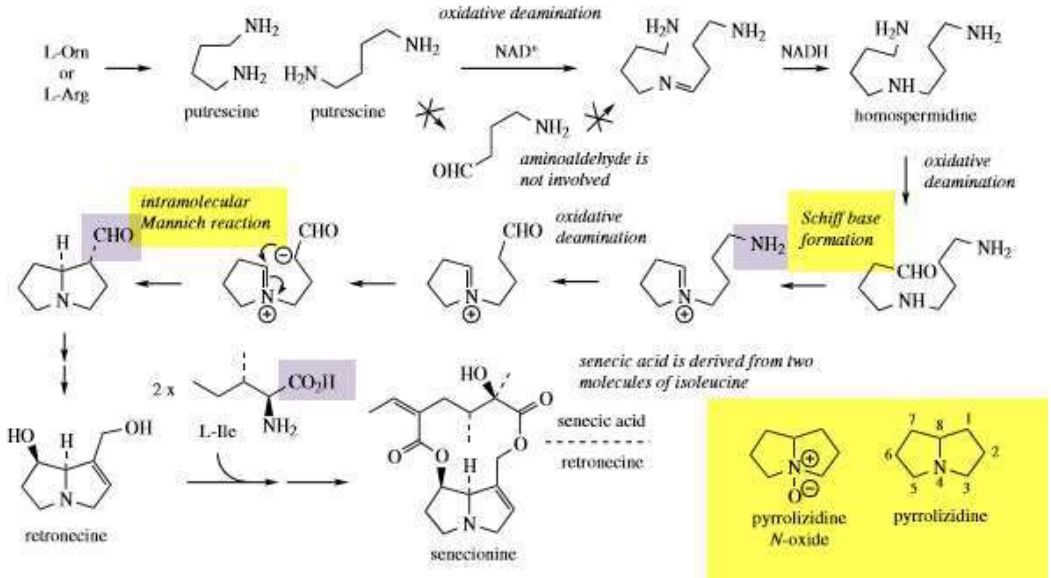
98

2. Ornithine alkaloids with **Pyrrolizidine nucleus**



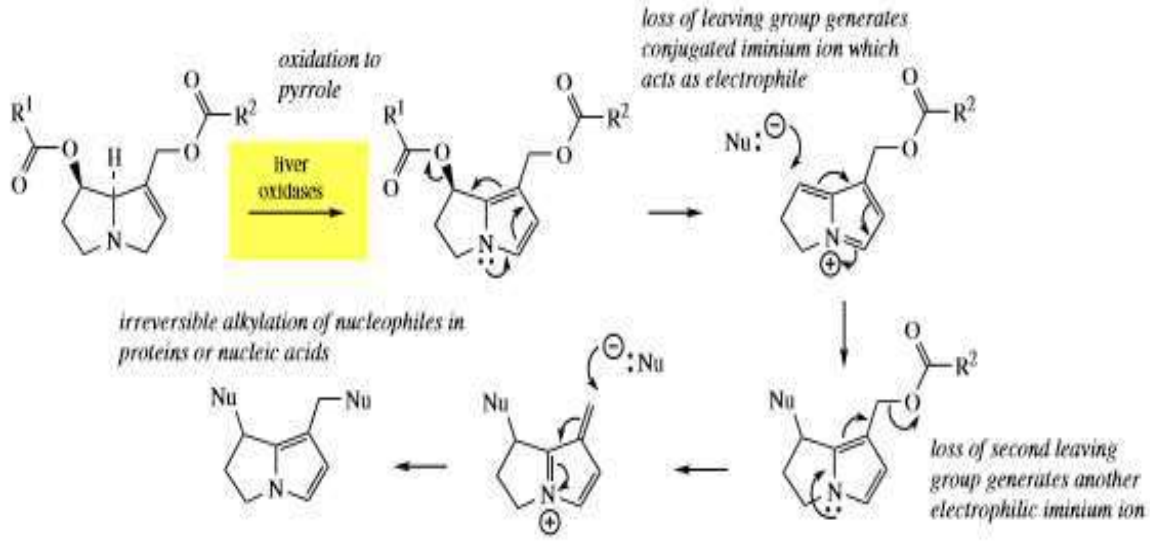
99

99



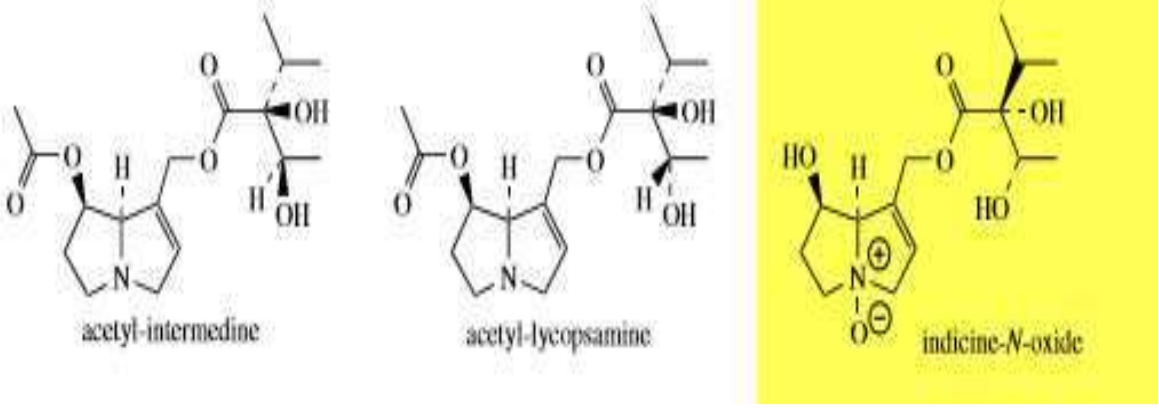
100

100



101

101



102

102

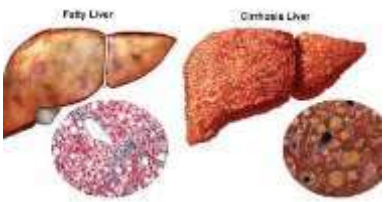
Drugs Containing Pyrrolizidine alkaloids

103

103



Borago officinalis	*Symphytum officinalis*	*Tussilago farfara*

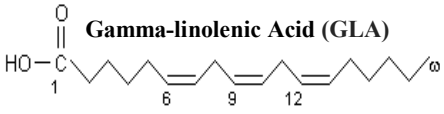



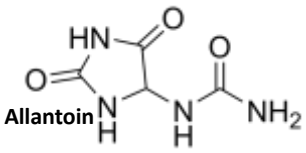
104

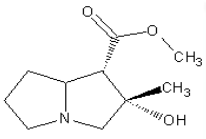
104



Borago officinalis	*Symphytum officinalis*	*Tussilago farfara*



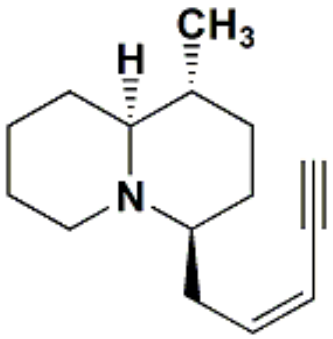




Tussilagin

105

3. Ornithine alkaloids with **Quinolizidine nucleus**



Quinolizidine Alkaloid

106

106

Lupinus albus (Lupinus termis)

107

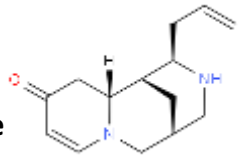
107

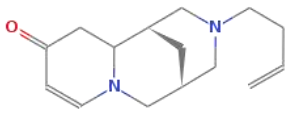
108

Lupinus albus

Chemistry

Albine





11,12-seco-12,13-didehydromultiflorine

Nutritive Value (1 cup), 166g

- **Glycemic load** = 7
- Kcal = 198 (from protein 89.7)
- **Total carbohydrate** = 16.4 (5%DV)
- Total fat = 4.8 (7%DV)
- **Thiamin** = 0.2mg (15%DV)
- Folate = 97.9mg (24%DV)
- **Manganese** 1.1mg (56%DV)
- Magnesium 89.7mg (22% DV)
- **Phosphorus** 212mg (21%DV)
- Selenium 4.3 mcg (6%DV)

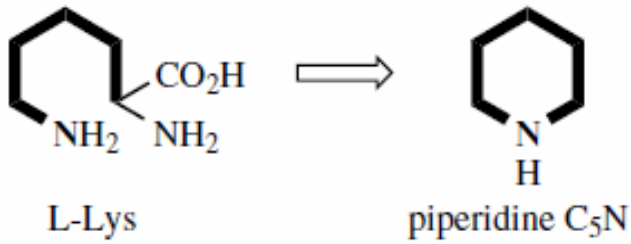
109

109

ALKALOIDS DERIVED FROM LYSINE

110

Lysine Alkaloids

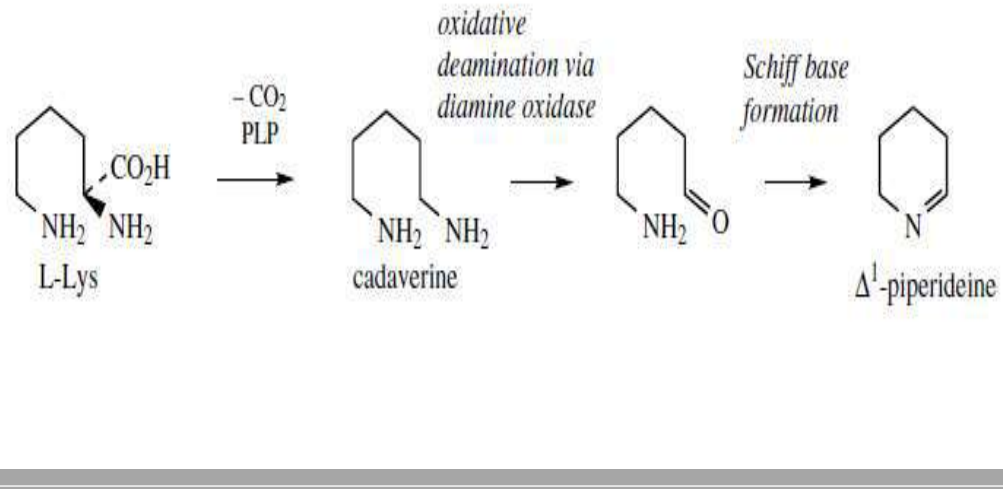


L-Lys piperidine C_5N

- L-Lysine is the homologue of L-Ornithine,
- The extra methylene group in lysine means this amino acid participates in forming six-membered piperidine rings

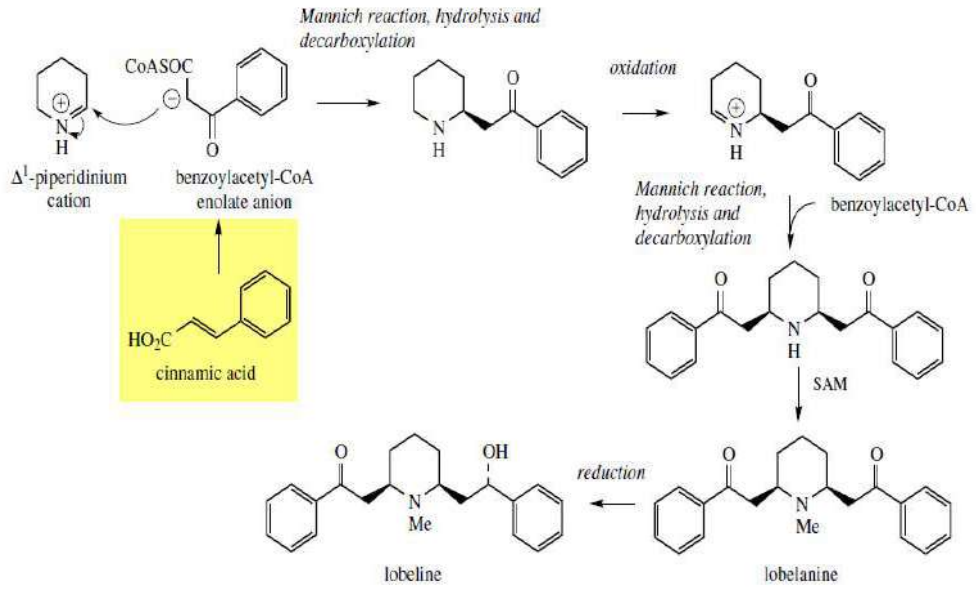
111

111



112

112


Mannich reaction, hydrolysis and decarboxylation
CoASOC
oxidation
Δ1-piperidinium cation
benzoylacetyl-CoA enolate anion
Mannich reaction, hydrolysis and decarboxylation
benzoylacetyl-CoA
HO2C
cinnamic acid
SAM
reduction
lobeline
lobelanine

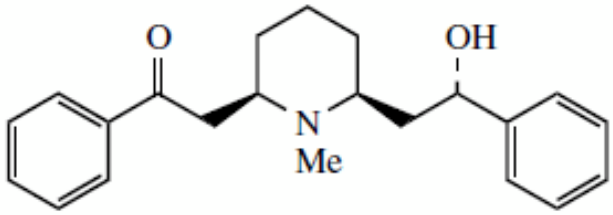
113

113


114
Lobelia inflata-
Lobiliaceae - Indian Tobacco

114

Phytochemicals



lobeline

- Includes:
  - **Lobeline**, **isolobeline**, lobelanine and lobelanidine.
  - The triterpene ester beta-amyrin and palmitate

115

115

Effect

- **Stimulate the respiratory center** of the **brain** resulting in **deeper and stronger breathing**.
- **Bronchodilator** & **antispasmodic**
- **Reduce anxiety and panic attacks**.
- Reduce swellings and as a pain reliever.

116

116

Mechanism of action

- The active ingredient, Lobeline, is a **both** a **nicotine agonist and antagonist nicotinic receptors.**
- Lobeline **inhibits nicotine-evoked dopamine release .**
- However, **lobeline does not release dopamine** from its presynaptic terminal,
- **Lobeline modifies dopamine function reveals that its primary mechanism is:**
  - **inhibition of dopamine uptake and**
  - **promotion of dopamine release from the storage vesicles within the presynaptic terminal.**

117

117

Indication

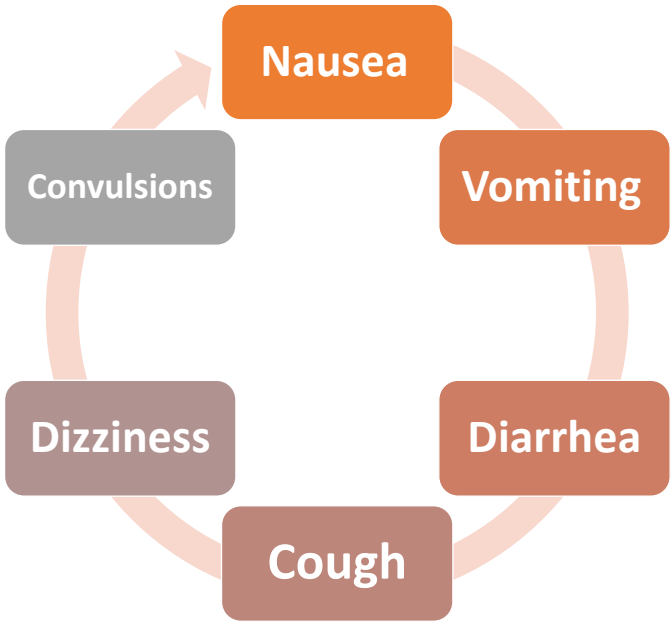
Remedy to **quit smoking**

Useful for **tobacco withdrawal.**

118

118

Side effects



119

119

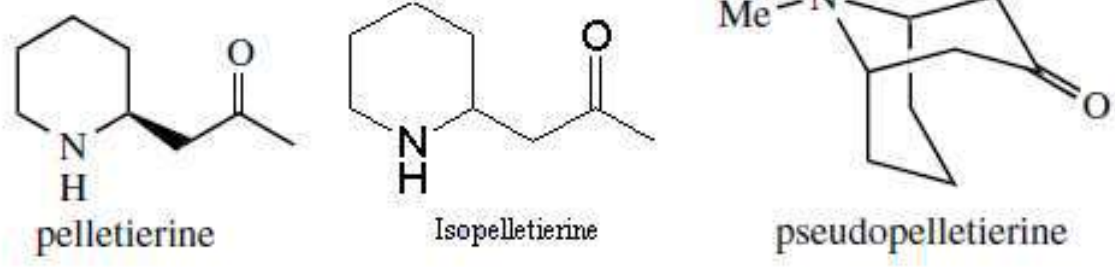
OVER DOSAGE

- Over dosage leads to:
  - **Dryness** of the mouth,
  - **Burning** in the urinary passages,
  - **Feelings of anxiety**, dizziness, headache, shaking,
  - **Respiratory difficulties**
  - **Cardiac arrhythmias**
  - **Bradycardia**
  - **Collapse**, **coma**, and possibly death.
- Dose of **0.6 to 1mg** from the leaves are said to be **toxic,**
- **LD_{50} is 4mg**

120

120

121



Phytochemicals

Piperidine Alkaloids

122

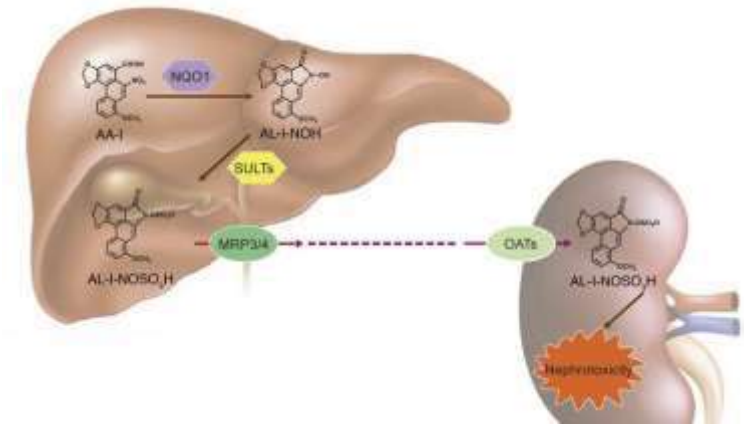
122

12 3

Indication

- As in folk medicine Pomegranate as **cortex** is used for infestation with tapeworm and other worms, for diarrhea and dysentery
- Abortifacient and astringent.
- Hemorrhoids

123

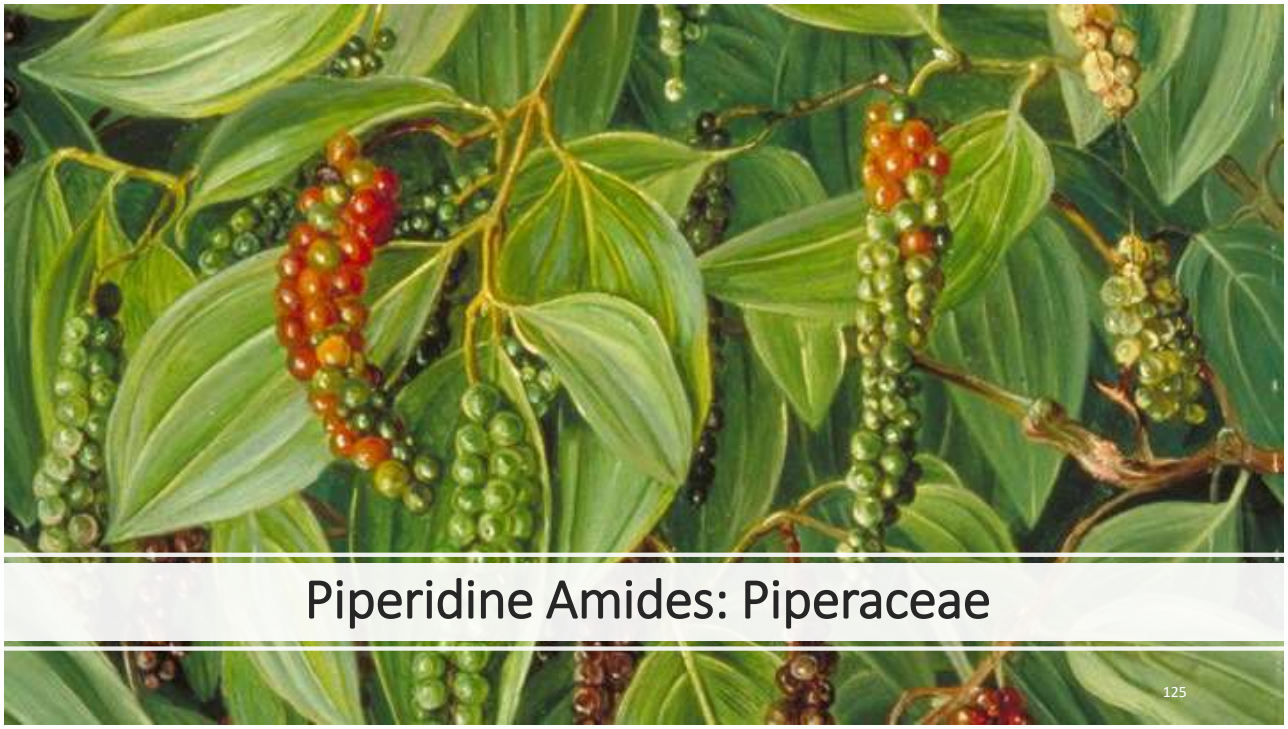


Precaution

Punica cortex lead to liver toxic & kidney damage

124

124



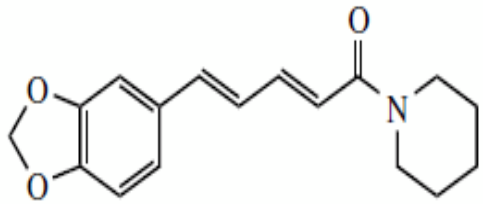
Piperidine Amides: Piperaceae

125

125

Piper nigrum

- **Black Pepper**
- ***pungent* substances (piperine)**
- ***3,4-dihydroxy phenyl ethanol glycosides*** *substratum for the enzymatic black* ***coloring****.*
- ***Volatile oil*** *1.2-2.6 :%* chief components **-sabinene**
- ***Polysaccharides 45%***
- ***Fatty oil 10%***



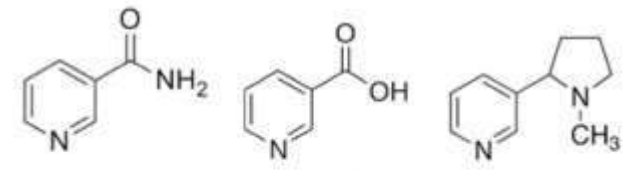
piperine

126

126

127

127



Nicotinamide
Niacinamide
Active form

Nicotinic acid
Niacin
(Converted to
active form
niacinamide)

Nicotine

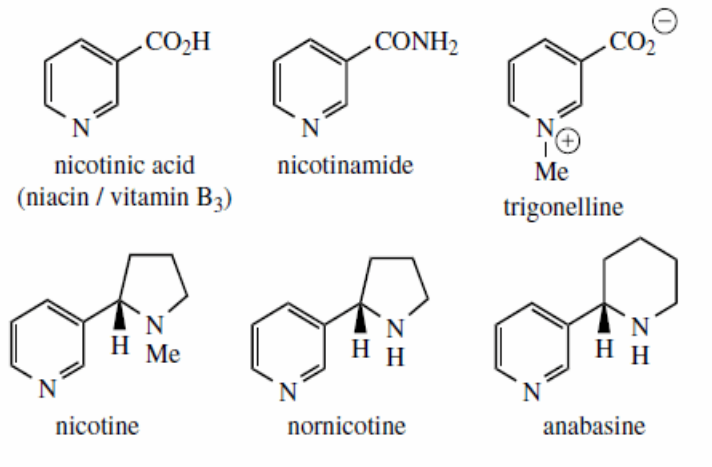
Alkaloids Derived from Nicotinic Acid

128

128

PYRIDINE
ALKALOIDS

Nicotiana tabacum



129

129

Nicotinic Acid B_3

The nicotinic acid component of nicotinamide is synthesized in animals by degradation of L-tryptophan.

Nicotinic acid reducing **triglycerides** made by the liver.

B_3 occurs naturally in food.

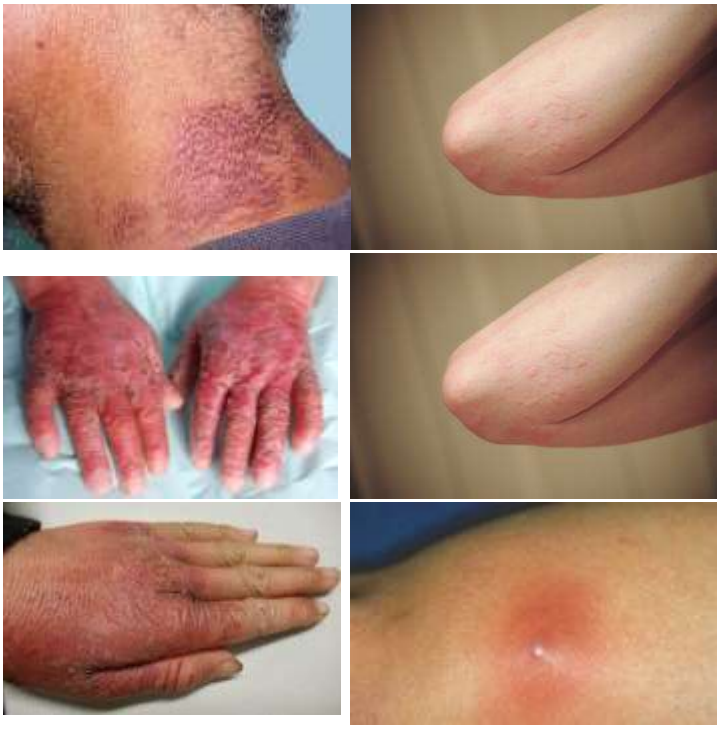
It can improve levels of blood fats (lipids) such as cholesterol and triglycerides.

130

130

B-3 Deficiency

- Pellegra
  - **disease caused by B-3 deficiency**
- **Gastrointestinal** disturbance, loss of appetite.
- Headache, insomnia, **mental depression**.
- **Fatigue**, aches, and pains.
- **Nervousness**, **irritability**.



131

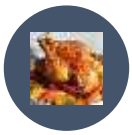
Toxicity - Warnings

- In doses of only 50-100 mg nicotinic acid can cause **dilation of blood vessels**
- Potentially painful **tingling** ("niacin flush"), diarrhea, nausea, vomiting, and long term **liver damage**.

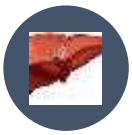
132

132

B_3 Food Sources



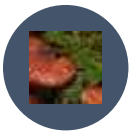
CHICKEN
(31MG/230G)



LIVER
(30MG/230G)

TUNA
(27MG/230G)

SALMON
(18MG/230G)



MUSHROOMS
(5.5MG/230G)

133

133

Health Conditions

- **Pellagra**
- **Depression**
- **Diabetes**
- Hallucinations
- **Headaches**
- Alzhiemer's disease
- **Vertigo**
- **Taste disorders**
- **IBS**
- **Hypothyroidism**
- **Menstrual pain**
- Multiple sclerosis
- Osteoarthritis
- Rheumatoid arthritis
- **Smelling disorders**

134

134

135

Nicotiana tabacum

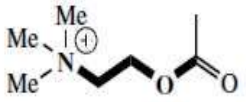
- Tobacco leaves may contain from 0.6–9 %of -(−)nicotine an oily, **volatile liquid alkaloid**.
- Nicotine in **small doses** can act as a **respiratory stimulant**, though in **larger doses** it causes **respiratory arrest and depression**.
- Tobacco smoke contains a number of highly **carcinogenic** chemicals including
  - benzopyrene,
  - 2-naphthylamine, and
  - 4-aminobiphenyl.
- Powdered tobacco leaves have long been used as an **insecticide**.

136

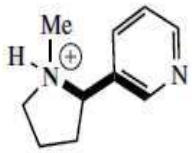
136

Nicotiana tabacum

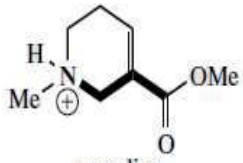
- Nicotine is **toxic** to animals & human due to its effect on the nervous system, interacting with the **nicotinic acetylcholine receptors**, though the close-fitting binding observed is only partially accounted for by the **structural similarity** between acetylcholine and nicotine.



acetylcholine



nicotine
(as conjugate acid)



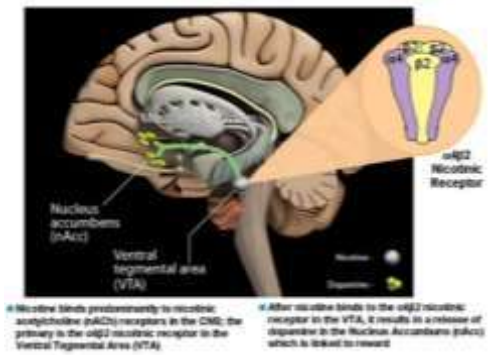
arecoline
(as conjugate acid)

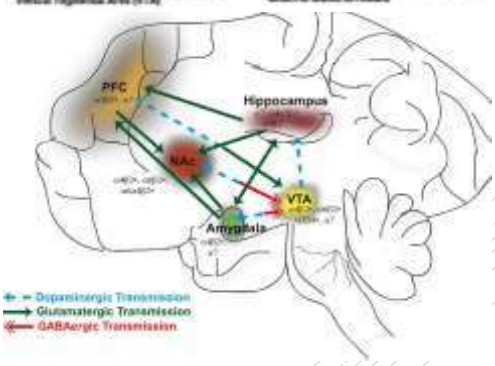
137

138

Location

- The **nicotinic acetylcholine receptors** are located **at nerve terminals and in central neurons either at synapses in ganglia or within the brain**.





What do nicotinic acetylcholine receptors?

- **Nicotinic acetylcholine receptors**, are **receptor** polypeptides that respond to the neurotransmitter **acetylcholine**.
- **Nicotinic receptors** get their name from **nicotine**, which **does** not stimulate the muscarinic **acetylcholine receptor**, but instead selectively binds to the **nicotinic receptor**.
- It has been demonstrated that **nicotine** interferes with acetylcholine, which is the major neurotransmitter of the brain.
- Acetylcholine can bind to two different kinds of **receptors**:
  1. **nicotinic receptors**, which are activated by **nicotine**, and
  2. **muscarinic receptors**, which are activated by muscarine.

139

139

Mechanism of Action

- Each neurotransmitter has its own specific family of receptors. Nicotine happens to imitate the neurotransmitter **acetylcholine**, and binds to those receptors (**specifically nicotinic receptors**).
- However, unlike acetylcholine, nicotine is not regulated by the body.
- **While neurons typically release small amounts of acetylcholine in a regulated manner, nicotine activates cholinergic neurons** .
- Thus, **unregulated stimulation and disruption, the body increases its release of acetylcholine, leading to heightened activity in cholinergic pathways throughout the brain**.
- Activity in the cholinergic pathways calls the body and brain into action, **and smoker feel re-energized**.

140

140

Mechanism of Action

- **Stimulating those cholinergic neurons also increases how much dopamine gets released by the limbic system**, **which activates reward pathways in the brain**.
- When drugs like **cocaine or nicotine activate the reward pathways, it reinforces your desire to use them again because it feels good**
- **Nicotine also stimulates the release of another neurotransmitter glutamate; glutamate is involved in learning and memory and enhances the connections between sets of neurons.**
- when smoker use nicotine, glutamate may create a memory loop of the good feelings you get and further drive the **desire to use nicotine**.

141

141

Mechanism of Action

- Nicotine also **increases** the level of other neurotransmitters and chemicals that modulate how the brain works. (**Endorphins**)

Nicotine Stimulates Dopamine Release

- **Stimulates release of** catecholamines, stress hormones, adrenaline, epinephrine, etc..
- **Constricts blood vessels** in skin, producing cold, thin, wrinkles (faster aging).
- **Inhibits stomach secretions**,
- **Stimulates bowel** (laxative in nontolerant person).
- **Increase metabolism of fat**;
- **Dull taste buds.**
- **Slows stomach contractions;**
- **Increases blood sugar.**

142

142

Pharmacokinetics

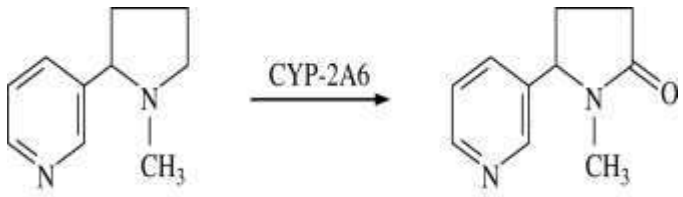
- Nicotine taken in by cigarette or cigar smoking **takes only 10-15 seconds to reach the brain** but has a **direct effect on the body for only ~30 minutes**
- Nicotine in smoke peaks in brain very rapidly, despite relatively slow increase in blood concentration
- A typical cigarette contains 20 mg of nicotine
- 3 mg of nicotine is absorbed
- Half-life: ~ 2 hours
- 80-90% metabolized in liver
- LD_{50}= 50-60mg (around 0.8 mg/kg)
- Ingestion of tobacco at doses up to 6 mg/kg nicotine was reported to evoke symptoms of intoxication without causing death.

143

143

Pharmacokinetics

- **Metabolism & Elimination**
  - About 80 percent of nicotine is broken down to cotinine by enzymes in your liver (e.g., CYP2A6)



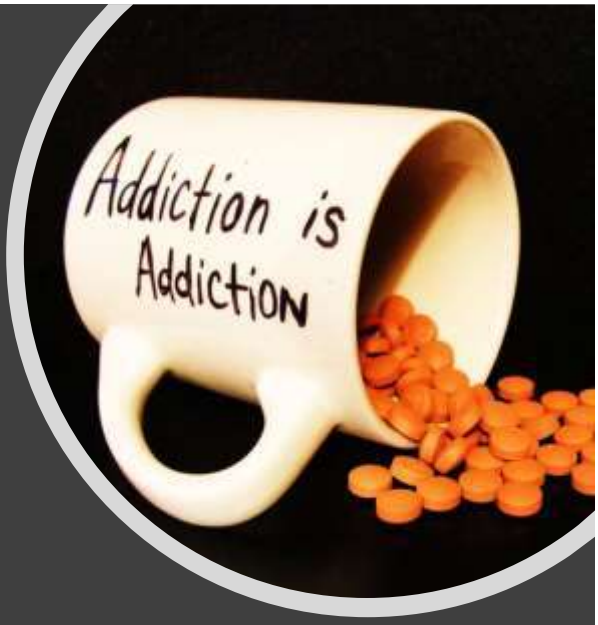
  - Nicotine is also metabolized in the lungs to cotinine and nicotine-N-oxide
  - Cotinine and the remaining nicotine is filtered from the blood by your kidneys and excreted in the urine.

144

144

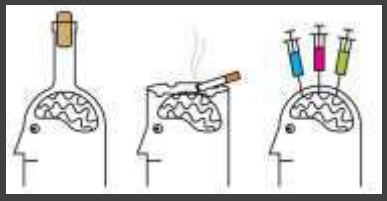
Withdrawal Symptoms

- Anxiety/Irritability
- Poor concentration
- Restlessness
- Craving
- Headaches
- Drowsiness
- Depression
- Hunger



145

145



146

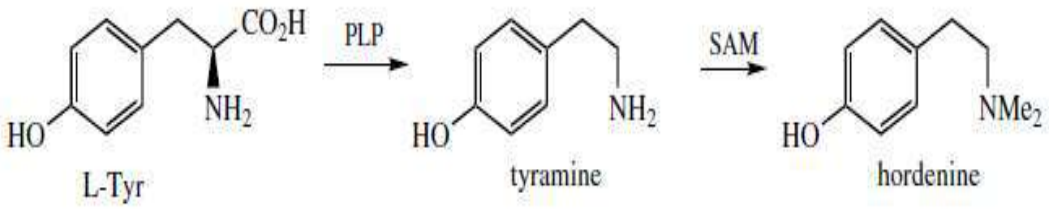
146

ALKALOIDS DERIVED FROM PHENYALANINE & TYROSINE

147

147

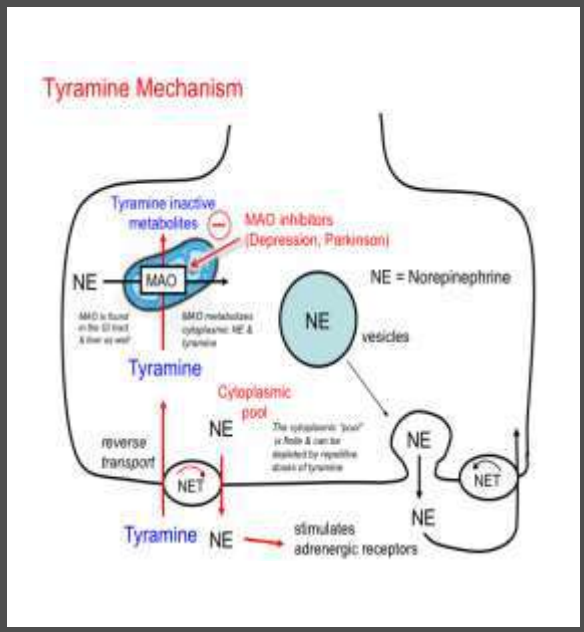
I. Phenylethylamine derivatives

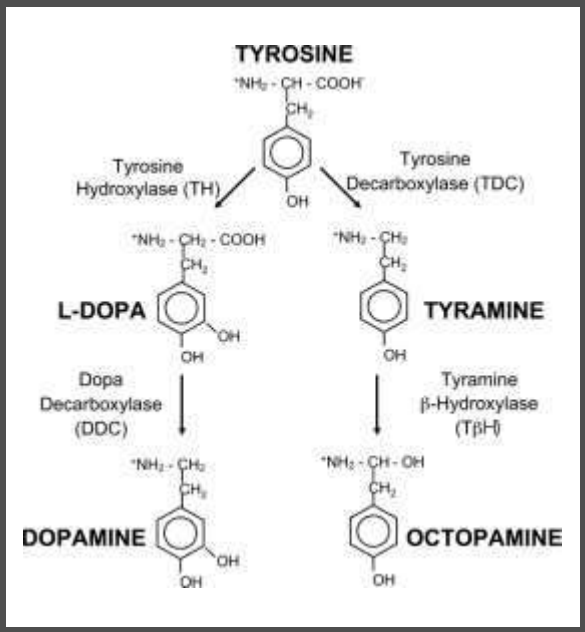


Barley - *Hordeum vulgare*; (Graminae/Poaceae)

148

148



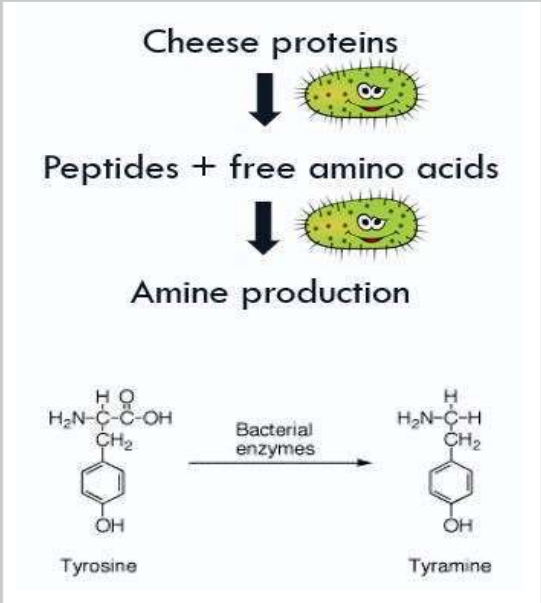


149

149

Tyramine

- Tyramine-rich foods:
- Aged chicken liver
- Aged cheese
- Aged cheddar, swiss and parmesan
- Meats that have been fermented or air-dried
- Smoked **meats** or **fish**, such as **sausage** or **salami**



150

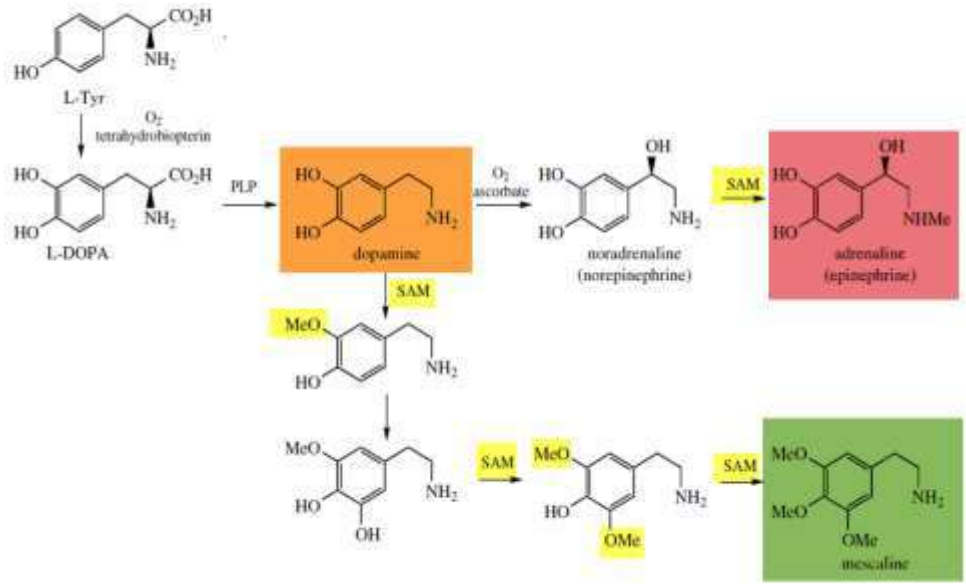
150

Hordeum vulgare – Barley- (Poaceae)

- Barley is used for lowering blood sugar, **blood pressure**, and **cholesterol**, and for promoting **weight loss**.
- Barley's **fiber**, potassium, **folate**, and vitamin B6 content, coupled with its lack of **cholesterol**, all support a healthy **heart**.
- It is also used for **digestive** complaints including **diarrhea**, stomach **pain**, and inflammatory bowel conditions.
- Some people use barley for increasing strength and endurance.

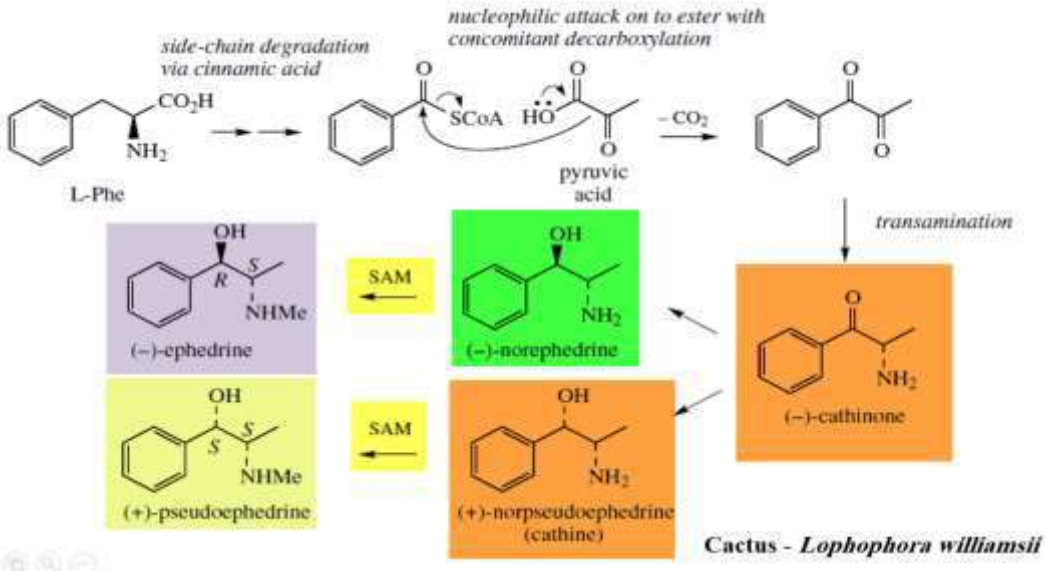
151

151



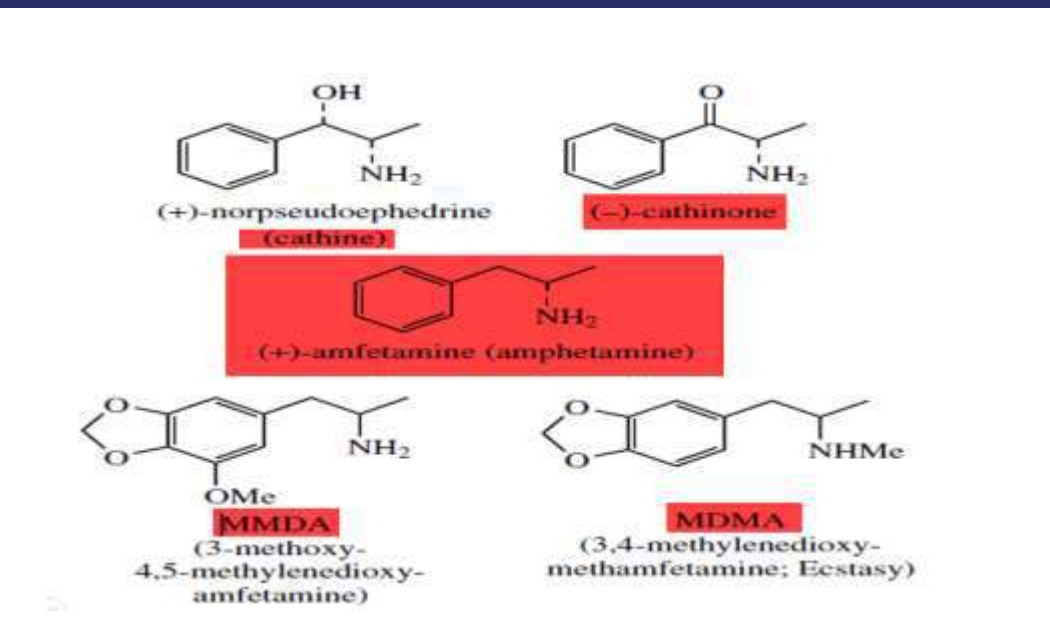
152

152



153

153



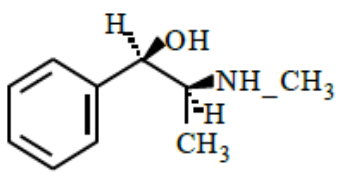
154

154

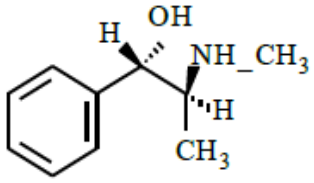
Ephedra spp.- Ephedraceae - Ma Huang

155

Ephedra spp.- Ephedraceae - Ma Huang



(-) Ephedrine



(+) Pseudoephedrine

156

156

Ephedra spp.- Ephedraceae - Ma Huang

- **Identification:**
  - **Color test: Chen's test (Copper sulphate test):**
    - **few drops of 5 %CuSO4 added to water extract**
    - **Alkalization with NaOH -------- Violet color**
    - **Extraction with benzene:**
      - **Organic phase: Purple color indicated present of ephedrine**
      - **Aqueous layer: blue color**
  - **Crystal test**
    - **Long plates crystals with Dragendorff**

157

157

EFFECTS

- **Ephedrine**
- Indirectly acting sympathomimetic amine with effects similar to noradrenaline .
- Lacking the phenolic groups of the catecholamines, it has only **weak action on adrenoreceptors**, but
- it is **able to displace noradrenaline from storage vesicles** in the nerve terminals, which can then act on receptors.
- It is **orally active** and has a **longer duration of action** than noradrenaline.
- It also has **bronchodilator** activity, giving relief in ***asthma***, plus
- A **vasoconstrictor** action on mucous membranes, making it an effective ***nasal decongestant***.
- **Ephedra** is **used** by **bodybuilders** and other athletes, and by those wanting to lose weight/body fat, for two main reasons. **First** of all it increases their energy and **second** for training drive.

158

158

Ephedrine

- Dietary supplements that **contain ephedrine** are **illegal** in the United States.
- While **ephedrine** is **excluded** in diet and sports supplements, it still is commonly used to treat allergic disorders such as bronchial asthma.
- It is also used in certain medical procedures involving anesthesia to prevent dangerous drops in blood pressure.
- **Increases the heart rate,**
- **Increases blood pressure,**
- **Expands bronchial tubes,**
- ***Brain Stimulant*** ***(Physical Dependent)***
- ***Thermogenic agent*** ***(FDA: Ephedra Free)***
- ***Precursor of methamphetamine = Herbal Ecstasy=***
- **Duration of action:** IV/IM (60 min), by mouth (2 h to 4 h)
- **Elimination half-life:** 3 h to 6 h

159

159

EFFECTS

• Pseudoephedrine

- Pseudoephedrine is a sympathomimetic drug of the phenethylamine and **amphetamine chemical classes**.
- It may be used as a **nasal/sinus decongestant**, as a stimulant, or as a wakefulness-promoting agent.
- Widely used in compound **cough and cold preparations** and **as a decongestant**.
- Pseudoephedrine **contraindication to a child younger than 4 years old**.

160

160

Side effects/Contraindication

- **Nausea**, **vomiting**, trouble sleeping, **dizziness**, anxiety, **headache**, or **nervousness** may occur.
- Stop taking this medication and tell your doctor promptly if you have **dizziness**, **nervousness**, or trouble sleeping.
- Avoid taking pseudoephedrine if you also take diet pills, caffeine pills, or other stimulants (such as ADHD medications).
- Taking a stimulant together with a decongestant can increase your risk of unpleasant side effects.
- Blood pressure medications
- An antidepressant such as amitriptyline

161

161

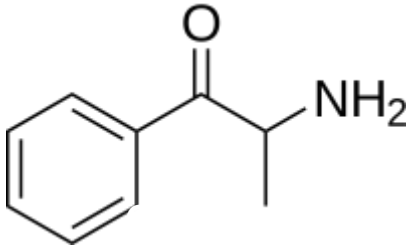
Catha edulis- Celastraceae- Khat

162

162

- *Phenyl alkyl amines*
  - *0.3 to 0.9 % (*khatamine, in fresh leaves as chief effective agent (S-(-)-(**cathinone**) 50 %in young leaves.
  - Norpseudoephedrine (**cathine**), -(-) norephedrine,
- *Sesquiterpene*
  - cathaedulines
- *Catechin tannins*
- *Volatile oil*

Phytochemicals



Cathinone

163

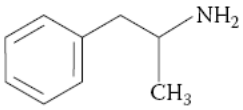
163

Lophophora williamsii – Cactaceae- Peyote

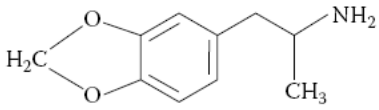
164

164

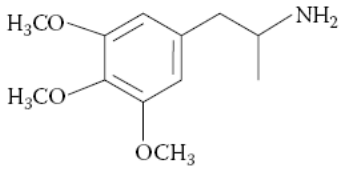
Amphetamine



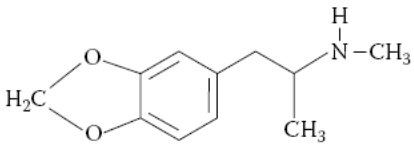
3,4-Methylenedioxyamphetamine (MDA)



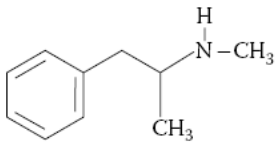
Mescaline



3,4-Methylenedioxymethamphetamine (MDMA)



Methamphetamine



Chemical structure of mescaline.

165

165

Phytochemistry

Active compounds: mescaline (3,4,5-trimethoxy-B-phenethylamine)

Percentage: 10% of the dried material.

Aside from mescaline Peyote also contains **tyramine**, **hordinenine**, anhalaninine, anhalonidine, pellotine, **N-methylmescaline**, **N-acetylmescaline**, anhalonnine, anhalonine, anhalamine, O-methyllanhalonidine and lophophorine.

166

166

Effect

Peyote is a small,
spineless cactus with psychoactive alkaloids, particularly mescaline.

common doses for pure mescaline range from roughly 300 to 500 mg.

This translates to a dose of roughly 10 to 20 g of dried peyote buttons of average potency; however, potency varies considerably between samples, making it difficult to measure doses accurately without first extracting the mescaline.

The effects last about 10 to 12 hours.

167

167

MEDICAL USE

Traditionally it has been used as an analgesic, against toothache, rheumatism, asthma and the cold.

In psychotherapy, under medical prescription, Peyote has been used for the treatment of the neurasthenia.

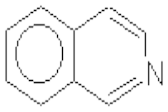
Mescaline has been used as a hallucinogen in experimental psychiatry.

Research has shown that it has powerful antibacterial properties,(Peyocactin) being able to eliminate bacteria that were resistant to penicillin.

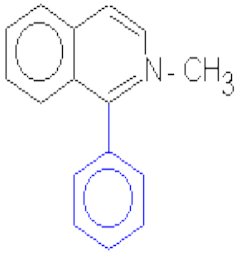
168

168

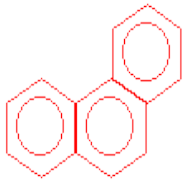
II. Benzyltetrahydroisoqunolines



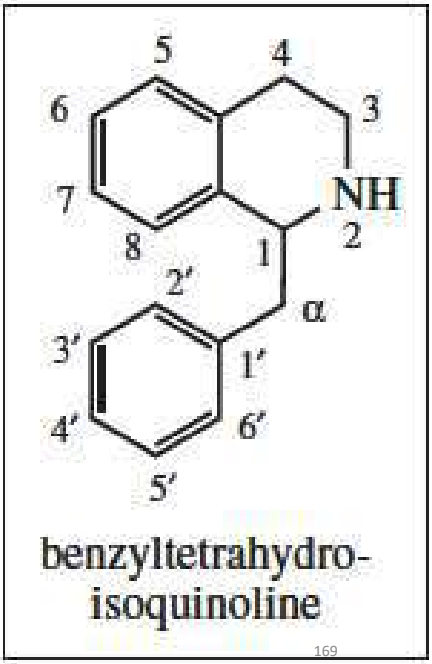
Isoquinoline structure



Benzyl-Isoquinoline

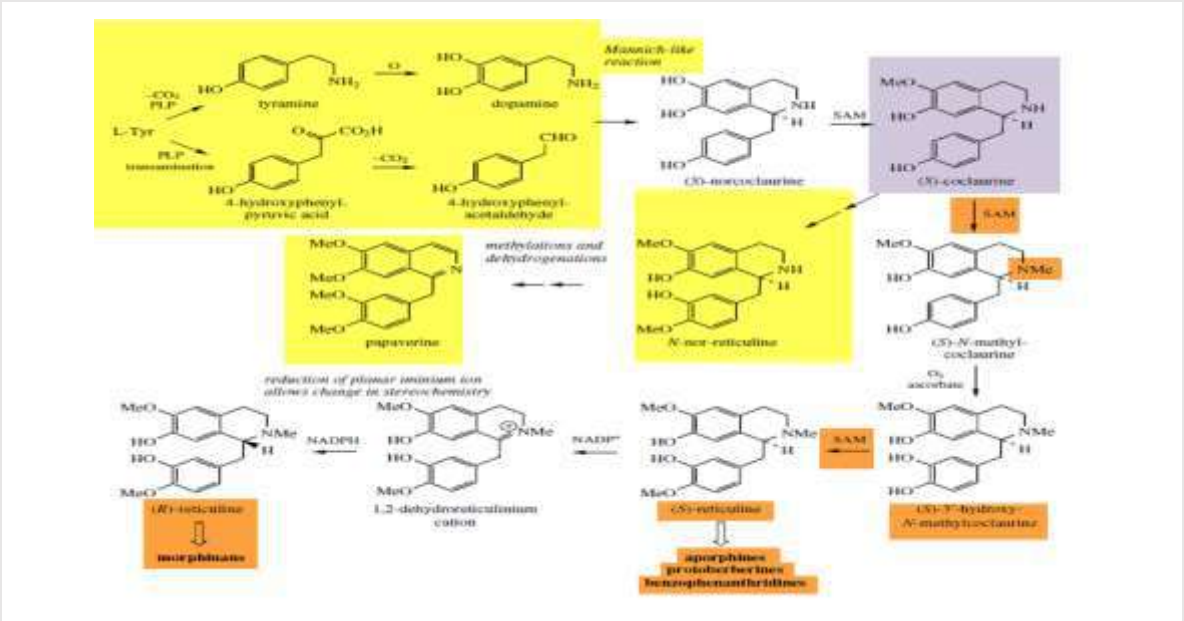


Phenanthrene



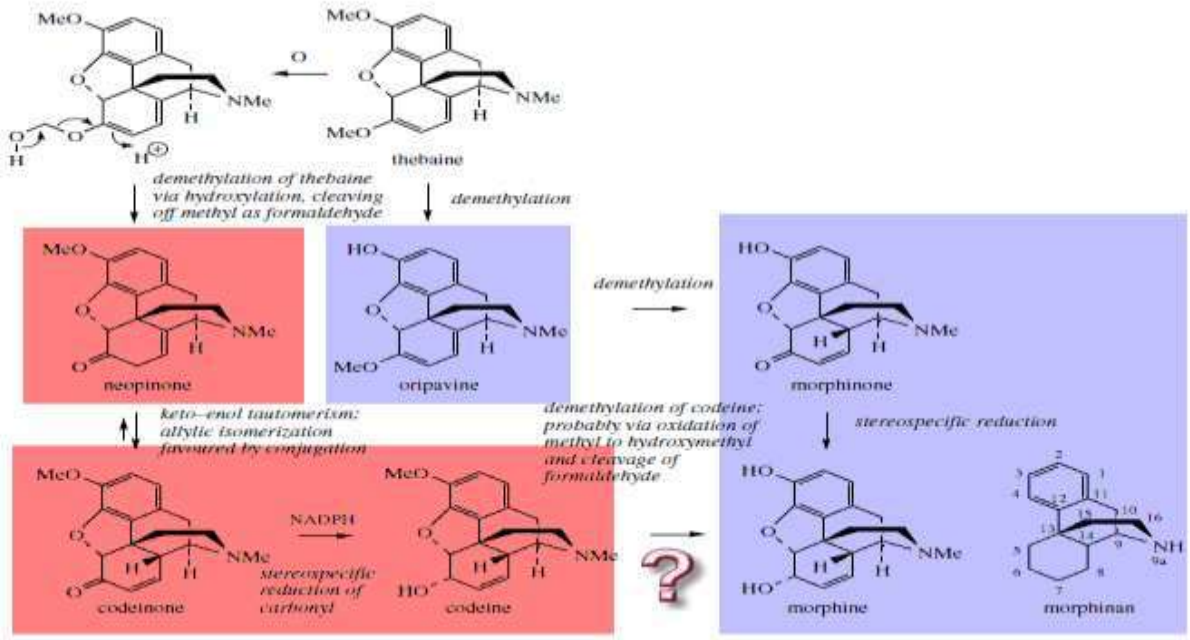
169

169



170

170


thebaine
demethylation of thebaine via hydroxylation, cleaving off methyl as formaldehyde
demethylation
neopinone
oripavine
demethylation
morphinone
keto–enol tautomerism; allylic isomerization favoured by conjugation
demethylation of codeine; probably via oxidation of methyl to hydroxymethyl and cleavage of formaldehyde
stereospecific reduction
NADPH
stereospecific reduction of carbonyl
codeinone
codeine
morphine
morphinan

171

172

172

173

173

Phytochemicals

Isoquinoline alkaloids (20-30%): chief alkaloids

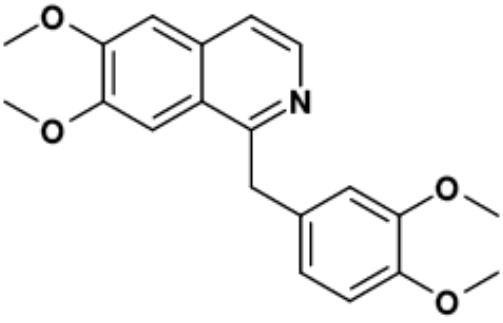
- **Morphine** (3-23%),
- Narcotine (2-10%),
- Codeine (0.2-3.5%),
- Papaverine (0.5-3%),
- Thebaine (0.2-1%).
- **Noscapine** (4-8%) of (non-addictive-cough suppressant)

Benzyl isoquinoline type: **papaverine** (0.5 to 3%).

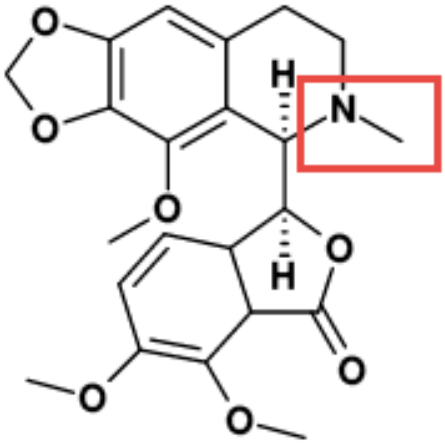
Phthalide isochinoline type: **narcotine**.

174

174



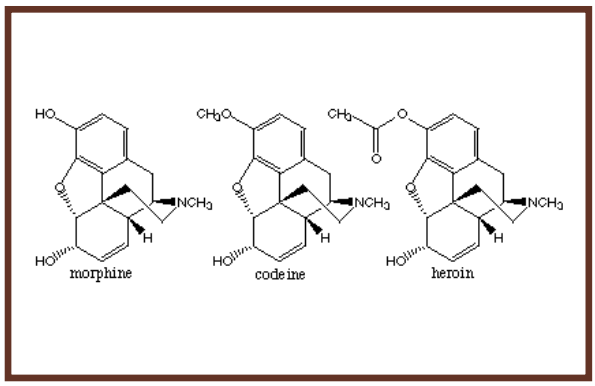
Papaverine

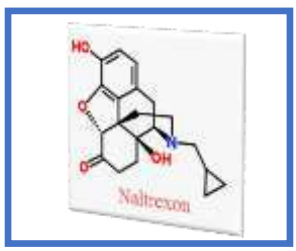


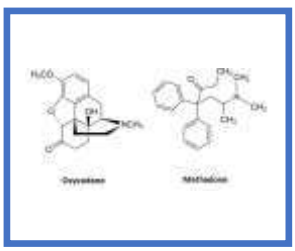
Noscapine

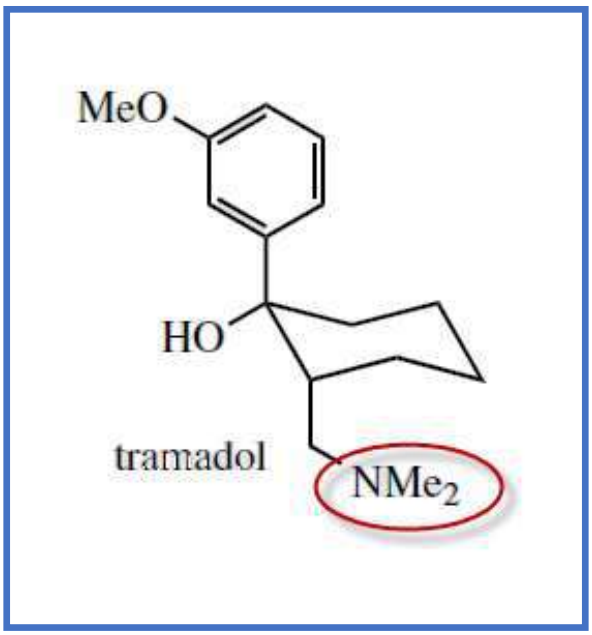
175

175



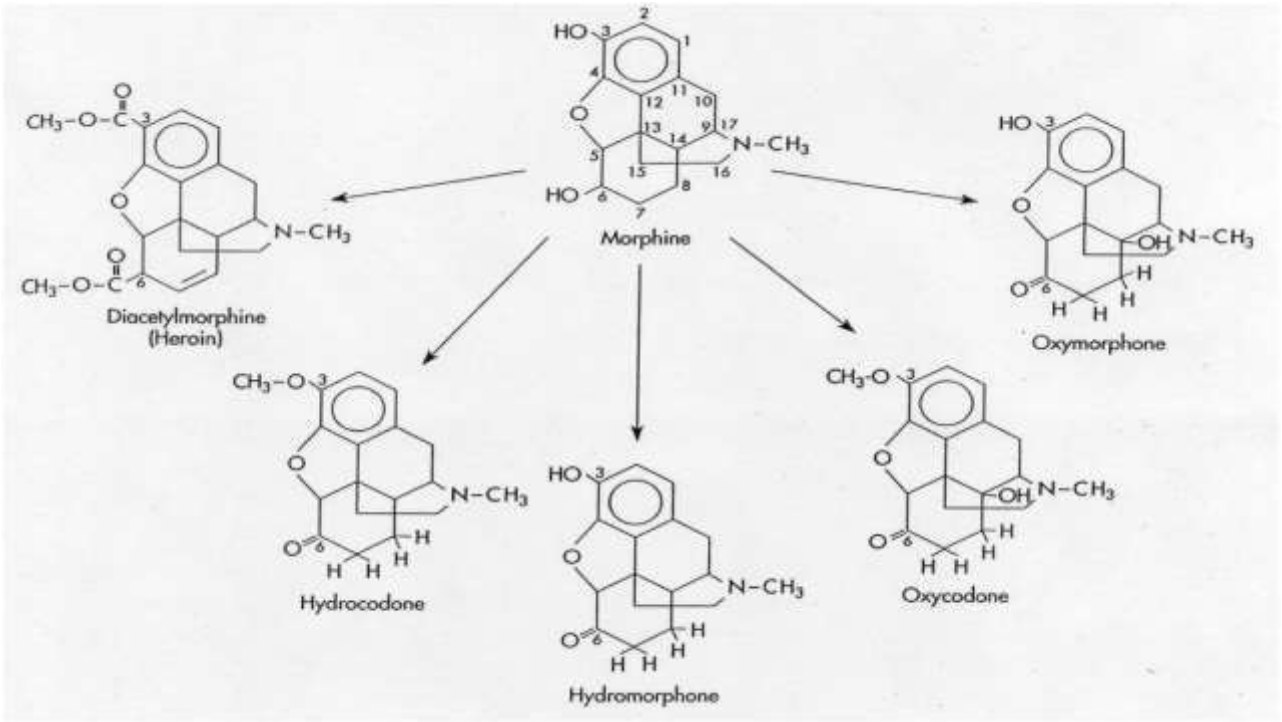






176

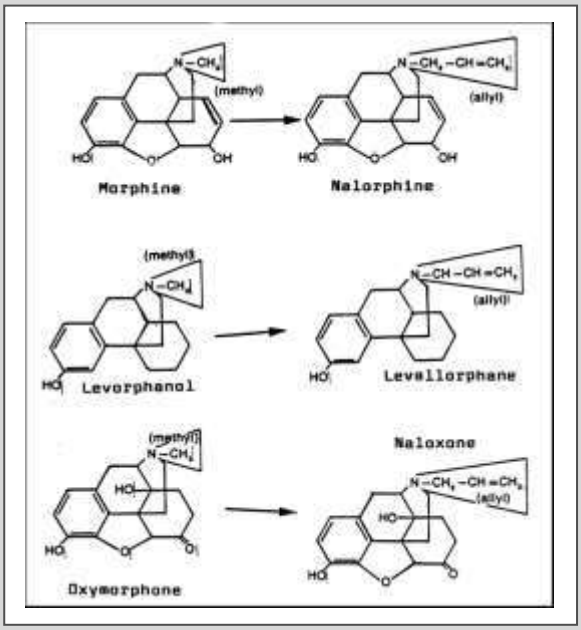
176

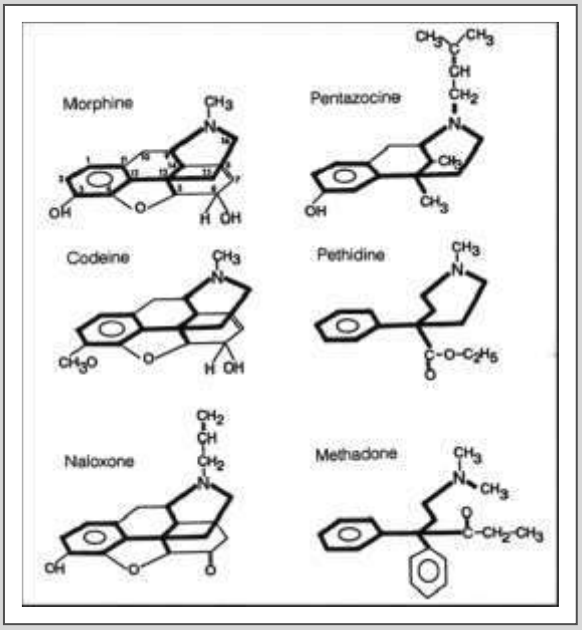


177

All Opioids have a similar structure in regard to their:
1. terminal morphine ring,
2. the distance between the ring and the N-substitution.

178

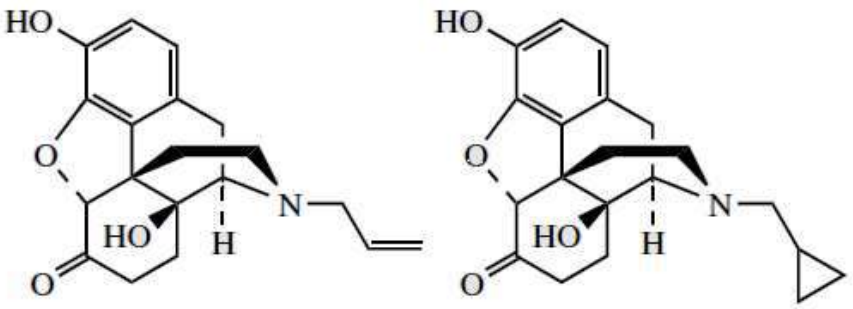




179

179

Antidot



180

180

- **Opioids** act by attaching to specific proteins called **opioid** receptors, which are found in the brain, spinal cord, gastrointestinal tract, and other organs in the body. When these drugs attach to their receptors, **they reduce the perception *(sensitivity)* of pain**.

181

181

Receptor	Location	Function
Delta (δ)	**Brain** **Peripheral sensory neurons**	• **Analgesia** • **Antidepressant** • **Convulsant effect** • **Physical dependency**
Kappa (Ķ)	**Brain** **Spinal cord** **Peripheral sensory neurons**	• **Analgesia** • **Anticonvulsant effect** • **Dysphoria** • **Neuroprotection** • **Sedation**
Mu (μ)	**Brain** **Spinal cord** **Peripheral sensory neurons** **Intestinal tract**	**μ 1:** • **Analgesia** • **Physical dependency** **μ 2:** • **Respiratory depression** • **Physical dependency** **μ 3:** • **Vasodilatation**
Nociceptin	**Brain** **Spinal cord**	• **Anxiety** • **Depression** • **Appetites** • **Tolerance to μ agonists**

182

182

Effect

- Euphoria
- Relaxation
- Reduced anxiety
- Sense of emotional detachment or floating outside one's self
- Reduced pain
- Reduced stress
- Sleepiness
- Altered mood, altered mental state
- Reduced appetite
- Weight loss
- Reduced energy
- Reduced sex drive
- Sweating
- Difficulty concentrating
- Impaired vision
- Coma
- Death

183

183

Symptoms of overdose

- Anxiety
- blurred vision
- blue lips and fingernails
- chest pain or discomfort
- coma
- confusion
- constricted, pinpoint, or small pupils
- depression
- difficult, fast, or noisy breathing, sometimes with wheezing
- difficulty sleeping
- Nervousness
- seizures
- hallucination
- headache
- increased hunger
- increased sweating
- irregular, fast or slow, or shallow breathing
- lethargy
- lightheadedness
- mood or other mental changes
- Shakiness
- Unconsciousness
- stopping of heart

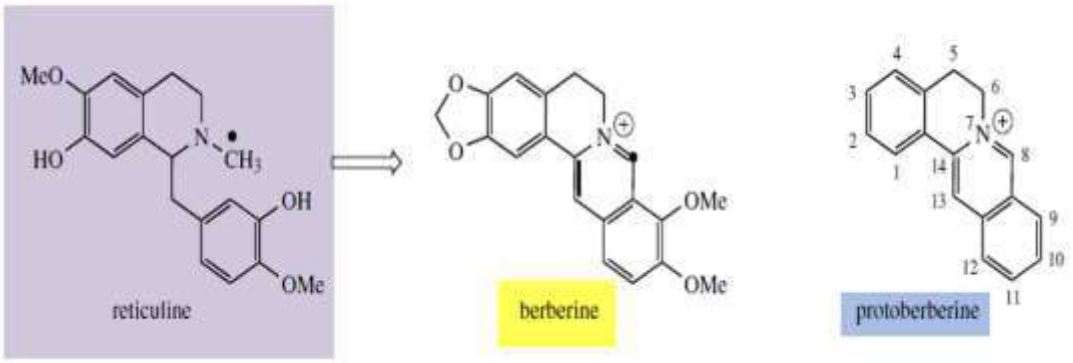
184

184

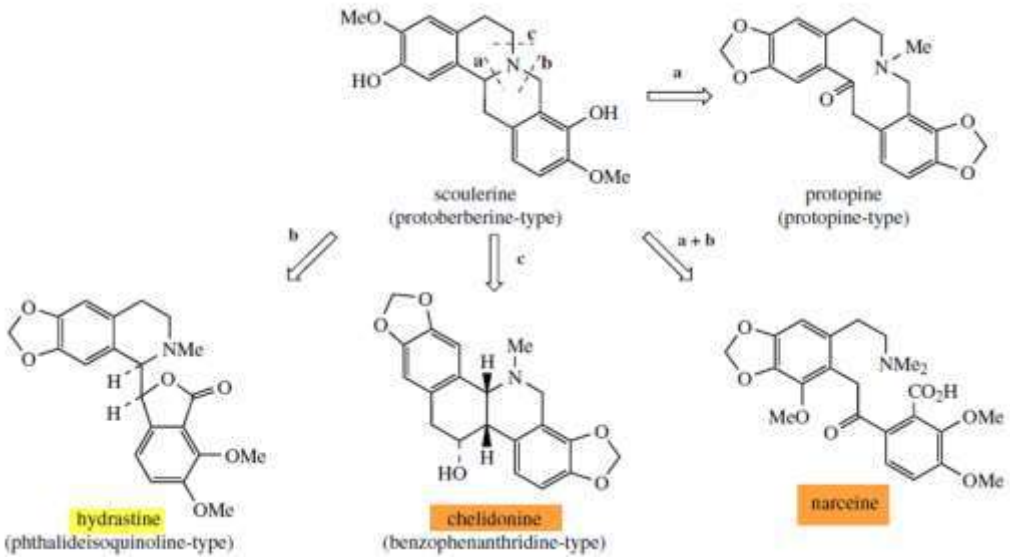
Top 5 Dangers of Opium Effects

- **Respiratory Depression**
- **Addiction**
- **Opium Injection Effects**
- **Intoxication Effects** *"slowed movement and reflexes"*
- **Depression**

185



186


scoulerine
(protoberberine-type)
protopine
(protopine-type)
hydrastine
(phthalideisoquinoline-type)
chelidonine
(benzophenanthridine-type)
narceine

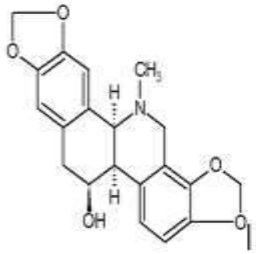
187

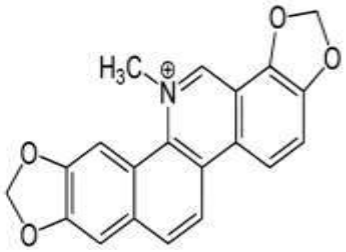

Chelidonium majus-
Papaveraceae
188

188

Phytochemicals

- *Isoquinoline alkaloids of the **protoberberine type**:* including **coptisine** (main alkaloid), and berberine.
- *Isoquinoline alkaloids of the **benzophenanthridine type**:* including **chelidonine** and sanguinarine.





189

189

EFFECT

- Celandine has mild analgesic, cholagogic, antimicrobial and central-sedative effects.
- It also acts as a spasmolytic on smooth muscles.
- In animal tests, Celandine is a cytostatic.
- It also has a nonspecific immune-stimulating effect.

190

190

INDICATIONS AND USAGE

- Liver and gallbladder complaints.
- Celandine is used also for spasmodic pain of the bile ducts and the gastrointestinal tract.

191

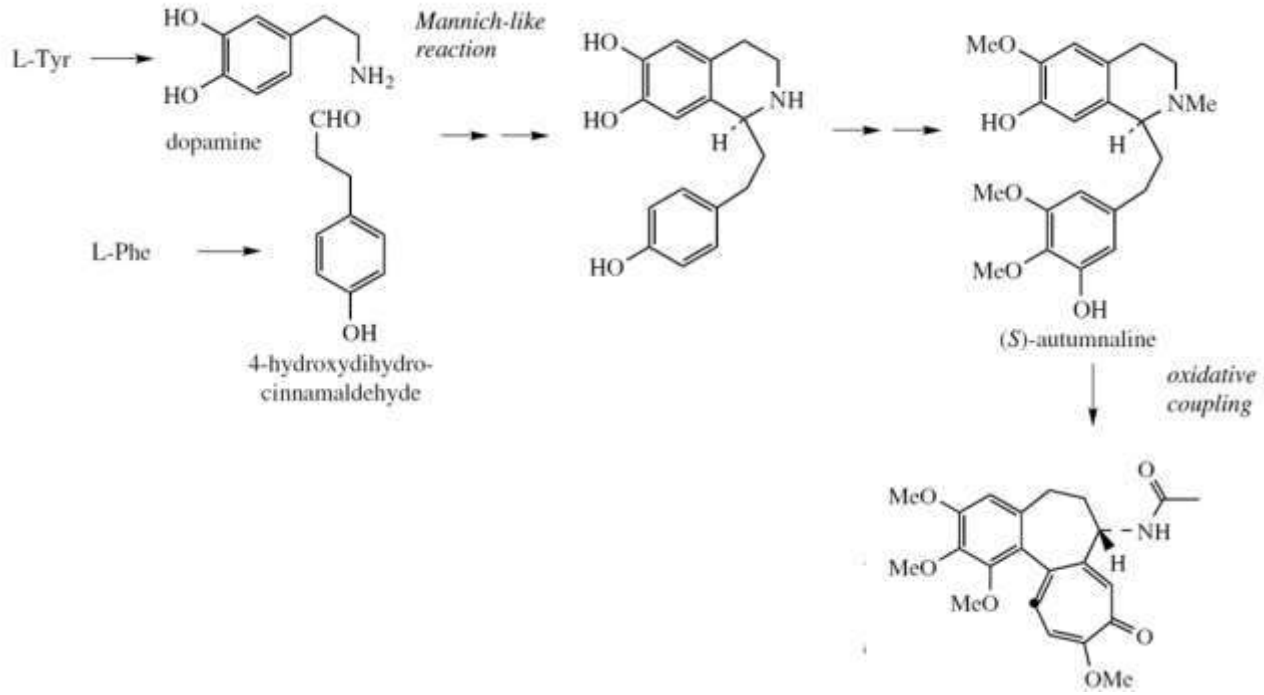
191

III. Isoquinoline Alkaloids
(Phenethylisoquinolines)

- ***Colchicum autumnale***

192

192



193

Phytochemicals

01

Tropolone alkaloids: Seeds contains 0.2 to 1.2- % alkaloids, which colchicine represents 65%. Colchicine does not display any significant basicity, and does not form well-defined salts.

02

Seeds contain 17% fatty acids as palmitic acid and linolic acid. In bulb we found salicylic acid, benzoic acid and tannins.

194

194

EFFECTS

- Colchicum inhibits mitosis through the inhibition of motility, particularly of the phagocytosing lymphocytes.
- This is of therapeutic use for blocking the immigration and the autolysis of phagocytes in inflammatory processes and thereby producing an antiphlogistic effect.

195

195

Dose & Toxicity:

01

Lethal dose is very appropriate to therapeutically dose. Colchicine is neurotoxic in leukemia.

02

The dose in the beginning of treatment is 1mg, and the maintenance dose is 0.5mg.

03

Maximum dose 6mg / 24h.

04

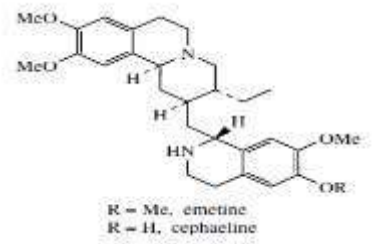
L.D = 6 - 20mg

196

196

IV. Terpenoid Tetrahydroisoquinoline Alkaloids

Cepahaelis ipecacuanha
Rubiaceae



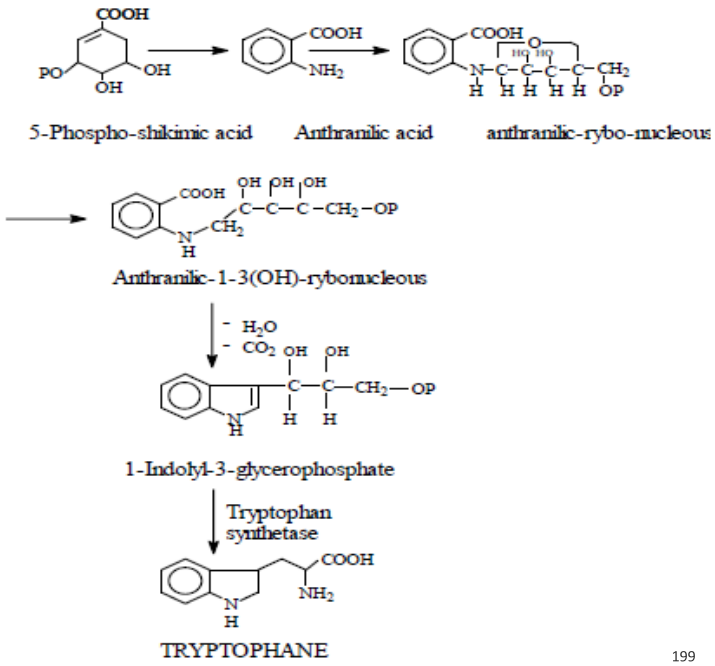
197

197

ALKALOIDS DERIVED FROM TRYPTOPHAN

198

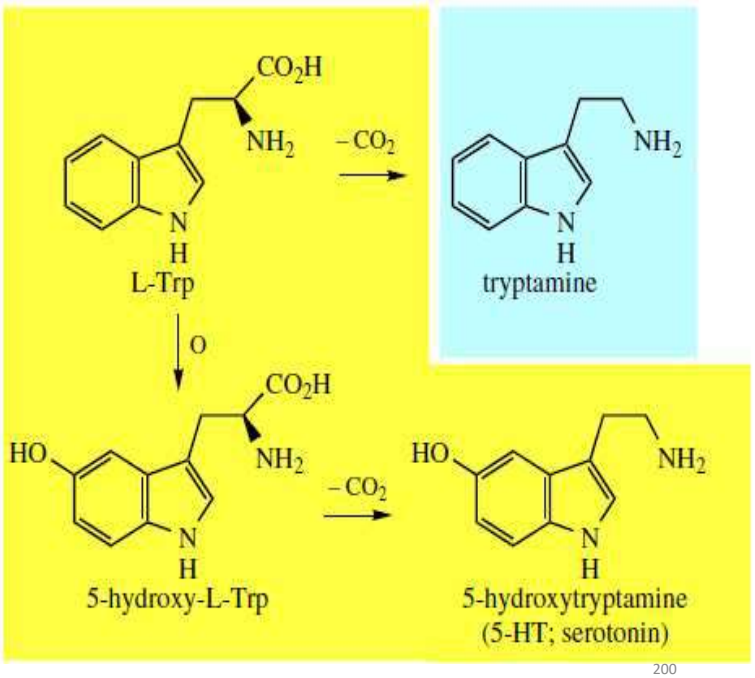
Biosynthesis



199

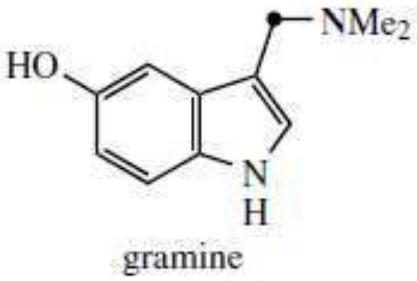
199

Simple Indole Alkaloids



200

200



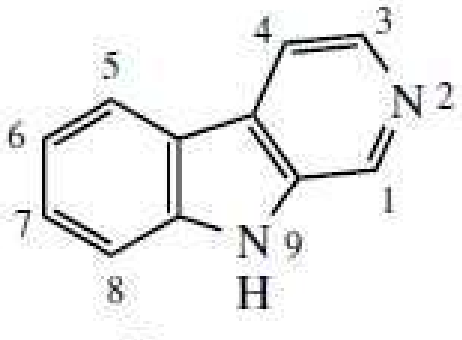
gramine

Hordeum vulgare
Barley
Graminae/ Poaceae

201

201

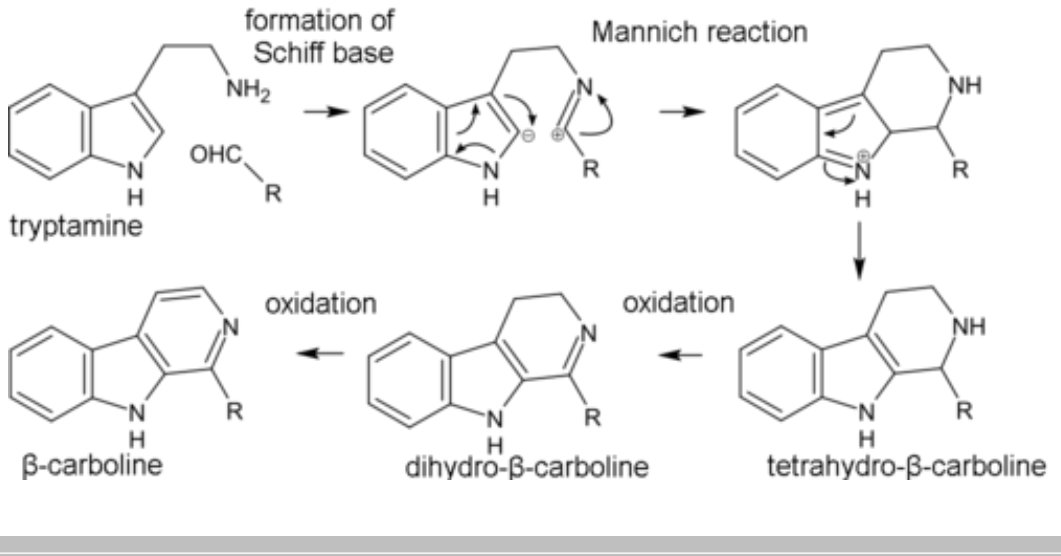
Simple β-Carboline Alkaloids



β-carboline

202

202



203

203

Peganum harmala

Harmal

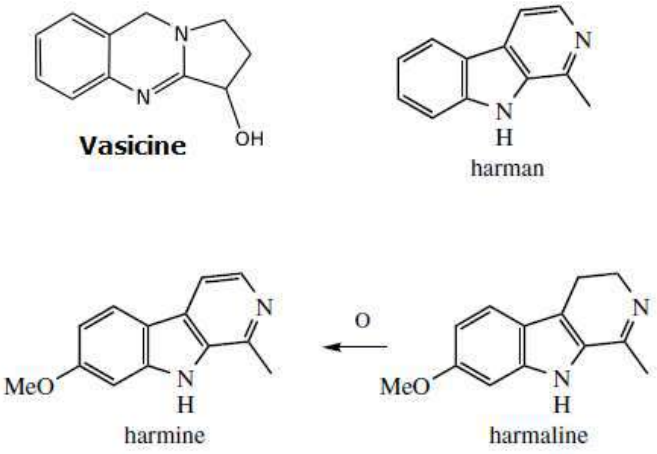
Zygophyllaceae

(Nitrariaceae)

204

204

Phytochemicals



205

205

EFFECT/ INDICATION

- *Peganum harmala* is used as an analgesic and anti-inflammatory agent.
- **In Yemen** it was used to **treat depression**, and it has been established in the laboratory that harmaline, an active ingredient in *Peganum harmala*, is a **central nervous system stimulant** and a "reversible inhibitor of MAO-A (RIMA)," a category of antidepressant.

- **Antidepressant**

206

206

Terpenoid Indole Alkaloids

Rauwolfia serpentine

Apocynaceae

207

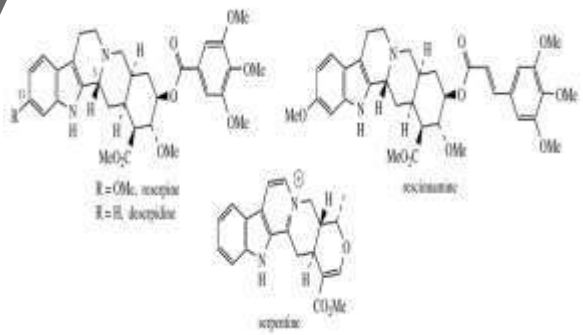
Traditional Medicine

- It was used as an antidote to snake-bite,
- to remove white spots in the eyes,
- against stomach pains,
- fever,
- vomiting,
- headache, and
- to treat irrationality.

208

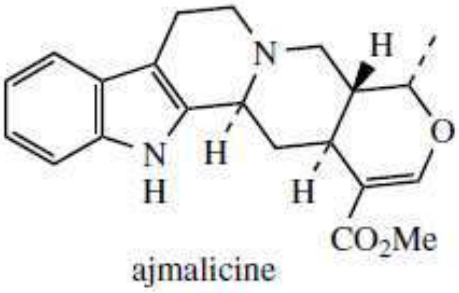
Phytochemicals

- Rauwolfia serpentine contains a wide range of indole alkaloids, totaling 0.7–2.4%, though only 0.15–0.2% consists of desirable therapeutically active compounds, principally reserpine, rescinnamine, and deserpidine.

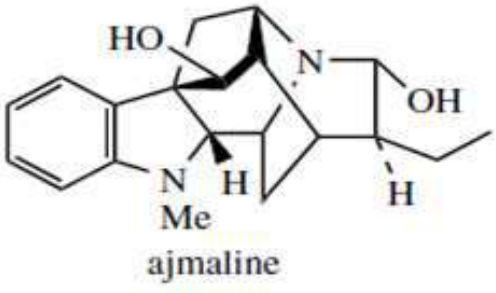


209

209



ajmalicine



ajmaline

210

210

EFFECT

Reserpine and **deserpidine** have been widely used as antihypertensive and mild tranquillizers.

They act by interfering with catecholamine storage, depleting levels of available neurotransmitters.

Prolonged use of the pure alkaloids, reserpine in particular, has been shown to lead to severe depression in some patients, a feature not so prevalent when the powdered root was employed.

211

211

Isolation

Powdered Rauwolfia root is moistened with 10 % $NaHCO_3$ solution and extracted with benzen,

solvent is evaporated,

residue dissolved in methanol, concentrated and crystallized,

assisted by addition of few crystals of reserpine.

The mother liquid (containing deserpidine, recinnamine and other alkaloids) is evaporated to dryness and

individual alkaloids are separated using column chromatography.

212

212

Uses

Reserpine:

- Small dose: Antihypertensive
- High dose: tranquillizers
- Neuropsychiatry disorders

Ajmaline:

- Treatment of cardiac arrhythmias.

213

213

Side effects

In small doses produce chronic diarrhea and

In big dose neuropsychiatries disorders, drowsiness, nasal congestion, salivary and gastric hypersecretion, anxiety and depression.

Doses

Adult: P.O. 0.5mg / 24h P.O (0.25mg) / daily (minimum dose)

214

214

Contra indications

- Pregnancy;
- Renal hypertension;
- Ulcer;
- Chirurgical intervention;
- Epilepsy;
- Depression;
- Breast Cancer
- Combination with MAO inhibitors or levodopa.

215

215

Catharanthus vinca roseus

- The Vinca plant extract is useful for the treatment of dysentery and diarrhoea.
- It is also anti-inflammatory in nature.
- The plant contains 2 types of active compound such as alkaloid and tannins. The plant contains **resperine**.
- Ornamental design

216

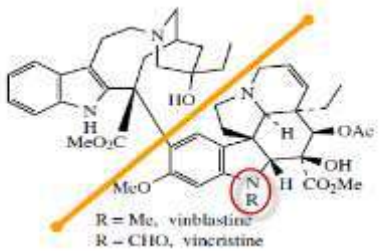
216

Catharanthus vinca roseus

- It decreases blood pressure
- It is also proved anti-diabetic.
- It has antibacterial and antiviral property.
- It is also anti-inflammatory in nature.
- The flower petals and seeds have antioxidant property.
- It cures various skin diseases such as acne, eczema and dermatitis.
- Anti-Helminthic

217

217



Phytochemicals

- The **root** contains bornesitol, d-yohimbine ajmalicine, olenolic acid, alstonine and urosolic acid.
- The root bark contains alstonine, serpentine, vincaline I and vincaline II.
- The **leaves** contain cartharanthine, leurosin, 21-oxo-leurosine, catharanthamine, coronaridine, vindoline, vimblastine, leurosidine, vincristine, tetrhydrolastonine, lochnerine, vincarodine,

218

218

Tests for identification

Vanillin /HCl reagent gives with;

Vinblastine a pink color, and

Vincristine an orange-yellow color.

para-dimethylaminobenzaldehyde (PDAB) reagent (**Van-Urk's reagent**): gives vinca alkaloids in presence glacial acetic acid and concentrated H_2SO_4 a **reddish - brown color**.

219

219

Effect

These active substances are **anti-carcinogen, anti-oxidative, hypoglycaemic, anti-allergic and antibiotic in nature.**

The anticancer alkaloids (vinblastine and vincristine) found in the leaf and stem of Catharanthus roseus inhibits cancer and tumor cells in the body.

The vinca alkaloids delay all fast-dividing cell types including cancer cells.

This suggests why vinblastine is used for treating neoplasms, choriocarcinoma (such as type of cancer that occurs in a woman's uterus and Hodgkin's disease (painless enlargement of the lymph nodes, liver, and spleen).

Vincristine *has superior antitumour activity compared to vinblastine but is more neurotoxic.*

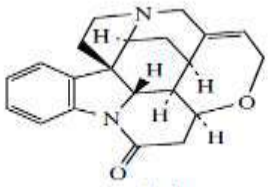
220

220

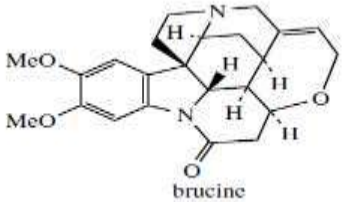
Strychnos nux-vomica Loganiaceae

The fruit is a large berry with a hard coat and a pulpy interior containing three to five flattish grey seeds.

These seeds contain 1.5–5% of alkaloids, chiefly strychnine (about 1.2%) and brucine (about 1.6%).



strychnine



brucine

221

Pharmacological properteis

- The powdered seeds are employed in atonic dyspepsia.
- The tincture of Nux Vomica is often used in mixtures for its stimulant action on the gastro-intestinal tract.
- In the mouth it acts as a bitter, increasing appetite; it stimulates peristalsis, in chronic constipation due to atony of the bowel it is often combined with cascara and other laxatives with good effects.
- **Strychnine**, the chief alkaloid constituent of the seeds, also acts as a bitter, increasing the flow of gastric juice; it is rapidly absorbed as it reaches the intestines, after which it exerts its characteristic effects upon the central nervous system.
- **Strychnine** is very toxic, affecting the CNS and causing convulsions.

222

222

Poisoning and Antidotes

In cases of poisoning by strychnine an emetic or the stomach pump should be used at once and tannin or potassium permanganate given to render the strychnine inactive.

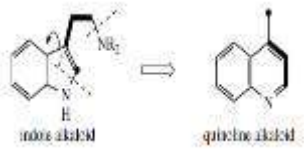
Violent convulsions should be controlled by administration of chloroform or large doses of chloral or bromide.

Urethane in large doses is considered an antidote.

Amyl nitrite is also useful owing to its rapid action during the convulsion, and in absence of respiration 3 to 5 minims may be hypodermically injected.

223

223



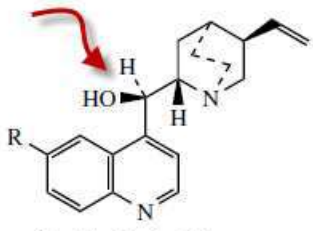
Quinoline Alkaloids - *Cinchona spp.*

224

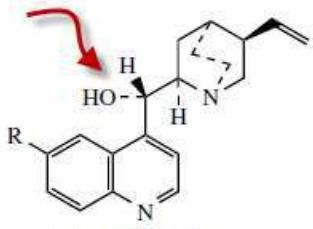
224

Phytochemicals

- A considerable number of alkaloids have been characterized in cinchona bark, four of which account for some 30–60% of the alkaloid content.
- These are **quinine, quinidine**, **cinchonidine** and **cinchonine,** long prized for their antimalarial properties.



R = H, cinchonidine
R = OMe, quinine



R = H, cinchonine
R = OMe, quinidine

225

225

EFFECT & USES

Quinine is a major alkaloid, continues to be used for treatment of **multidrug-resistant malaria**, though it is not suitable for prophylaxis.

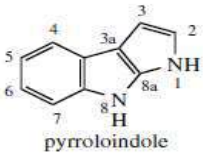
Quinidine is the principal cinchona alkaloid used therapeutically, and is administered to treat cardiac arrhythmias.

- It inhibits fibrillation, the uncoordinated contraction of muscle fibers in the heart.

226

226

Calabar beans



Pyrroloindole Alkaloid

Physostigma venenosum

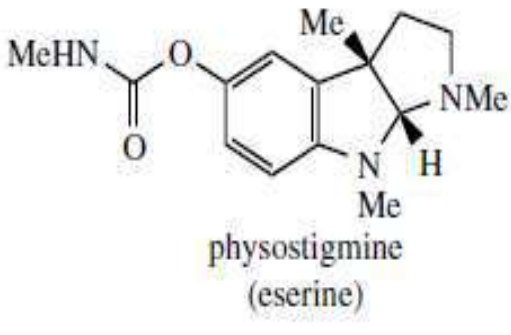
Leguminosae/Fabaceae

227

227

Phytochemicals

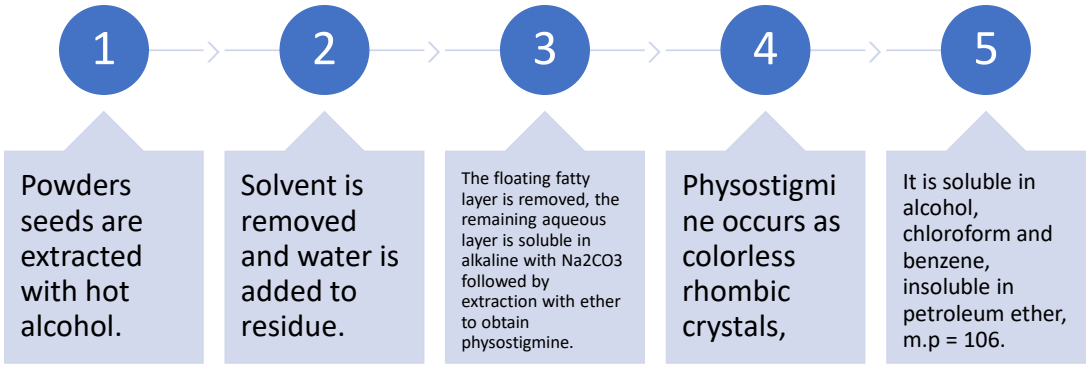
- The seeds contain several alkaloids (alkaloid content about 1.5%), the major one (up to 0.3%) being physostigmine (eserine).



228

228

Isolation



229

229

EFFECT

- Increase in tone in the parasympathetic system and the striated muscles.
- Eserine is a reversible inhibitor of cholinesterase, preventing normal destruction of acetylcholine and thus enhancing cholinergic activity.
- Its major use is as a miotic, to contract the pupil of the eye, often to combat the effect of mydriatics such as atropine.
- It also reduces intraocular pressure in the eye by increasing outflow of the aqueous humour, and is a valuable treatment for glaucoma, often in combination with pilocarpine.
- physostigmine can be used as an antidote to anticholinergic poisons such as hyoscyamine/atropine

230

230

Indication

1

In the treatment of glaucoma

2

A poison antidote

231

231

Precautions and adverse reactions

01

Symptoms of poisoning
Diarrhea , dizziness, nausea, salivation, stupor, sweats and vomiting.

02

Lethal doses can cause muscle twitching, spasms, tachycardia and **cyanosis** through asphyxiation.

LD:6 to 10 mg of physostigmine (2-3 seeds)

232

232

Ergot Alkaloids

233

233

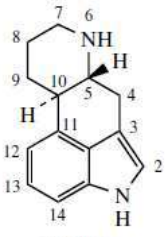
Claviceps purpurea
- Secale cereale –
Graminae/Poaceae

- The ergot sclerotia contain from 0.15–0.5% alkaloids, and more than 50 have been characterized.
- Medicinally useful compounds are derivatives of (+)-lysergic acid and can be separated into two groups:
  - Water-soluble amino alcohol derivatives (up to about 20% of the total alkaloids), like **Ergometrine** (an amide of lysergic acid) and
  - water-insoluble peptide derivatives (up to 80% of the total alkaloids), like **ergotamine, ergoxine and ergotoxine** (a cyclized tripeptide fragment bonded to lysergic acid via an amide linkage, based on 3 aminoacids).

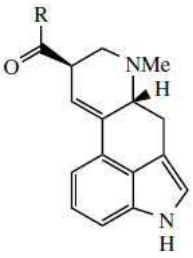
234

234

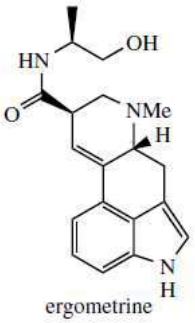
Phytochemistry



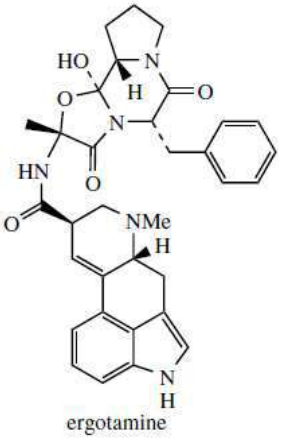
ergoline



R = OH, (+)-lysergic acid
R = NH_2, ergine



ergometrine



ergotamine

235

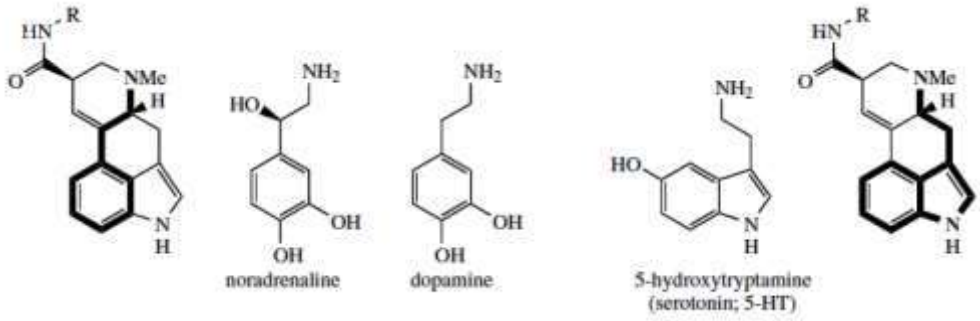
235

Effect

- The pharmacologically active ergot alkaloids are based on (+)-lysergic acid,
- The pharmacological activity of ergot alkaloids due to their ability to act at **α-adrenergic, dopaminergic and serotonergic receptors.**
- The relationship of the general alkaloid structure to those of noradrenaline, dopamine, and **5-hydroxytryptamine** (5-HT, serotonin) is shown in the following structures

236

236



237

237

Symptoms & Management in Serotonin Syndrome:

Mild	Moderate	Life Threatening
Mydriasis Shivering Sweating Tachycardia (mild)	**Altered Mental Status** (agitation, disorientation, excitement) **Autonomic Hyperactivity** (rigidity, tachycardia, hyperthermia of >40°C) **Neuromuscular Abnormalities** (tremor, clonus, hyperreflexia)	Delirium Hypertension Hyperthermia Muscle rigidity Tachycardia

Management stages:

Observe for at least 6 hrs
Benzodiazepines

→ Admit to hospital
Cardiac monitoring
Cyproheptadine

→ Intensive care unit
Esmolol or nitroprusside
Cooling measures,
Sedation, SkM paralysis, ventilation

238

238

Indication

- **Ergometrine** is used as an oxytocic, and is injected during the final stages of labor and immediately following childbirth, especially if haemorrhage occurs.
- Caesarian operations. It is sometimes administered in combination with oxytocin itself.
- Ergometrine is also orally active. It produces faster stimulation of uterine muscle than do the other ergot alkaloids, and probably exerts its effect by acting on α-adrenergic receptors, though it may also stimulate 5-HT receptors.

239

239

Indication

1. **Ergotamine**: partial agonist of α-adrenoceptors and 5-HT receptors.
2. In the treatment of acute attacks of migraine, where it reverses the dilatation of cranial blood vessels.
3. The activity is enhanced with caffeine.
4. The semi-synthetic **dihydroergotamine** is hydrogenation of the lysergic acid Δ9,10 double bond is claimed to produce side-effects, especially digestive upsets.

240

240

TOXICITY

- Alimentary upsets, e.g. diarrhoea, abdominal pains, and vomiting.
- Circulatory changes, e.g. coldness of hands and feet due to a vasoconstrictor effect, a decrease in the diameter of blood vessels, especially those supplying the extremeties.
- Neurological symptoms, e.g. headache, vertigo, convulsions, psychotic disturbances, and hallucinations.
- Abortion (Rupture of uterus).

241

241

LSD

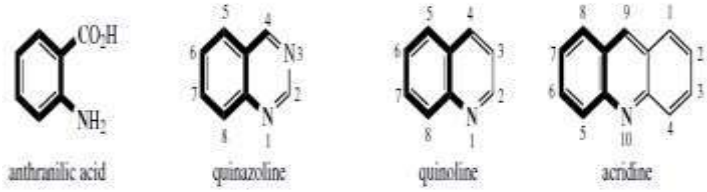
The lysergic acid derivatives is lysergide (lysergic acid diethylamide or LSD). This widely abused hallucinogen.

LSD is a mixed agonist–anatagonist at 5-HT receptors.

242

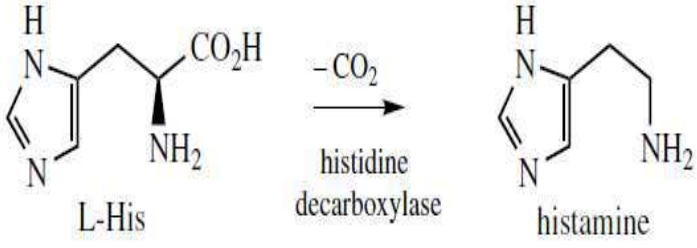
242

Alkaloids derived from ANTHRANILIC ACID

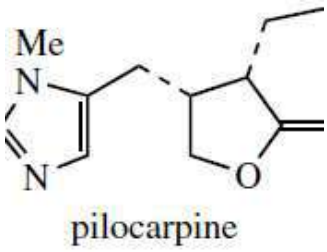


243

ALKALOIDS Derived from HISTIDINE



244



pilocarpine

245

245

Imidazole Alkaloids

Pilocarpus microphyllus

Pilocarpus jaborandi

Rutaceae

- *Imidazole alkaloids (0.5-1.0%):* chief alkaloid is pilocarpine.
- Also includs:
  - isopilocarpine, companion alkaloids including pilocarpidine, pilosine and others.
- *Volatile oil (0.5%):* chief component is limonene.

- Powdered Jaborandi leaves are treated with sodium carbonate then extracted with benzene,
- followed by shaking the benzene extract with dilute HCL or nitric acid.
- The aqueous solution is then made alkaline and shaken with chloroform.
- The chloroform solution is then shaken with acid, and the alkaloidal salt allowed crystallizing.

246

246

Identification

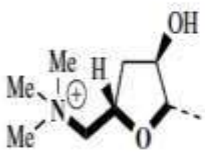
- **Helche's test:** Aqueous solution of pilocarpine salt when treated with H_2O_2, few drops of diluted $K_2Cr_2O_7$ SOLUTION, **a violet color** is formed; upon shaking with benzene, the benzene layer will give a **blue** color while the aqueous layer becomes **yellow**.

247

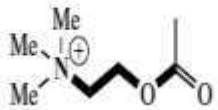
247

EFFECT

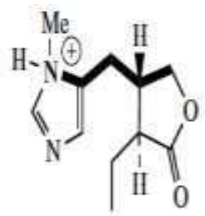
- **Pilocarpine** salts are valuable in ophthalmic practice and are used in eyedrops as miotics and for the treatment of glaucoma.
- Pilocarpine is a cholinergic agent and stimulates the muscarinic receptors in the eye, causing constriction of the pupil and enhancement of outflow of aqueous humour.



Muscarine



Acetylcholine



Pilocarpine

248

248

INDICATIONS

In folk medicine, it has been used for epilepsy, convulsions.

In modern medicine Jaborandi has been used in the treatment of glaucoma.

249

249

Side Effects

The incorrect administration of pilocarpine eyedrops can lead to **poisoning** through leakage into the nose or mouth.

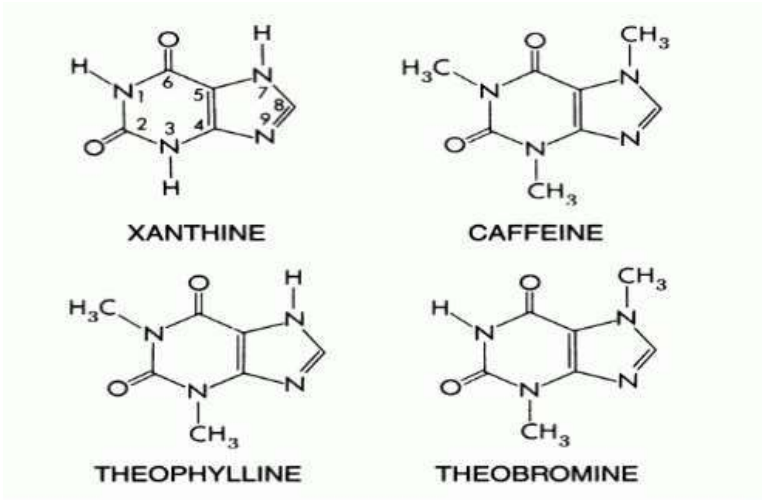
Symptoms include bradycardia, bronchial spasms, colics, collapse and possible cardiac arrest, convulsions, drop in blood pressure, dyspnea, nausea, severe salivation, strong secretion of sweat and vomiting.

The **lethal dose** is approximately 60 mg of pilocarpine, corresponding to 5 to 10 mg of the drug.

250

250

PURINE ALKALOIDS



251

Purine Alkaloids

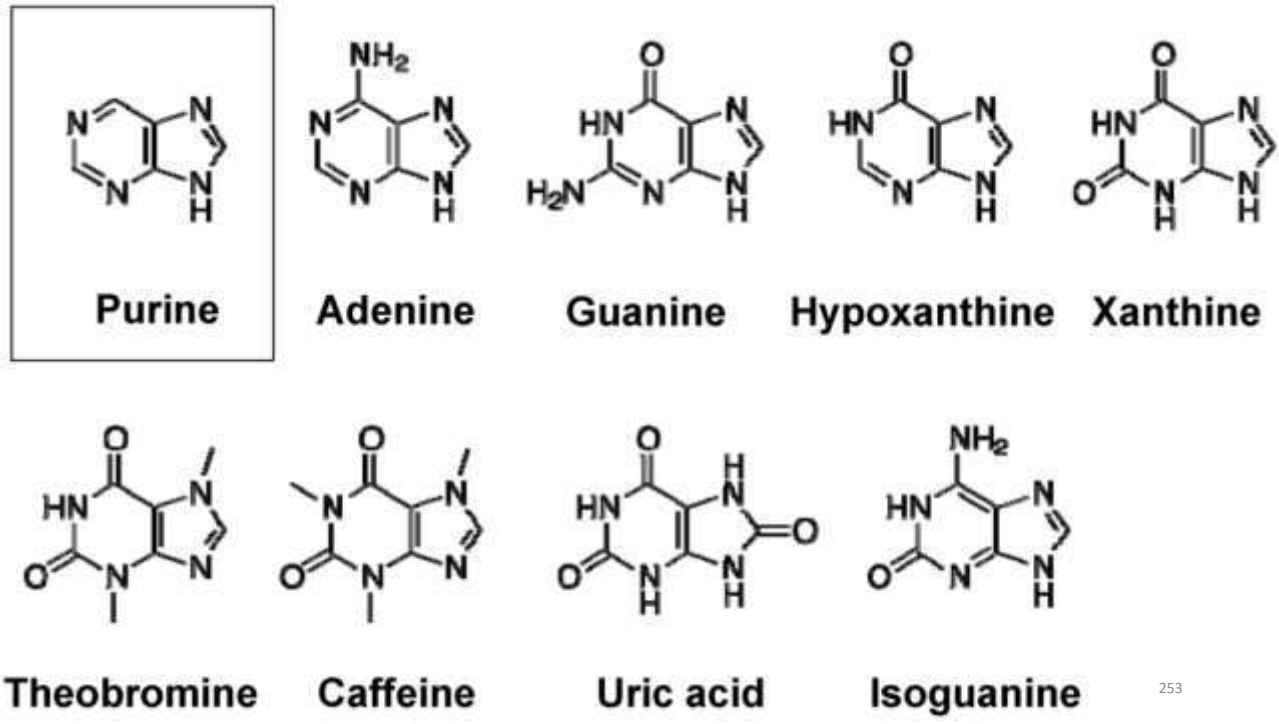
Purine origins are very closely linked with those of the purine bases adenine and guanine, fundamental components of nucleosides, nucleotides, and the nucleic acids.

The purine alkaloids caffeine, theobromine, and theophylline are all methyl derivatives of xanthine and they commonly co-occur in a particular plant.

The major sources of these compounds are the beverage materials such as tea, coffee, cocoa, and cola, which owe their stimulant properties to these water-soluble alkaloids.

252

252



253

253

Characters

Caffeine is used medicinally as a CNS stimulant, usually combined with another therapeutic agent, as in compound analgesic preparations.

Theobromine is of value as a diuretic and smooth muscle relaxant, but is not now routinely used.

Theophylline is an important smooth muscle relaxant for relief of bronchospasm, and is frequently dispensed in slow release formulations to reduce side-effects.

254

254

Characters

Purine alkaloids are **weak bases**, form salts only with strong acids; they can combine with organic acids, as citric, or with salts of organic acids as sodium acetate or benzoate.

They **do not give precipitate with Mayer's reagent**, but give a **brown precipitate with Wagner's reagent** and are precipitated, as well, by tannic acid.

They give **positive Murexide test**.

255

255

Isolation of Caffeine

Powder Tea leaves is extracted with boiling water, filtered, filtrate is treated with lead acetate solution, to precipitate tannins and other impurities, and again filtred.

Filtrate is concentrated and delayed by sodium hydrogen phosphate and filtred again.

Caffeine is extracted from the filtrate with chloroform and is purified by recrystallization from water.

256

256

Identification

- Murexide test: little of solid alkaloid is mixed with conc. HCL and traces of $KCLO_3$ are added , evaporate on water bath, a **reddish color is produced changing to purple on exposure to ammonia vapor.** The color is destroyed by fixed alkalies.
- Tannic acid: Caffeine is precipitated from its concentrated solution by tannic acid; the precipitate is soluble in excess of the reagent.
- Caffeine gives precipitates with Wagner's (in acid solution) and Dragendorff's reagents.

257

257

Caffeine equivalents

Food/Drink	Average amount of caffeine (mg)
Brewed coffee (8 ounces)	137 mg
Instant coffee (8 ounces)	76 mg
Coffee ice cream or frozen yogurt (4 ounces)	2 mg
Brewed tea (8 ounces)	48 mg
Instant tea (8 ounces)	26 to 36 mg
Soft drinks (like cola) (12 ounces)	37 mg
Energy drinks (8 ounces)	100 mg
Hot cocoa mix (3 teaspoons or 1 packet)	8 to 12 mg
Chocolate milk (8 ounces)	5 to 8 mg
Dark chocolate (1.45 ounce bar)	30 mg
Milk chocolate (1.55 ounce bar)	11 mg
Chocolate syrup (1 tablespoon)	3 mg

258

258

Oolong tea - Theaceae

- *Oolong tea* is semi-fermented. Tea contains 1–4% caffeine, and small amounts (up to 0.05%) of both theophylline and theobromine.

Cola acuminate - Sterculiaceae

- Cola seeds contain up to 3% caffeine and about 0.1% theobromine, partly bound to tannin materials.

Ilex paraguensis - Aquifoliaceae

Mate´ or Paraguay tea, the dried leaf contains 0.8–1.7% caffeine and smaller amounts of theobromine (0.3–0.9%) with little or no theophylline.

259

259

Paullinia cupana - **Sapindaceae**

- The seeds of the Brazilian plant *Paullinia cupana* are used to make a stimulant drink.
- The principal constituent, previously called guaranine, has been shown to be identical to caffeine, and the seeds may contain 3–5%. Small amounts of theophylline (0–0.25%) and theobromine (0.02–0.06%) are also present.

260

260

261