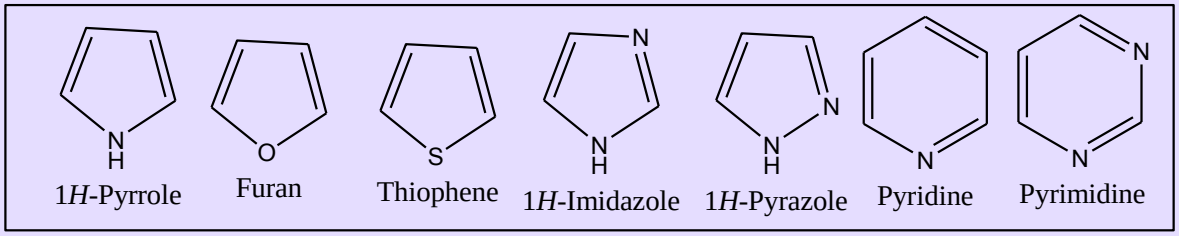
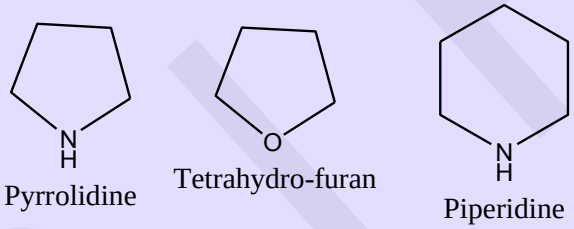
HETEROCYCLIC COMPOUNDS

- Cyclic compound which have at least one hetero atom along with carbon in the formation of ring are called heterocyclic compound.

Eg.



- Many important organic, biochemical, drugs and no of carbohydrates, vitamins, alkaloids, glycosides, antibiotics and amino acid are also contain heterocyclic system.
- Heterocyclic may or may not be aromatic. Example of some non-aromatics heterocyclic compounds are-



- Hetero atom present in the compound play an important role in deciding the physical and chemical properties.

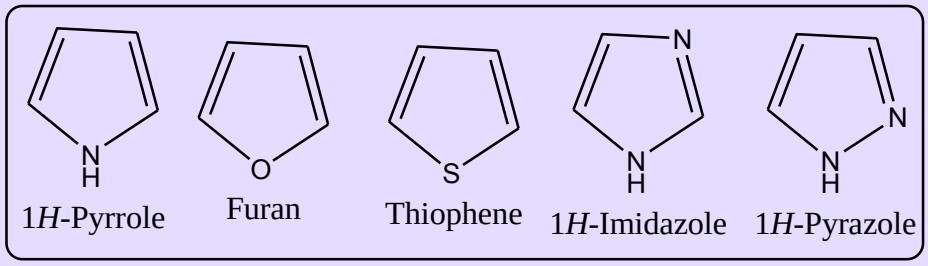
CLASSIFICATION OF HETEROCYCLIC COMPOUNDS

- Heterocyclic compounds may be classified-

I. Based on their structure

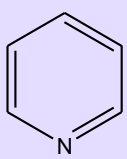
a) Five membered heterocylic compound-

- The compound with 5-membered ring and one or more heterocyclic atom in them are referred to as five membered heterocyclic.

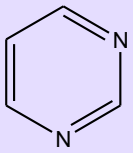


b) Six membered heterocyclic compound-

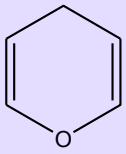
- Compound with six membered ring and one are more hetero atom referred to as six membered heterocyclic. Eg.



Pyridine



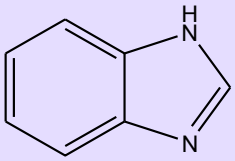
Pyrimidine



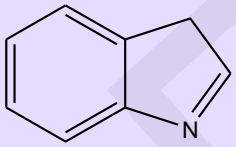
4*H*-Pyran

c) Condensed heterocyclic compound-

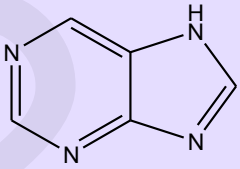
- They consist of two or more ring fused together, all the rings in a compound not necessarily be heterocyclic in nature. Eg.



1*H*-Benzoimidazole



3*H*-Indole



7*H*-Purine

NOMENCLATURE OF HETEROCYCLIC COMPOUNDS

- According to IUPAC (International Union of Pure and Applied Chemistry) system of nomenclature, the name of heterocyclic compound are made up of three parts-
  i. a 'stem' that indicate the ring size.
  ii. a 'prefix' that describe the hetero atom.
  iii. A 'suffix' that denotes the degree of unsaturation.

Size of ring	Stem	Nitrogenous ring		Non-Nitrogenous ring	
		unsaturated	saturated	unsaturated	saturated
3	-ir-	-irine	-iridine	-irene	-irane
4	-et-	-ete	-etidine	-etc	-etane
5	-ol-	-ole	-olidine	-ole	-olane
6	-in-	-ine	-olidine	-in	-ane
7	-ep-	-epine	-	-epine	-epane
8	-oc-	-ocine	-	-ocine	-ocane

- In the numbering of heterocyclic ring the hetero atom is always given number 1.

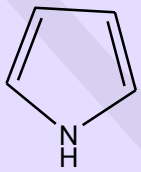
- When more than one hetero atom is present in the same ring, they are numbered in the following order given in table-

Element	Symbol	Valance	Prefix
Oxygen	O	2	oxa-
Sulfur	S	2	Thia-
Selenium	Se	2	Selena-
Nitrogen	N	3	Aza-
Phosphorus	P	3	Phospha-
Arsenic	As	3	Arsa-
antimony	Sb	3	Stiba-
Bismuth	Bi	3	Bisma-
Silicon	Si	4	Sila-
Tin	Sn	4	Stanna-
Lead	Pb	4	Plumba-

PYRROLE (azacycle-2, 4-diene)

CHEMISTRY:

- **Structure:**



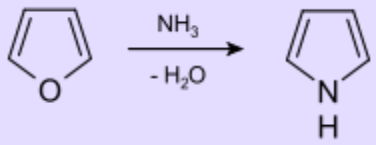
1*H*-Pyrrole

- Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in Pyrrole.
- Due to its aromatic character, pyrrole is difficult to hydrogenate, does not easily react as a diene in Diels-Alder reactions, and does not undergo usual olefin reactions.
- Its reactivity is similar to that of benzene and aniline, in that it is easy to alkylate and acylat.
- Under acidic conditions, pyrroles polymerize easily, and thus many electrophilic reagents that are used in benzene chemistry are not applicable to Pyrrole.

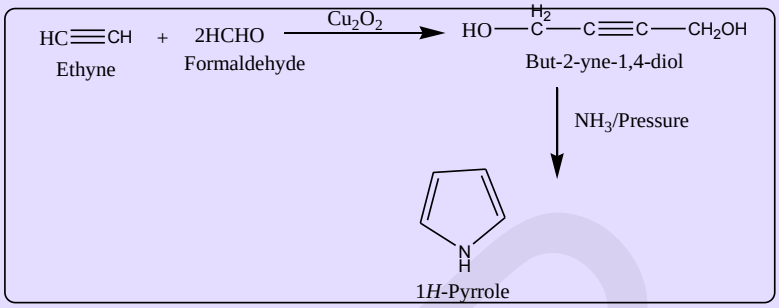
Preparation-

1. **Synthesis from furan-**

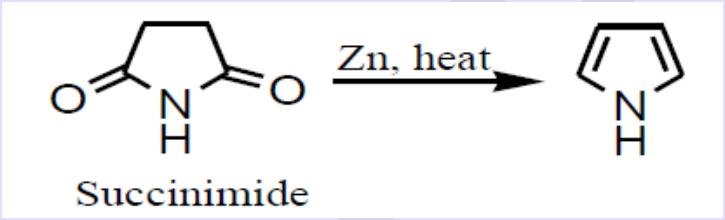
- Pyrrole is prepared industrially by treatment of furan with ammonia in the presence of solid acid catalysts, like SiO_2 and Al_2O_3.



2. Synthesis from acetylene-



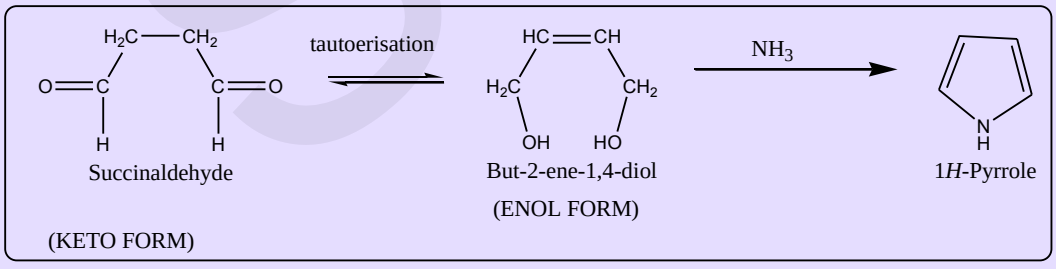
3. Pyrrole is obtained by distillation of succinimide over zinc dust.



Laboratory routes

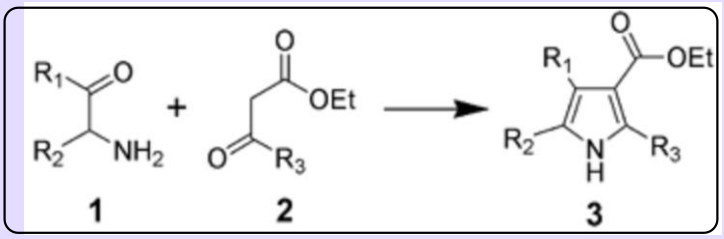
1. Paal-Knorr pyrrole synthesis

- In the Paal-Knorr pyrrole synthesis, a 1,4-dicarbonyl compound reacts with ammonia or a primary amine to form a substituted Pyrrole.



2. Knorr Pyrrole synthesis

- The Knorr pyrrole synthesis involves the reaction of an α-amino ketone (1) or an α-amino-β-ketoester with an activated methylene compound.
- The method involves the reaction of an α-amino-ketone and a compound containing a methylene group α- to (bonded to the next carbon to) a carbony group (2).



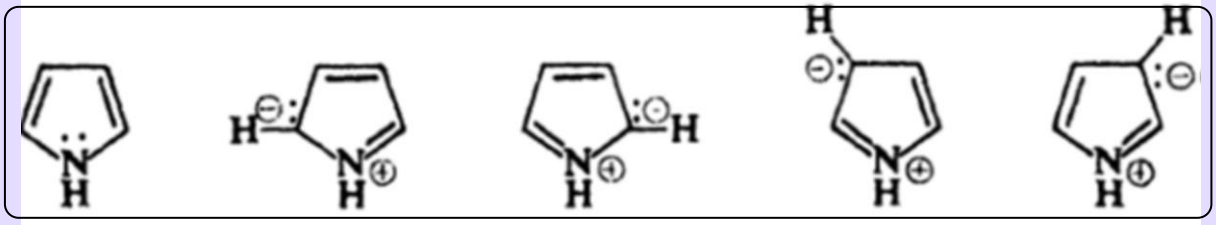
Properties-

Physical properties-

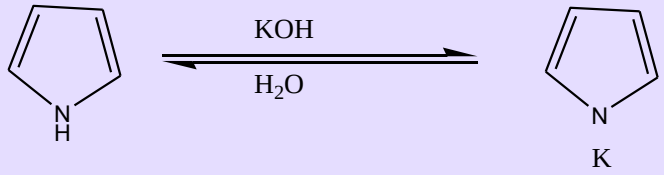
- colorless liquid
- B. P.-131^{0}C
- Slightly soluble in water. Soluble in organic solvent.
- It rapidly darkens on exposure to air.
- It vapors turn to red when moistened with HCl, hence name Pyrrole (Greek, *pyrros*-fiery red)

Chemical properties-

- Pyrrole is aromatic in nature as it follow Huckels rule (4n+2) π electrons.
- The grading of aromaticity is in the order of: furan< Pyrrole < thiophene< benzene, this order is consistent with the order of electronegativity values for oxygen (3.44), nitrogen (3.04) and thiophene (2.56).
- It behave as a resonance hybrid of flowing canonical forms-



- **<u>Basic character of pyrrole</u>-**
- From the resonating structure it is clear that two loan pair of electrons on nitrogen atom is not readily available for protonation and hence pyrrole behaves as a weak base (pK_b=13.6). **Pyrrole is much weaker base than pyridine?**
- The loan pair of electrons (responsible for the basic character) in pyrrole is involved in forming aromatic sextet whereas pyridine does not. That's why pyrrole is much weaker base than pyridine.
- **Acidic characters-**
- Presence of sec. amino group in pyrrole is weakly acidic in nature because it form potassium pyrrole on reaction with KOH.

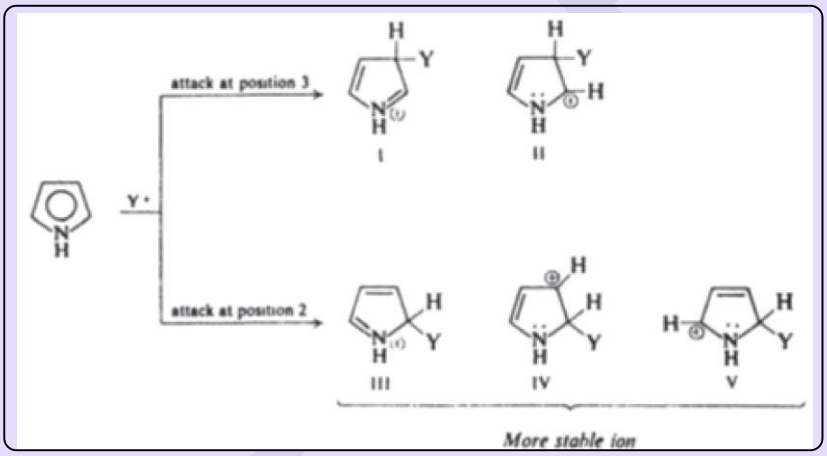


- Two reasons may explain the acidic behavior of pyrrole-
  1. Pyrrole is a resonance hybrid of five structure, four of which exhibit a positive charge on nitrogen which helps in the release of proton.
  2. The pyrrole anion formed by the deprotonation of pyrrole is resonance stabilized.

ELECTROPHILIC SUBSTITUTION REACTION

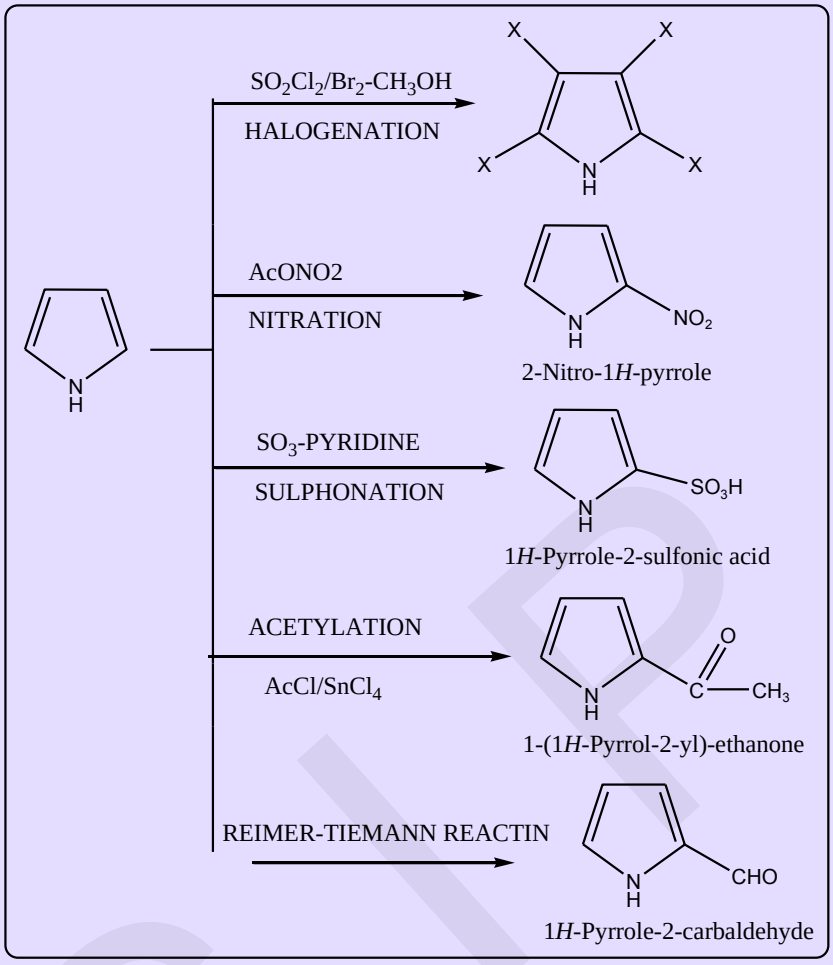
- Pyrrole is more reactive than benzene towards electrophilic substitution reaction as it contains the electron withdrawing nitrogen atom.

Orientation of substitution in pyrrole-

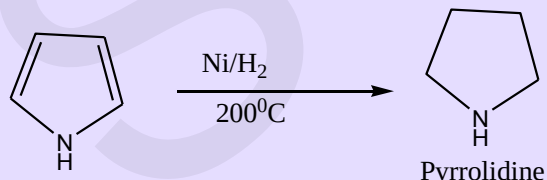


- Thus attack at position-2 is have greater no. of resonating structure (greater stability) as compare to attack at potion-3.
- So from the above discussion it is clear that reaction at two position is favored for electrophilic substitution reaction.

Important electrophilic substitution reaction of pyrrole



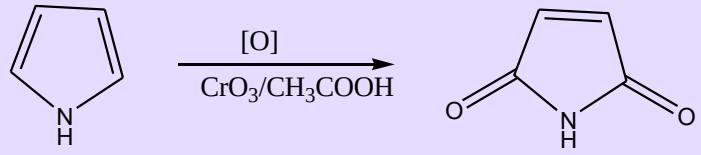
Reduction:



1*H*-Pyrrole

Pyrrolidine
(10^{11} time more basic than pyyrole)

Oxidation:

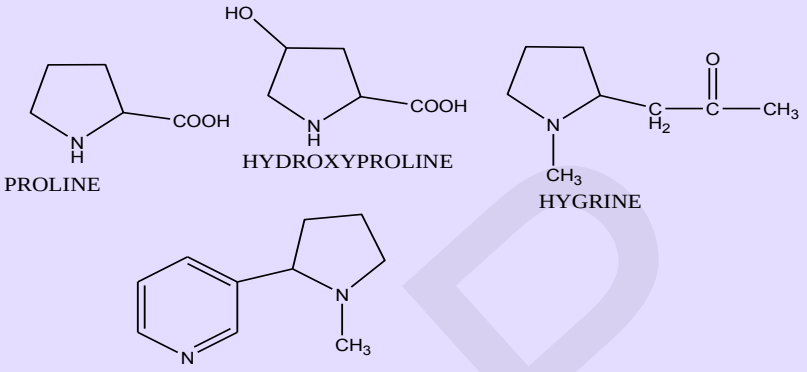


1*H*-Pyrrole

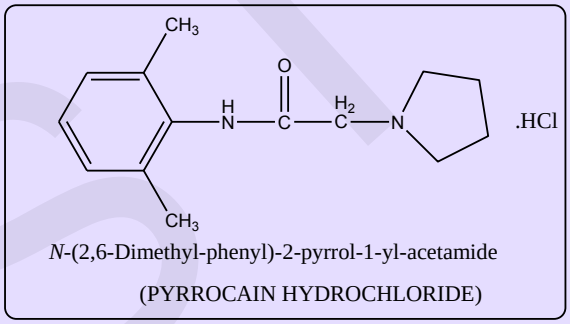
Pyrrole-2,5-dione

P'CEUTICAL IMPORTANCE OF PYRROLE

1. Pyrrole and its hydrogenated compound (pyrrolidine) are found to be fundamental nucleus of various important natural product.
   - Eg.- Haemin, vitamin $B_{12,}$ etc.
   - Pyrrolidine nucleus is present in two essential amino acid Proline and hydroxyproline.
   - Alkaloid-Hygrine and Nicotine



2. **Pyrrocain hydrochloride**-it is pyrrolidine derivative and used intravenously for jaundice, for pain of burns and arthritis.

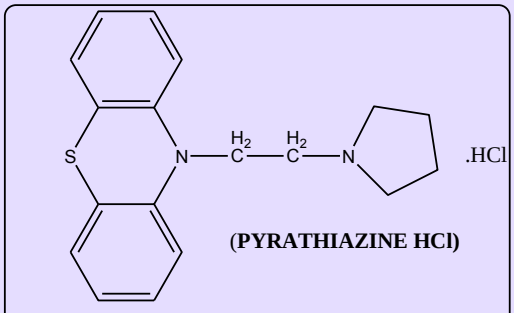


N-(2,6-Dimethyl-phenyl)-2-pyrrol-1-yl-acetamide

(PYRROCAIN HYDROCHLORIDE)

3. **Pyrathiazine HCl-**

- It is Pyrrolidine and Phenothiazine derivative.
- It is long acting drug and used in relieving of **vasomotor rhinitis, Urticaria and Bronchial asthma**.

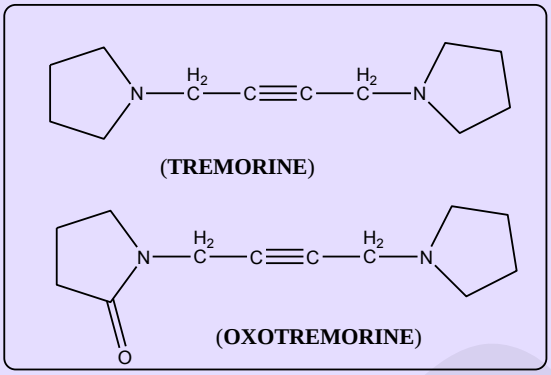


(**PYRATHIAZINE HCl)**

10-(2-Pyrrolidin-1-yl-ethyl)-10*H*-phenothiazine

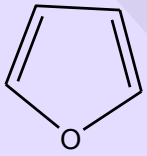
4. **TREMORINE AND OXOTREMORINE-**

- It is pyrrolidine derivative. Used in increasing acetylcholine level in rat up to 40% in treatment of **Parkinsonism (Paralysis agitants**).



5. **ROLITETERACYCLINE (Prodrug of tetracycline)**-It is pyrrolidine derivative and used as antibiotics in form of IM and IV injection.
6. **LINCOMYCINE HCl**- It is pyrrolidine derivative and used in the treatment of bacterial infection.
7. **CLINDAMYCINE HCl-** It is pyrrolidine derivative and used in the treatments of upper respiratory, skin and tissue infection.

FURAN (Oxacyclopenta-2, 4-diene)



Furan

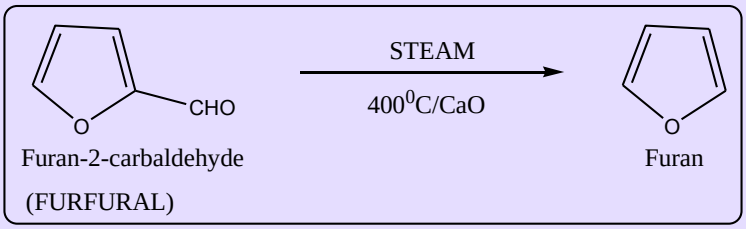
Chemistry-

- **Furan** is a heterocyclic organic compound, consisting of a five-membered aromatic ring with four carbon atoms and one oxygen.
- Furan is a colorless, flammable, highly volatile liquid with a boiling point close to room temperature.
- It is soluble in common organic solvents, including alcohol, ether and acetone, but is slightly soluble in water.
- It is toxic and may be carcinogenic.
- Furan is aromatic because one of the lone pairs of electrons on the oxygen atom is delocalized into the ring, creating a 4n+2 aromatic system (Huckels rule) similar to benzene.
- Because of the aromaticity, the molecule is flat and lacks discrete double bonds.

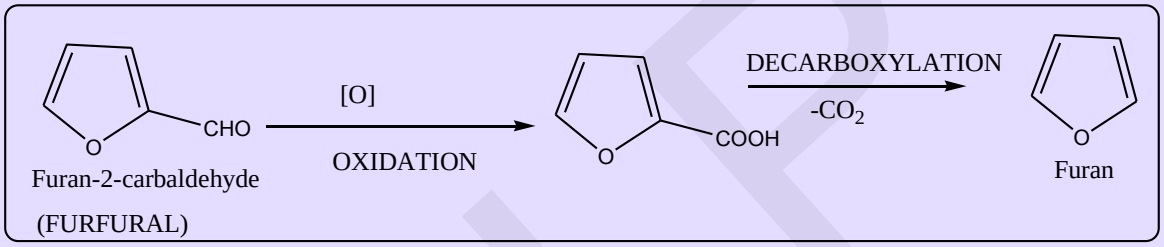
- The other lone pair of electrons of the oxygen atom extends in the plane of the flat ring system.

Method of Preparation-

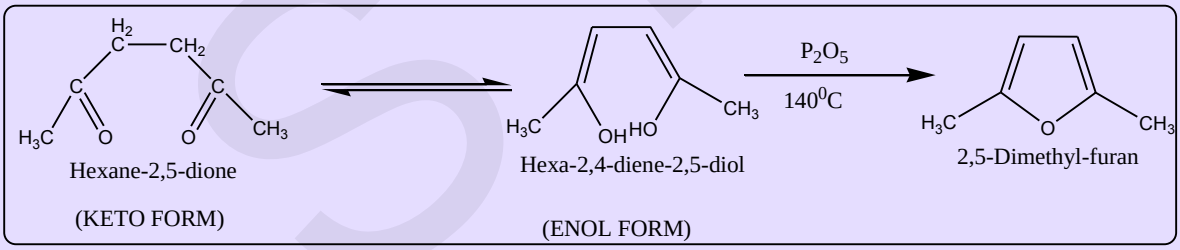
1. **By catalytic decomposition of Furfural.**



2. **By oxidation of furfural followed by decarboxylation.**

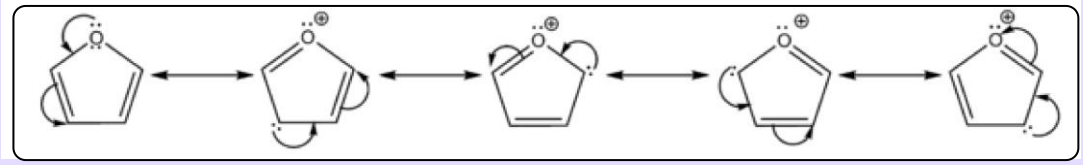


3. **Paal-Knorr Synthesis of Furan-**
   - This method used for preparation of furan derivative.
   - It is prepared by dehydration of enol form of 1, 4-diketone.



CHEMICAL PROPERTIES-

- Furan is aromatic because one of the lone pairs of electrons on the oxygen atom is delocalized into the ring, creating a 4n+2 aromatic system (Huckels rule) similar to benzene.
- It is considerably more reactive than benzene in electrophilic substitution reactions, due to the electron-donating effects of the oxygen heteroatom.
- Examination of the resonance contributors shows the increased electron density of the ring, leading to increased rates of electrophilic substitution.

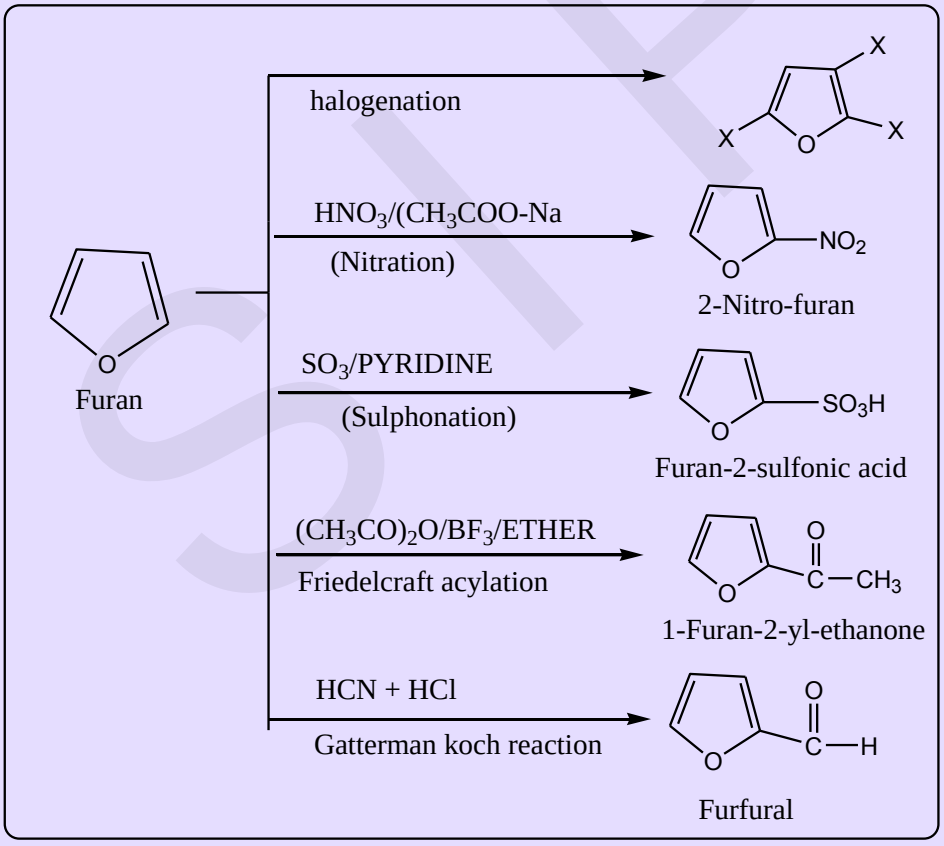


- It behaves both as diene and an aromatic compound.
- Furan is **less reactive than pyrrole** because it accommodates positive charge less readily than nitrogen pyrrole.

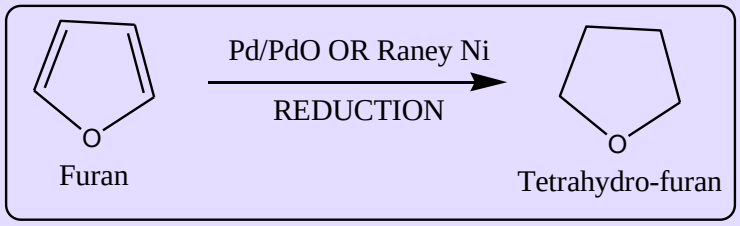
REACTION-

1. Electrophilic Substitution Reaction of Furan

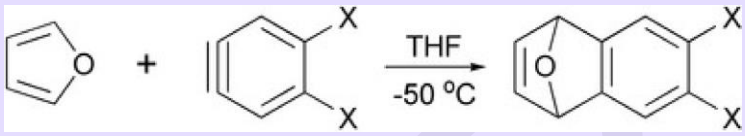
- Substitution occurs preferentially at position-2 than at position-3, the reason being explained as pyrrole.



2. **Reduction-** On reduction of furan it give furfural.



3. **Diels-Alder reaction of furan-**
   - Diels-Alder reaction of furan with arynes provides corresponding derivatives of dihydro-naphthalenes which are useful intermediates in synthesis of other polycyclic aromatic compounds.

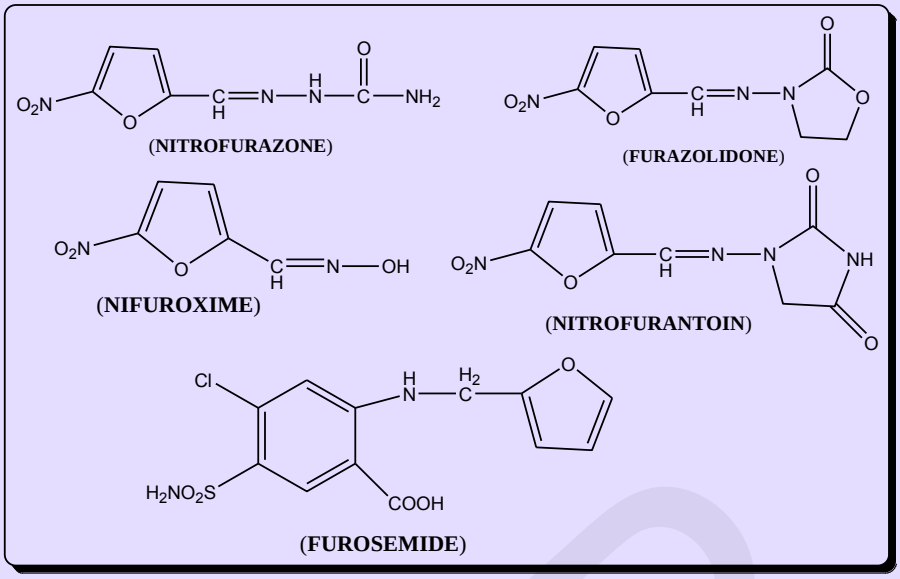


FURAN ARYNES DERIVATIVE dihydronaphthalenes

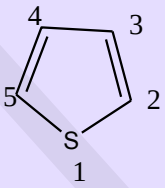
P'CEUTICAL IMPORTANCE OF FURAN

- Different nitro furan derivative and some other compound containing furan ring in their structure are widely used in medicinal compound.

1. **NITROFURAZONE**
   - It is available in form of its solution, ointment and suppositories.
   - Nitrofurazone have good bacteriostatic and bactericidal properties.
   - It is also used in burns, ulcer, wound and some skin disease.
2. **Furazolidone**
   - It is used orally in the treatment of **bacterial diarrheal disorder** and **enteritis**.
3. **Nifuroxime**
   - It is used in combination with Furazolidone under the name Tricofuran.
   - Used in vaginal infection caused by *Candida abicans or Trichomonas vaginalis*
4. **Nitrofurantoin**
   - Nitrofurantoin used orally for the treatment of UTI (urinary tract infection).
5. **Furosemide**
   - Furosemide is a diuretics.
   - It inhibit the reabsorption sodium, potassium etc. through the renal tubules.



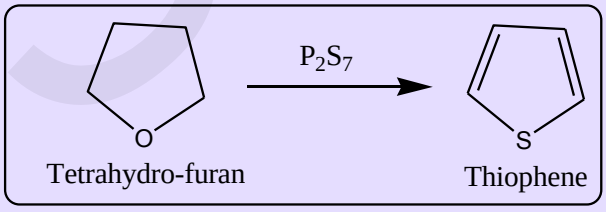
THIOPHENE



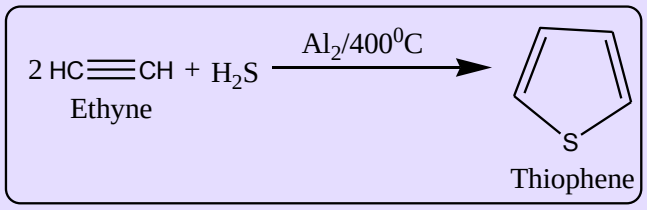
Thiophene

PREPARATIO-

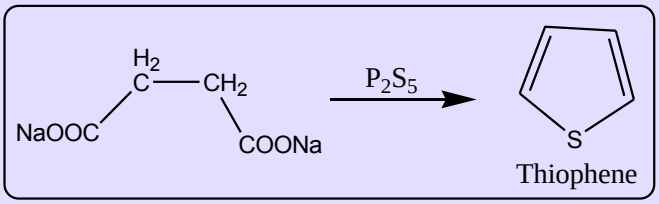
1. From coal tar.
2. Treatment of furan with P_4S_7 (tetra phosphorus heptasulphide)



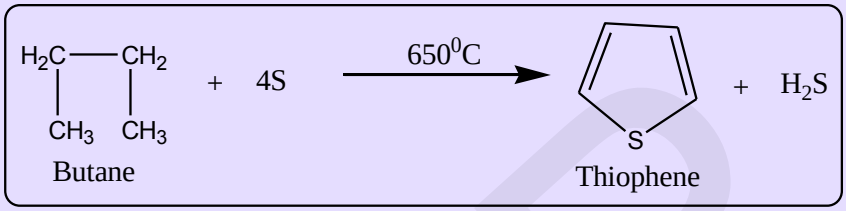
3. **Commercial methods**-passing a mixture of acetylene and H2S over alumina at about 400^0C.



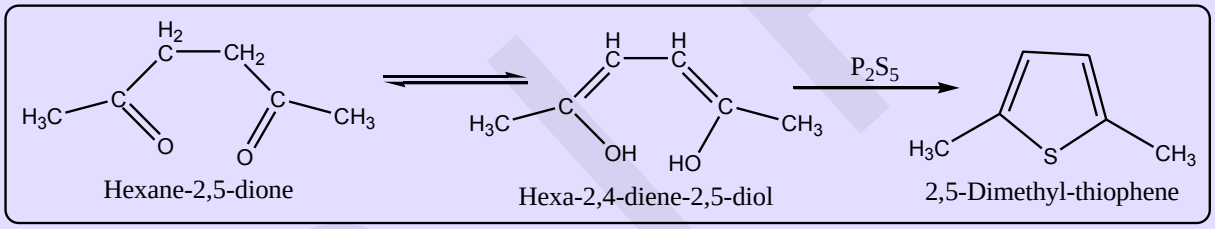
4. **Laboratory methods**- thiophene obtain by treatment sodium succinate with P_4S_7.



5. **Industrial methods**- thiophene is obtained by the reaction with n-butane and sulphur at about 650^0C.



6. **Paal knor synthesis**- 1, 4-diketone is treated with P_2O_5 to give thiophene.



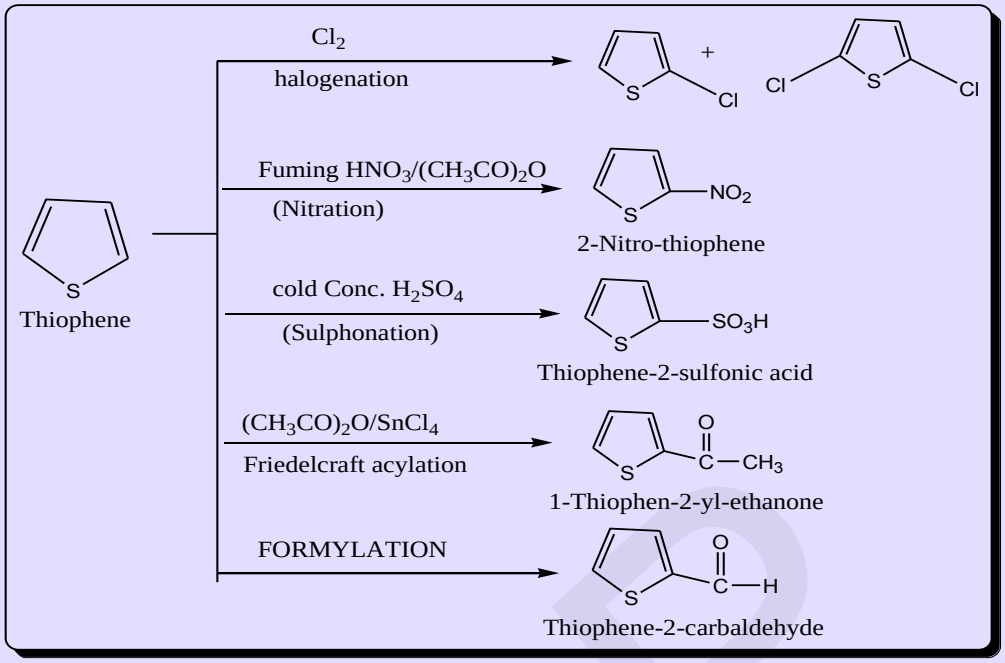
Physical and chemical properties-

- Colorless liquid, B. P. 84^0C , Inflammable
- Toxic in nature

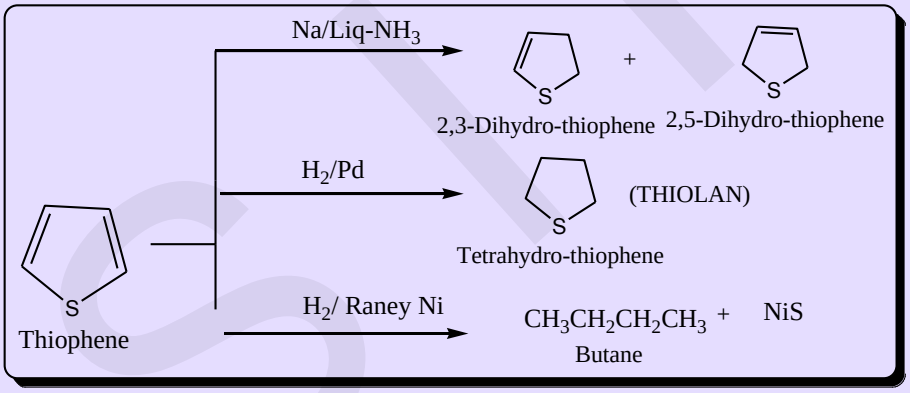
Chemical properties-

- Thiophene is aromatic in nature follow huckels rule (4n+2) π electrons.
- S is less electronegative than O & N
- It have vacant d-orbital and utilization of its vacant d-orbitals a greater no of resonating hybrid structure is possible for thiophene.

IMPORTANT REACTION OF THIOPHENE

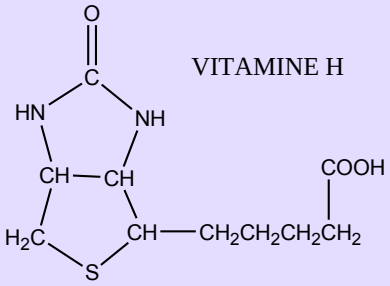


REDUCTION-



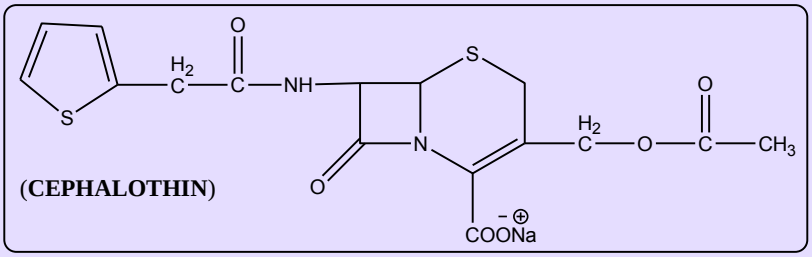
P'CEUTICAL IMPORTANCE OF THIOPHENE

- β-Biotin (Vitamin H) is the only important natural compound is containing thiophene.

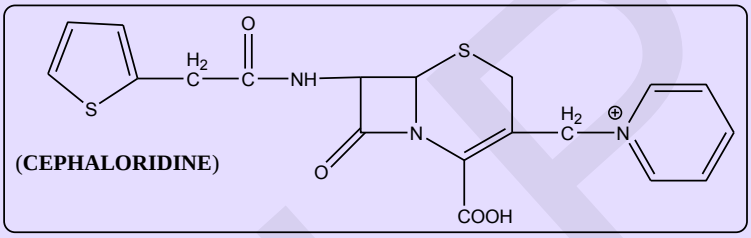


Some pharmaceuticals drugs which contain thiophene ring-

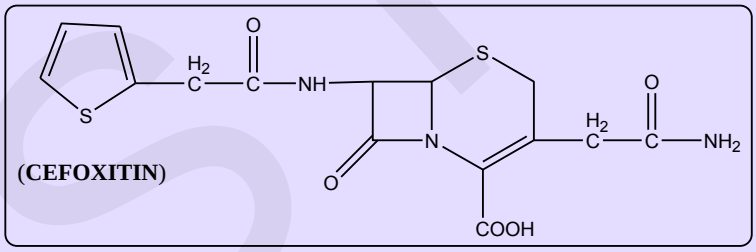
1. **CHEPHALOTHIN SODIUM-**
   - It is thiophene derivative.
   - It is used as antibacterial.



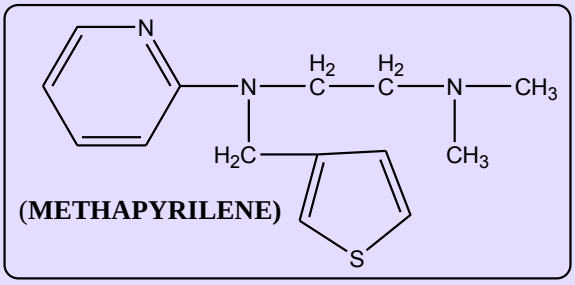
2. **CEPHALORIDINE-**
   - It is used as i.m. Injection (reconstituted) for the treatment of infection.



3. **CEFOXITIN-**
   - It is semi synthetic derivative of cephamycin and used as anti-bacterial.

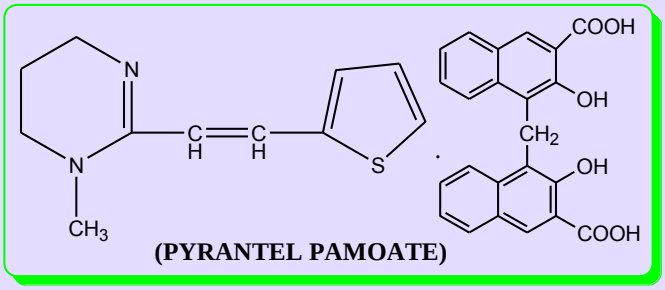


4. **METHAPYRILENE-**
   - It used in treatment of allergies, hay fever, allergic rhinitis, acute and chronic Urticaria, allergic dermatitis and asthma.



5. **PYRANTEL PAMOATE-**
   - It is used again pinworm and round worm infection.

- It act as anti-helminthic.

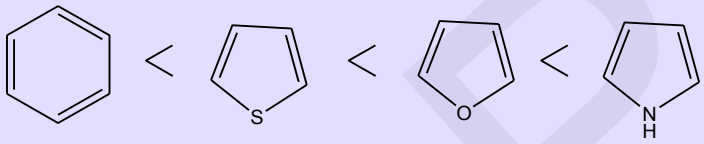


(PYRANTEL PAMOATE)

REACTIVITY COMPARISON OF HETEROCYCLIC COMPOUN WITH BENZENE

- The increasing order of reactivity of these compound is-

Benzene < thiophene < furan < pyrrole



- Greater reactivity of heterocyclic compound with reference to (w.r.t.) benzene is due to the presence of electron withdrawing hetero atom.
- Furan is more reactive than thiophene because +M effect of oxygen is greater than sulphur.
- While lesser reactivity of furan w.r.t. pyrrole is due to greater electronegativity of oxygen, due to which it can accommodate the positive change less readily than nitrogen.

COMPARISON OF THE AROMATIC CHARACTER OF PYRROLE, FURAN AND THIOPHENE

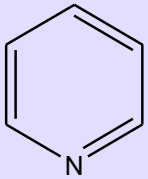
- The order of decreasing aromatic character of these three compound is-

Thiophene > Pyrrole > Furan

- The relative ease of reduction of the heterocyclic is-

Pyrrole > Furan > Thiophene > Benzene

PYRIDINE (AZABENZENE OR AZINE)

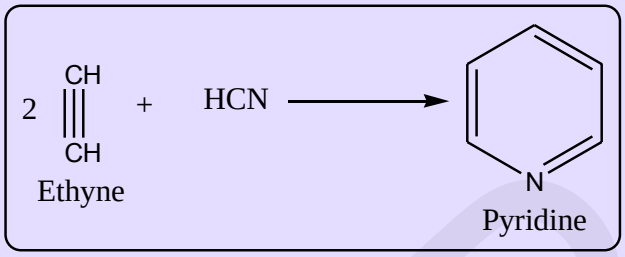


Pyridine

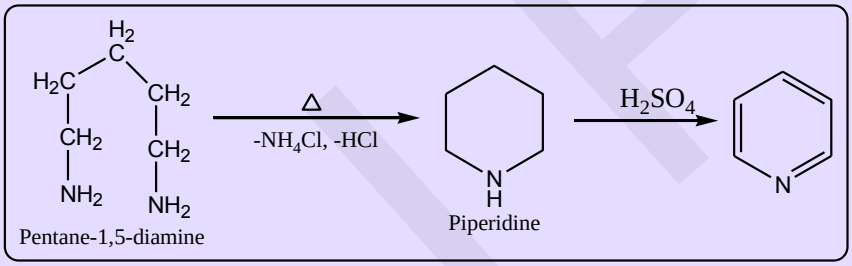
- **I**n this compound one of the methane (=CH-) group of benzene is replaced by nitrogen (=N-).
- Pyridine occurs in natural product e. g- alkaloid, vitamins, nucleotide etc.

PREPARATION OF PYRIDINE-

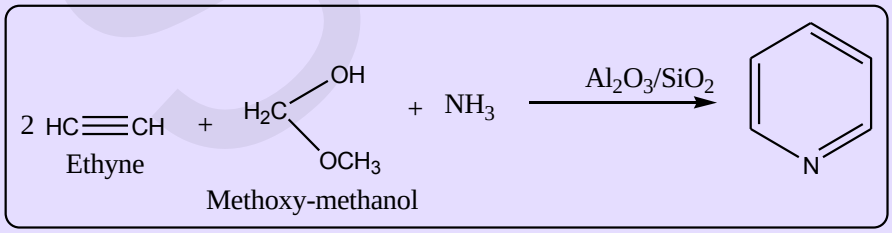
1. From Coal Tar
2. By passing a mixture of acetylene and HCN through a red hot tube.



3. By heating the pentamethylene diamine hydrochloride followed by oxidation.

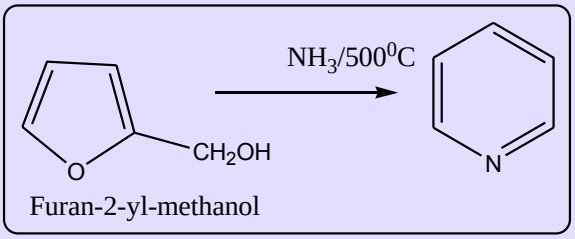


4. **Commercial method-**
   - Passing a mixture of acetylene formaldehyde hemi methyl and ammonia over alumina silica catalyst at 500^0C.

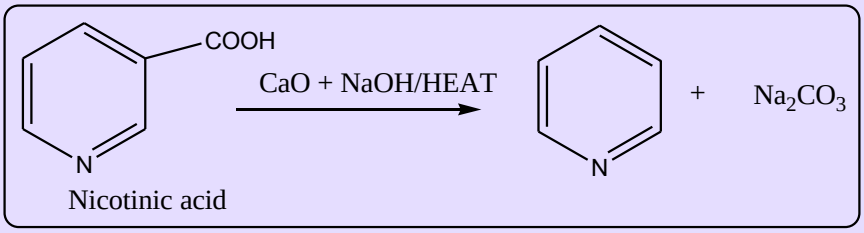


5. **Industrial method-**

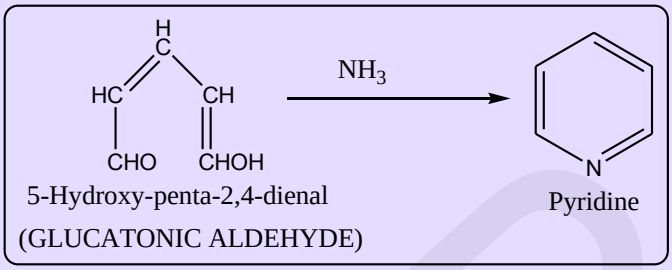
- Pyridine is obtained by heating tetrahydrofurfuryl alcohol with ammonia at about 500^0C.



6. **Lab methods-**



7. Reaction of glucatonic aldehyde and ammonia.

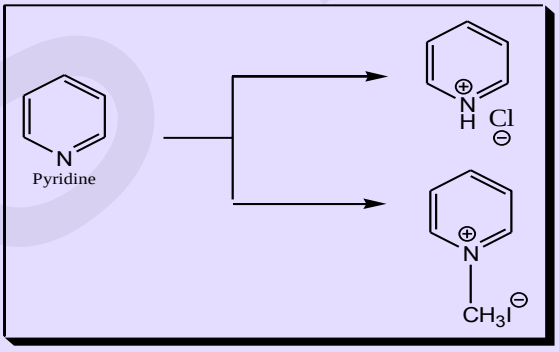


CHEMICAL PROPERTIES-

- Pyridine is aromatic in nature because it follow huckels rule (4n+2) π electron.
- It is resonance hybrid.
- Electrophilic substitution at position-3 is **more stable** as compare to position-2 and 4.

BASIC PROPERTIES OF PYRIDINE

- Pyridine is basic in nature due to the presence of lone pair of electron on nitrogen atom and form the salt with acid.



Pyridine is stronger base than pyrrole. Why?

- Because of the lone pair of electron in pyrrole is involved in forming the sextet, making it aromatic and is also involve in resonance,
- While in pyridine, lone pair of electron is involve in resonance but is not utilized in sextet formation.
- Thus, in pyridine the lone pair of electron is available for donation, which contribute to its more basicity than pyrrole.

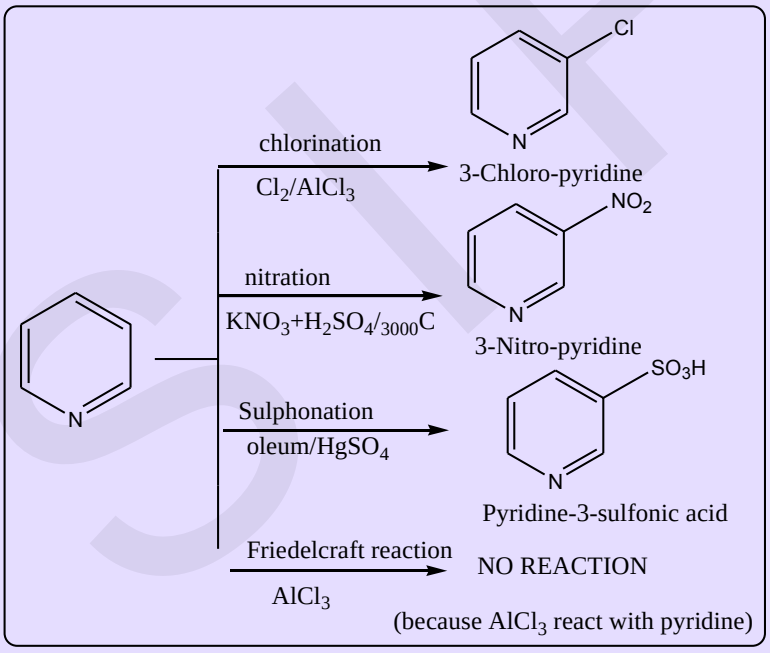
Pyridine is much weaker base than aliphatic amine. Why?

- Because the lone pair of electron in pyridine is involved in resonance which is not possible in aliphatic amine.
- In pyridine electron present in sp^2 orbital, while it is in sp^3 orbital in aliphatic amine, so due to more s character, sp2 orbital is more tightly held and less available for donation in pyridine.
- The order of basicity may be expressed as-

Aliphatic amine > pyridine > pyrrole

ELECTROPHILIC SUBSTITUTION REACTION (ESR)

- Pyridine is less reactive towards electrophilic substitution reaction than benzene due to more electronegative N atom in pyridine, which decrease the electron density in the ring and deactivating it towards ESR.
- ESR in pyridine may be take place at position2 or 3 or 4 but position-3 yield comparatively more stable structure.



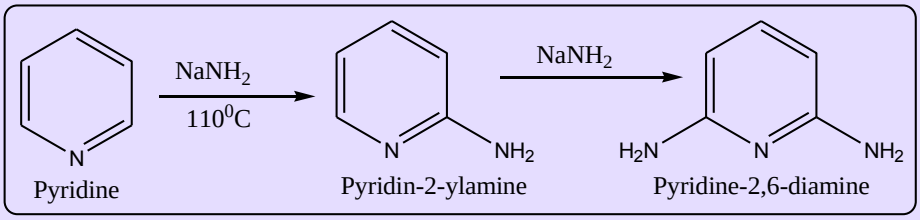
NUCLEOPHILIC SUBSTITUTION REACTION (NSR)

- The electron deficient nature of the 2 and 4 position of pyridine makes these position very reactive towards nucleophilic reagent.

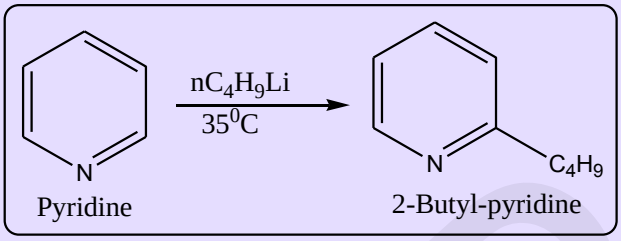
1. Important NSR of pyridine-

i. Chichibabin reaction-

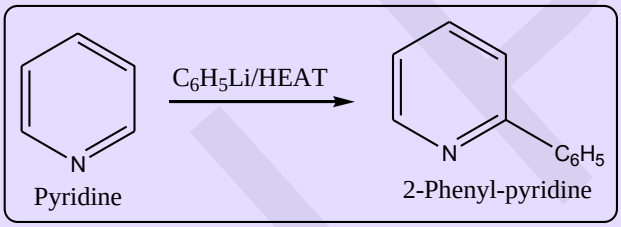
- In toluene solution, pyridine react with sodamide to give 2-aminopyridine.
- Excess of sodamide produce 2, 6-diamine pyridine.



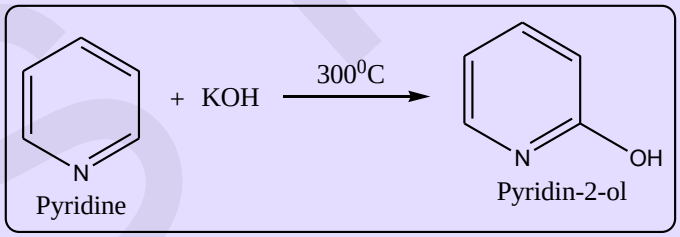
ii. Alkylation-



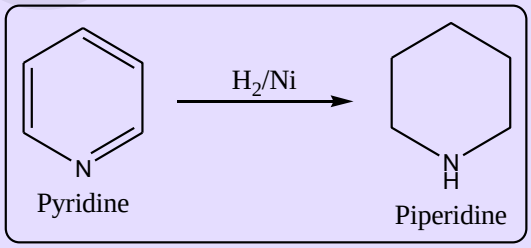
iii. Arylation-



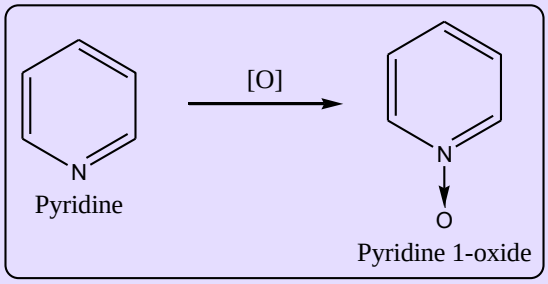
iv. With KOH-



2. REDUCTION-



3. OXIDATION-

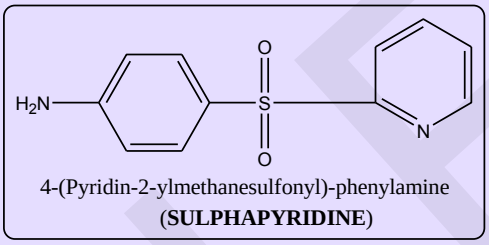


PHARMACEUTICAL IMPORTANCE OF PYRIDINE

Derivative of pyridine used in pharmacy are-

1. SULPHAPYRIDINE-

- It mainly used in treatment of dermatitis and Pneumonia.

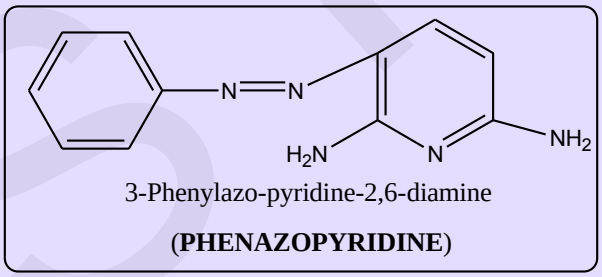


4-(Pyridin-2-ylmethanesulfonyl)-phenylamine

(**SULPHAPYRIDINE**)

2. PHENAZOPYRIDINE-

- It used as urinary antiseptic.

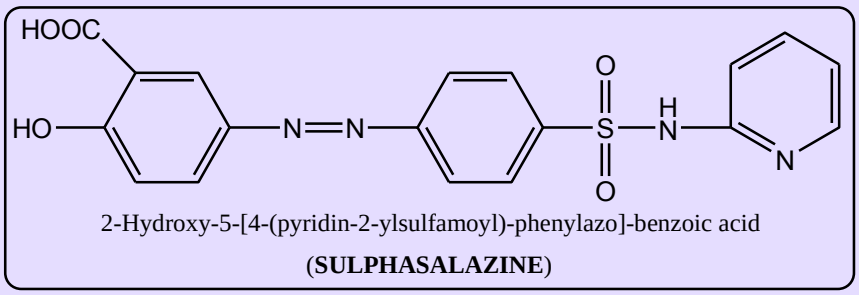


3-Phenylazo-pyridine-2,6-diamine

(**PHENAZOPYRIDINE**)

3. SULPHASALAZINE-

- It is used in chronic ulcerative colitis.
- It is a mutual Prodrug (after metabolism it give two active compound, 5-aminosalicylic acid and sulphapyridine)

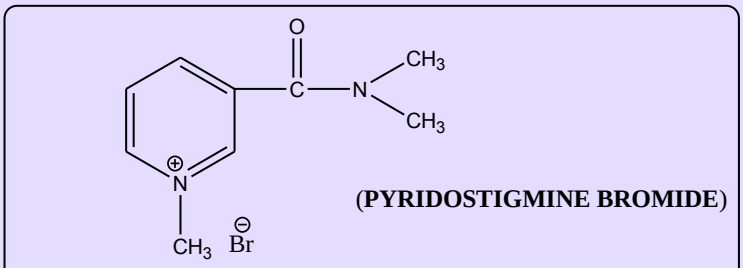


2-Hydroxy-5-[4-(pyridin-2-ylsulfamoyl)-phenylazo]-benzoic acid

(**SULPHASALAZINE**)

4. PYRIDOSTIGMINE BROMIDE-

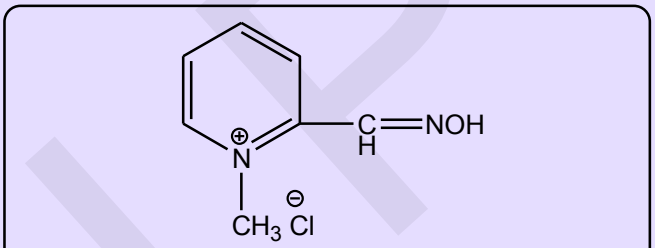
- It is used in treatment of myasthenia gravis (an autoimmune neuromuscular disease leading to fluctuating muscle weakness and fatigue)



(**PYRIDOSTIGMINE BROMIDE**)

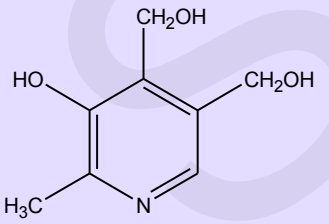
3-Dimethylcarbamoyl-1-methyl-pyridinium; bromide

5. PRALIDOXIME CHLORIDE

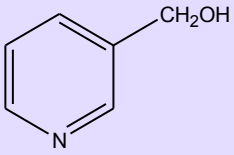


2-(Hydroxyimino-methyl)-1-methyl-pyridinium; chloride

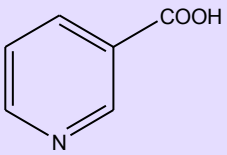
[**PRALIDOXIME CHLORIDE**]



(**PYRIDOXINE, Vit-B6)**

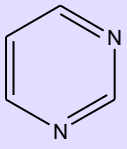


Pyridin-3-yl-methanol (**NICOTINYL ALCOHAL**)

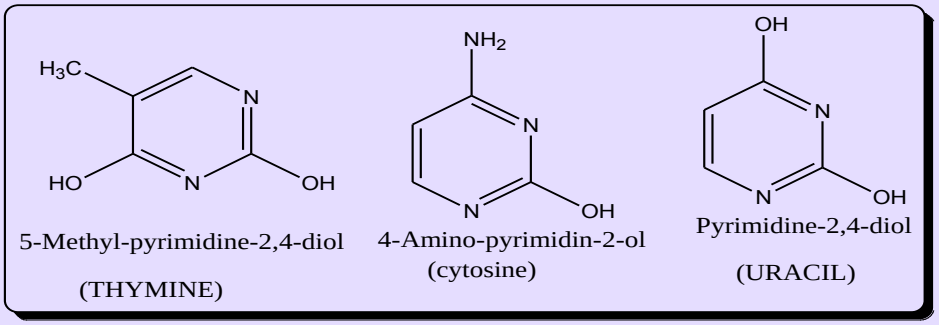


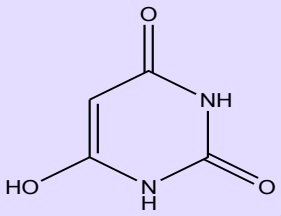
Nicotinic acid (**NIACIN**)

PYRIMIDINE (1, 3-DIAZINE)



- Pyrimidine nucleus is found in purines, nucleic acid and synthetic barbiturates.
- Four pyrimidine are found in nucleic acid.



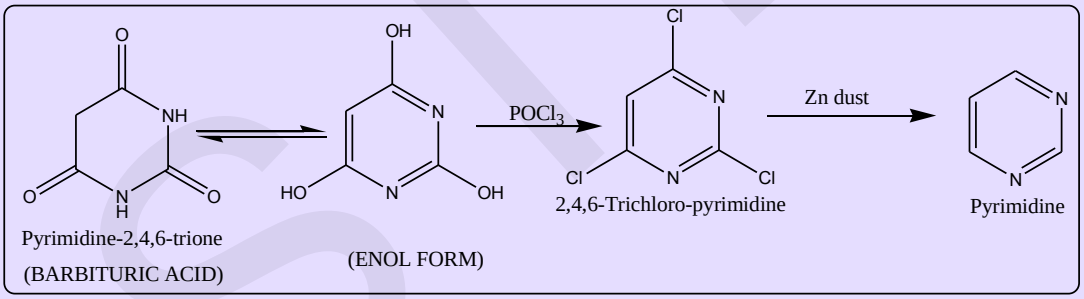


(**BARBITURIC ACID**)

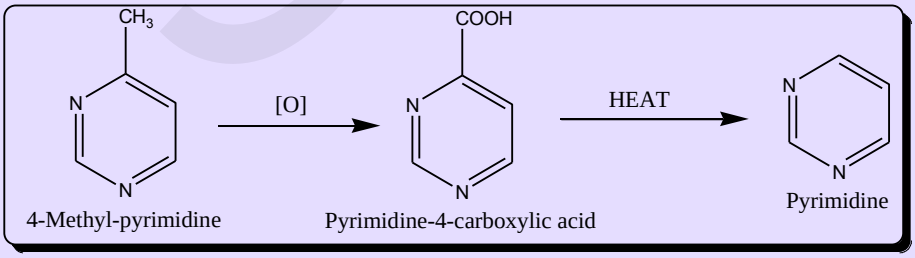
METHODS OF PREPARATION-

1. Gabriel method-

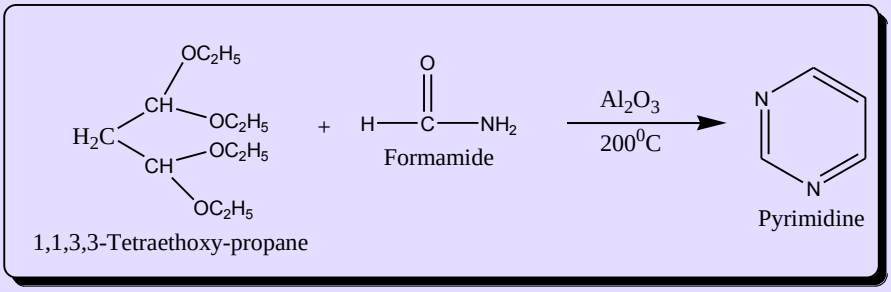
- Treating Barbituric acid with $POCl_3$ and then treating the halogenated product with Zn dust.



2. Oxidation and further decarboxylation of alkyl pyridine.

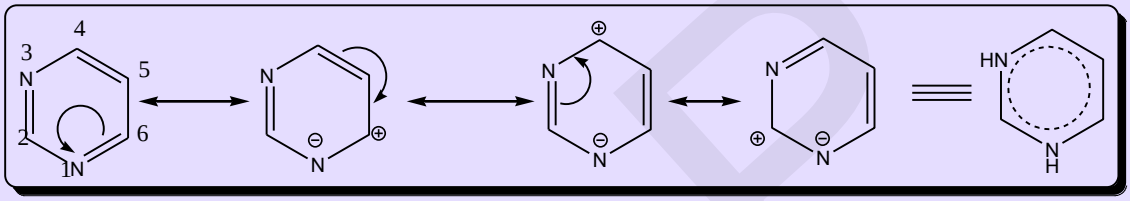


3. Reaction of 1, 1, 3, 3-Tetraethoxy Propane and Formamide.



PROPERTIES-

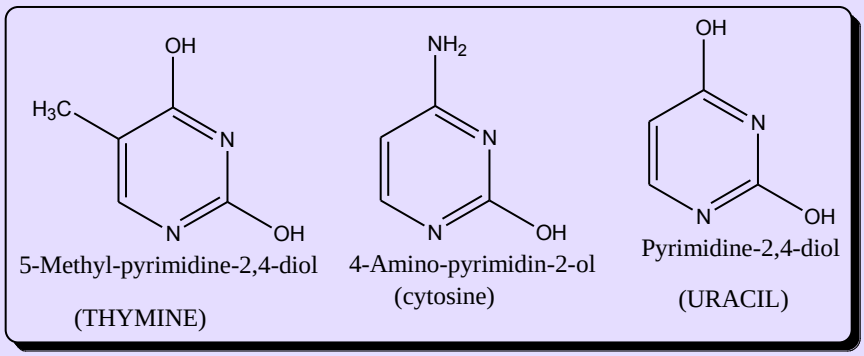
- Pyrimidine is neutral in solution but forms salt with acid.
- It is deactivated towards electrophilic substitution reaction but it undergoes nucleophilic substitution reaction.



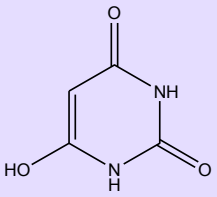
- From above resonating structure the position-5 has high electron density so electrophilic substitution reaction occurs at 5th position.
- Nucleophilic substitution occurs at position 2, 4 & 6.
- The introduction of –OH or NH_2 group at position 2, 4 & 6, reduced the aromatic properties of the compound.
- Pyrimidine undergoes electrophilic substitution if an electron releasing group (-OH, -NH_2) is present in the 2, 4, 6 position.

P'CEUTICAL IMPORTANCE OF PYRIMIDINE

- Uracil, Thymine and cytosine have the pyrimidine ring which is constituent of Nucleic acid.
- Nucleic acid is essential constituent of all cells.
- Uracil is present only in RNA.



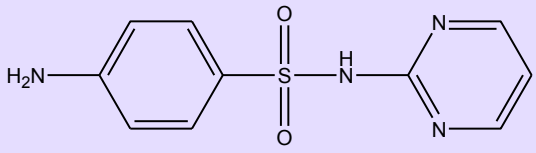
- Pyrimidine ring also found in VitamineB1 and Barbituric acid.



(**BARBITURIC ACID**)

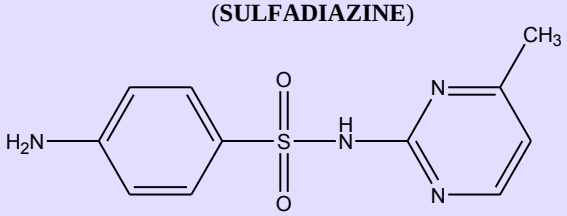
- **Pyrimidine nucleus is also found in some drugs of pharmaceutical importance-**

1. **Sulfadiazine**
   - It is Pyrimidine derivative.
   - Sulfadiazine is widely used in a number of infection including H. influenza, Pneumococcal infection.
2. **Sulfamerazine**
   - It is Pyrimidine derivative.
   - It used in treatment of infection.
   - It have slightly bitter taste
   - Less potent than sulfadiazine
3. **Silver sulfadiazine-**
   - It is Pyrimidine derivative.
   - It is an effective topical anti-microbial agent especially against pseudomonas species.
   - It also used in burn therapy.
4. **Pyrimethamine-**
   - It is Pyrimidine derivative.
   - It used as anti-malarial.



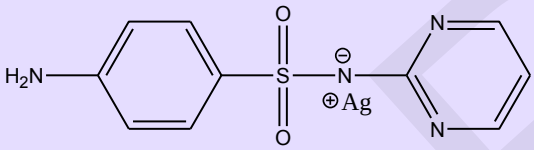
4-Amino-*N*-pyrimidin-2-yl-benzenesulfonamide

(**SULFADIAZINE**)

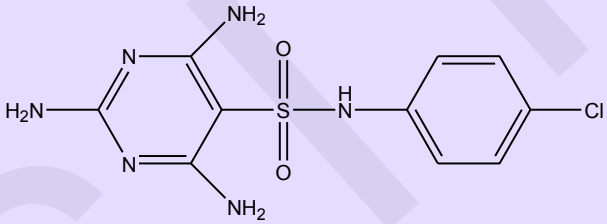


4-Amino-*N*-(4-methyl-pyrimidin-2-yl)-benzenesulfonamide

(**SULPHAMERAZINE**)



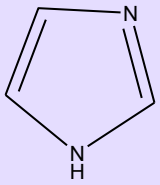
(**SILVER SULFADIAZINE**)



2,4,6-Triamino-pyrimidine-5-sulfonic acid (4-chloro-phenyl)-amide

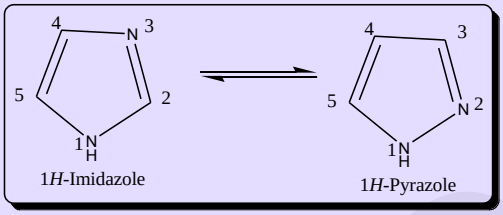
(**PYRIMETHAMINE**)

IMIDAZOLE (Glyoxalin OR Iminazole)



1*H*-Imidazole

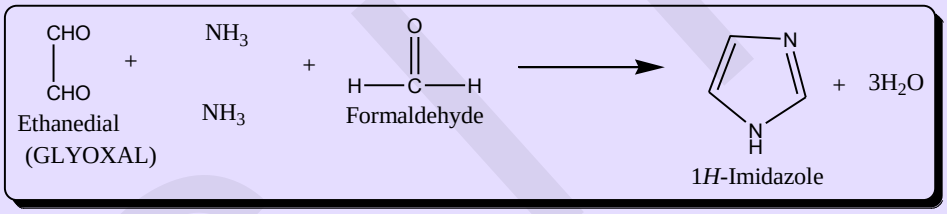
1. Imidazole is isomeric with Pyrazole.



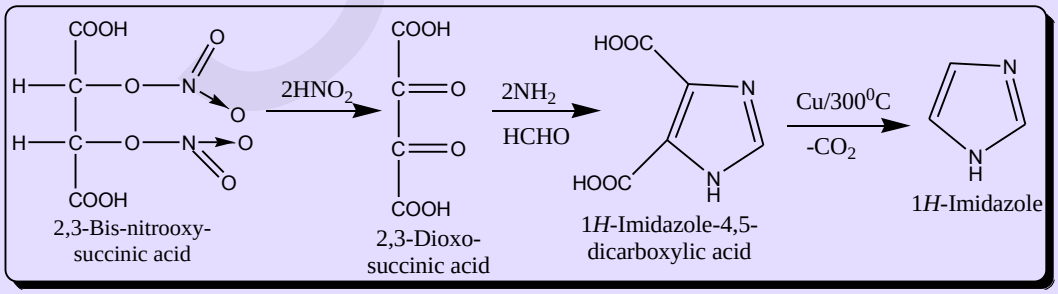
2. It occur in Purine and Histidine.

METHODS OF PREPARATION

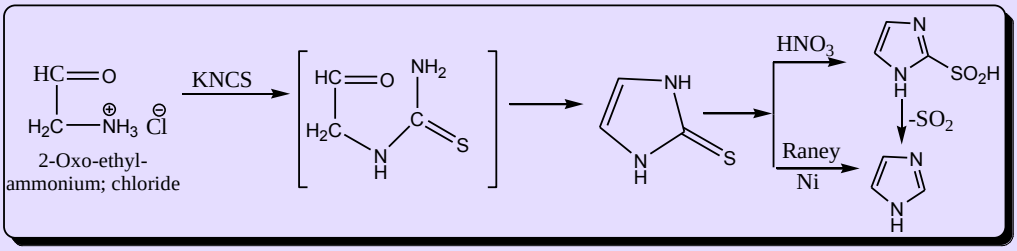
1. By the action of ammonia and Glyoxal and Formaldehyde.



2. Action of ammonia on a mixture of Formaldehyde and di-nitro tartaric acid followed by decarboxylation.

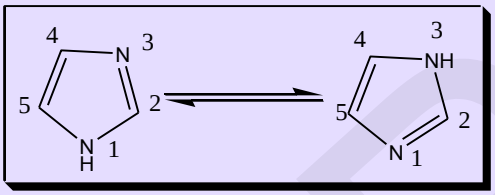


3. Action of Potassium Isothiocynate on hydrochloride of α-amino aldehyde or ketone followed by desulphurisation with Raney Ni or oxidation.

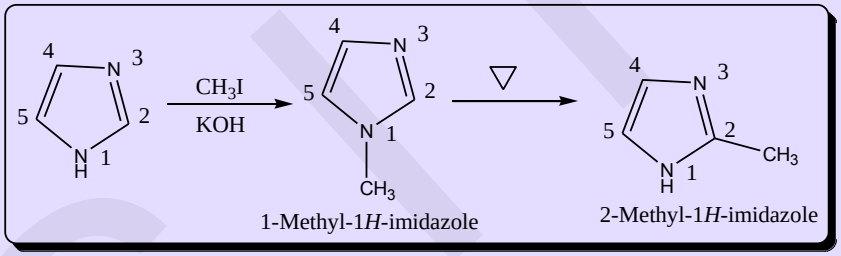


Properties-

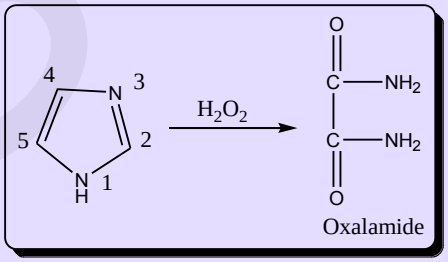
1. It is a weak base, but more basic than Pyrazole.
2. It exist in two tautomeric forms having 4 and 5 position equivalent.



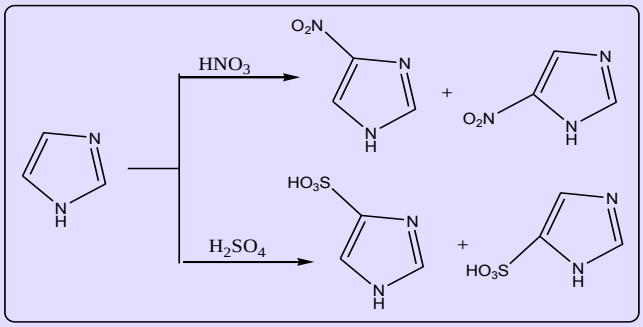
3. On treatment with methyl iodide it give 1-methyl imidazole which isomerised to 2-methyl imidazole on heating.



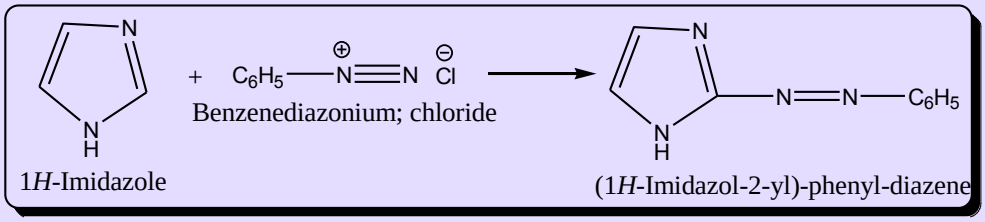
4. **Reaction with H_2O_2, ring to open to give oxalamide.**



5. **Nitration and sulphonation-**



6. On diazotization, coupling occurs at position-2



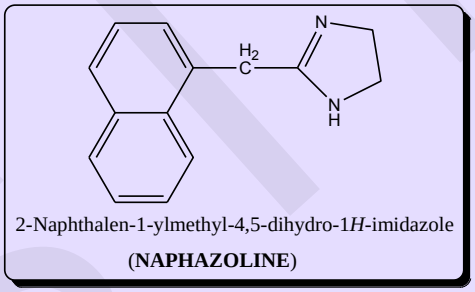
PHARMACEUTICAL IMPORTANCE OF IMIDAZOLE

- Imidazole nucleus is found in many biologically active compound like as-Purines, Histamine, alkaloids, amino acid and Histidine.

Imidazole nucleus is found in many pharmaceutical drugs.

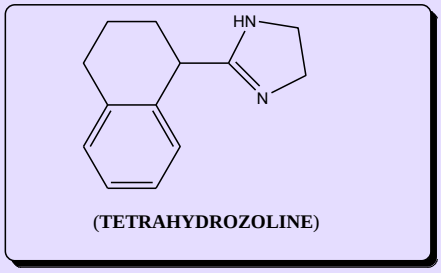
1. NAPHAZOLINE-

- It is potent vasoconstrictor and used in the treatment of disorder of upper respiratory tract (nasal drops)
- Naphazoline is a bitter, soluble in water and alcohol.



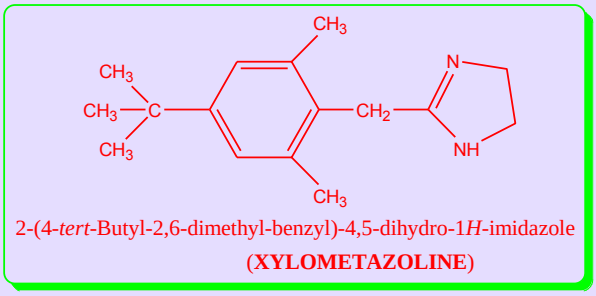
2. Tetrahydrozoline-

- It is imidazole derivative.
- It applied topically to nasal mucosa.
- It causes vasoconstriction, resulting in reduction of local swelling and congestion.



3. Xylometazoline-

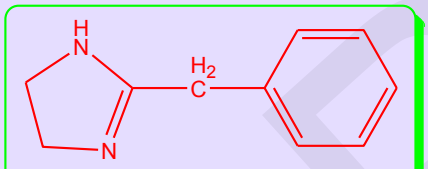
- It also used as nasal vasoconstrictor.
- It have high duration of action



2-(4-*tert*-Butyl-2,6-dimethyl-benzyl)-4,5-dihydro-1*H*-imidazole

(**XYLOMETAZOLINE**)

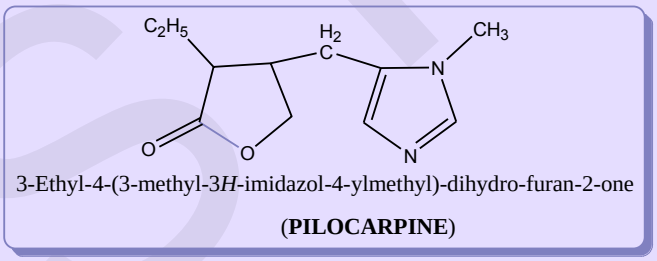
4. **Tolazoline-**
5. It used in the treatment of peripheral vascular disorder eg. Arteriosclerosis (Thickening, hardening and loss of elasticity of the walls of arteries).



2-Benzyl-4,5-dihydro-1*H*-imidazole

(**TOLAZOLINE**)

6. **PHENTOLAMINE-**
   It Used as Anti Adrenergic.
7. **PILOCARPINE-**



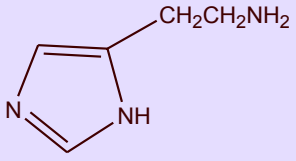
3-Ethyl-4-(3-methyl-3*H*-imidazol-4-ylmethyl)-dihydro-furan-2-one

(**PILOCARPINE**)

- It used in treatment of glaucoma.
- This is alkaloid obtain from the dried leaflet of *Pilocarpus microphyllus.*
- It helps in production of sweating, salivation and gastric secretion.

8. **Histamine-**

It has a stimulating action on certain excretory glands eg. Lacrimal and nasal secretion glands.

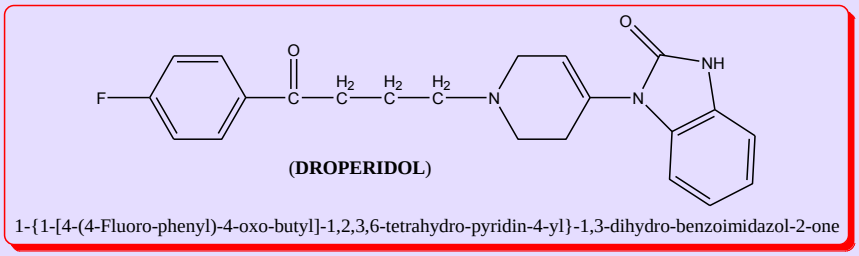


2-(3*H*-Imidazol-4-yl)-ethylamine

(**HISTAMINE**)

DROPERIDOL-

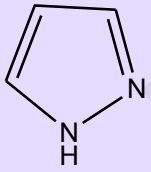
It is used as anti-psychotics and antiemetic agent.



(**DROPERIDOL**)

1-{1-[4-(4-Fluoro-phenyl)-4-oxo-butyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1,3-dihydro-benzoimidazol-2-one

PYRAZOLE

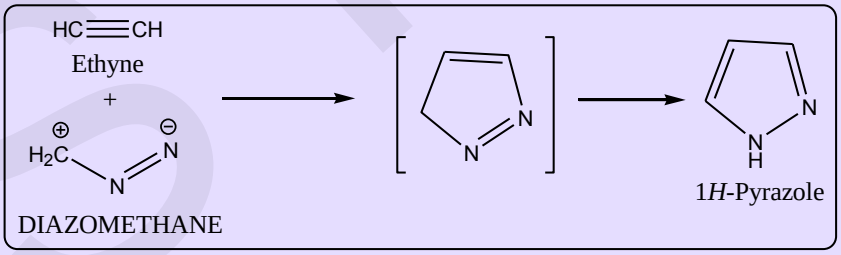


1*H*-Pyrazole

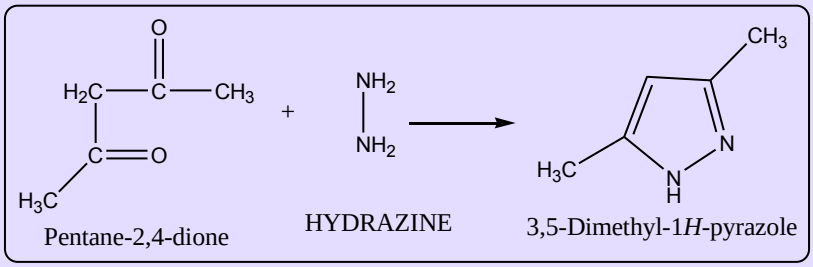
PREPARATION-

1. **Von Pechmann methods-**

- Pyrazole was prepared by passing acetylene into a cold ethereal solution of diazomethane.

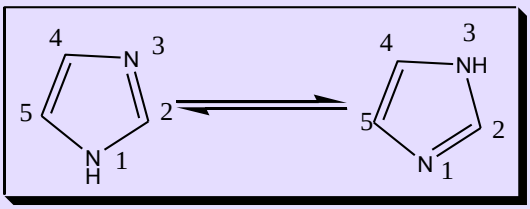


2. **By the condensation of hydrazine with β-carbonyl compound**

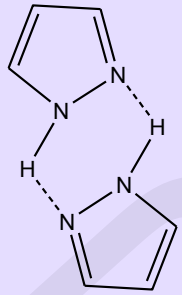


PROPERTIES-

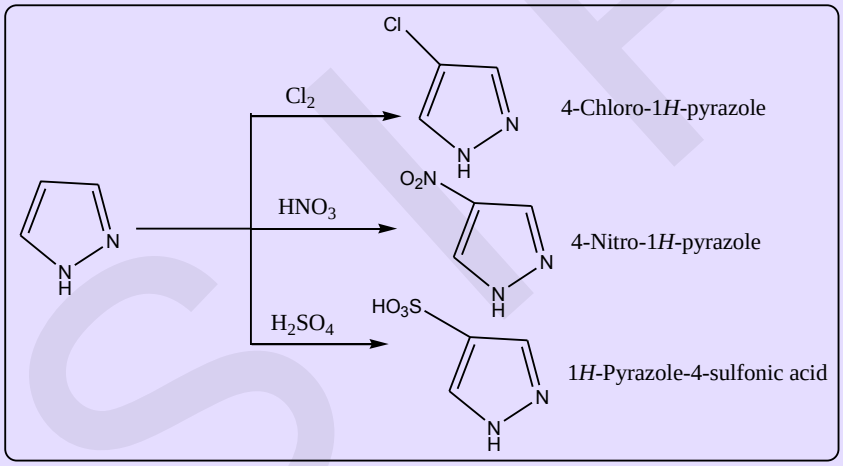
- M. P.-70^{0}C
- It exist in 2 tautomeric forms with 3 with 4 position identical



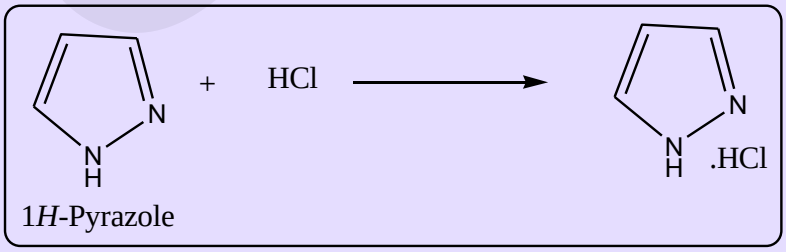
- It exist as dimer due to intermolecular hydrogen bonding.



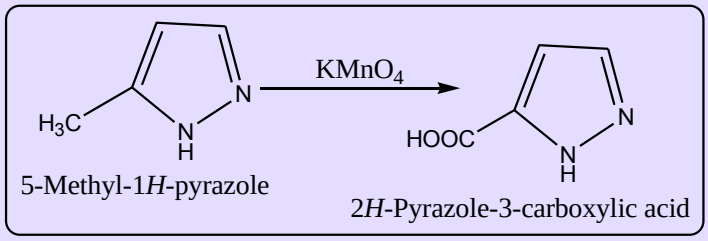
- It is aromatic in nature and undergoes electrophilic substitution reaction at position 4.



- It is weakly basic in nature & form salts with inorganic acid.

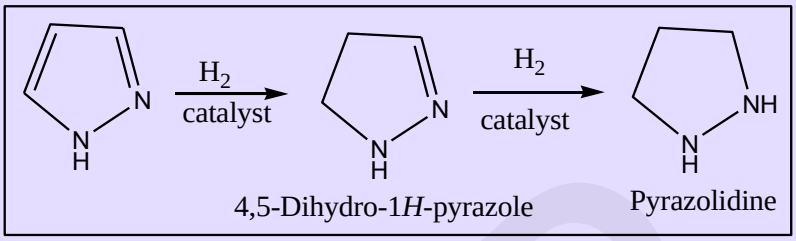


- **Oxidation-**



5-Methyl-1*H*-pyrazole 2*H*-Pyrazole-3-carboxylic acid

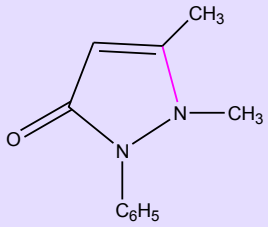
- **Reduction-**



4,5-Dihydro-1*H*-pyrazole Pyrazolidine

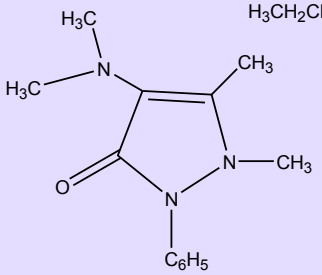
P'CEUTICAL IMPORTANCE OF PYRAZOLE

1. **ANTIPYRINE (PHENAZONE)**
   - Most important Pyrazole derivative is the synthetic drugs antipyrine.
   - It is used orally to reduce pain and fever in neuralgia, myalgia, migraine, headache, chronic rheumatism & neuritis
2. **AMINOPYRINE-**
   - It is used as antipyretic as well as an analgesic.
3. **PHENYLBUTAZONE-**
   - It is used in treatment of painful symptoms associated with Gout, Rheumatoid, Arthritis and painful shoulder.
4. **ALLOPURINOL-**
   - It useful in the control of uric acid levels associated with gout and other condition.
   - It also inhibit the enzymatic oxidation of mercaptopurine which is used as an anti-neoplastic antimetabolites



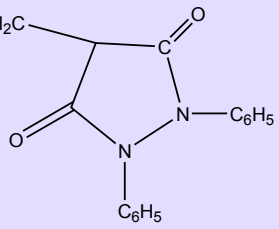
1,5-Dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one

(**ANTIPYRINE**)



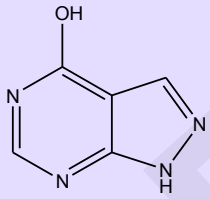
4-Dimethylamino-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one

(**AMINOPYRINE**)



4-Butyl-1,2-diphenyl-pyrazolidine-3,5-dione

(**PHENYLBUTAZONE**)



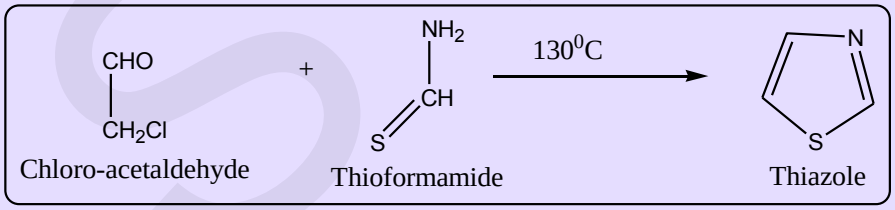
1*H*-Pyrazolo[3,4-*d*]pyrimidin-4-ol

(**ALLOPURINOL**)

THIAZOLE

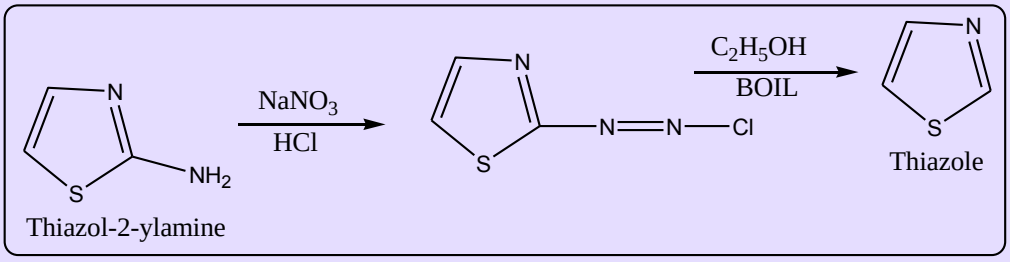
PREPARATION-

1. **Condensation of chloro-acetaldehyde and thioformamide.**



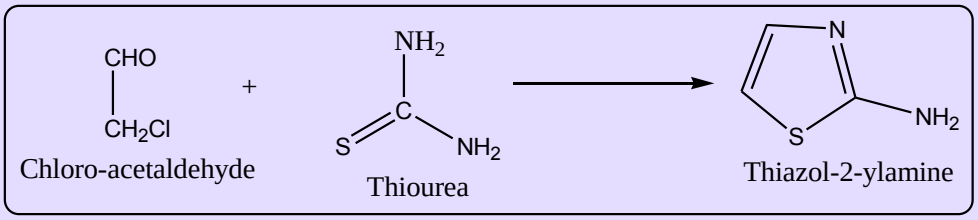
Chloro-acetaldehyde Thioformamide Thiazole

2. **Diazotisation of 2-aminothiazole.**



Thiazol-2-ylamine Thiazole

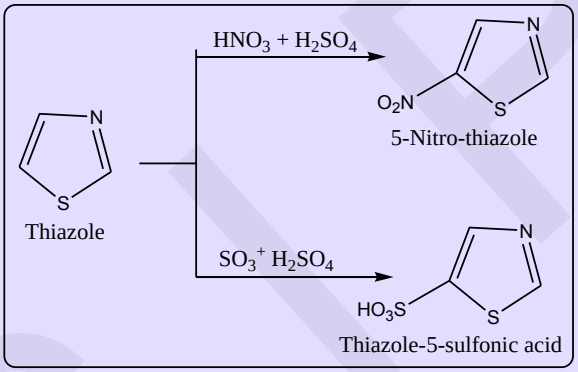
3. **2-aminothiazole may be prepared using thiourea.**



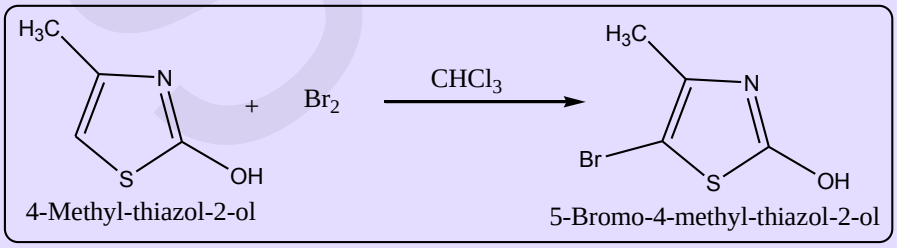
Properties-

- B. P.-117^{0}C
- Weakly basic in nature.

1. It is stable towards reducing agent but ring cleavage by Na/C_2H_5OH.
2. Electrophilic substitution reaction-



3. It is resistant towards substitution reaction but if $–NH_2$ OR OH group is present in position-2, electrophilic attack at position-5

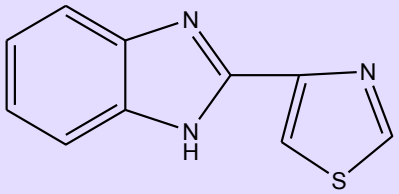


PHARMACEUTICAL IMPORTANCE OF THIAZOLE

Following Thiazole derivative find application in pharmacy-

1. THIABENDAZOLE-

- It is effective in treatment of several helminthic disease.
- It highly active against hookworm & Pinworm.
- It also effective as a fungicide.

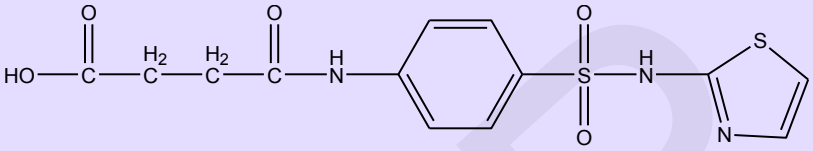


2-Thiazol-4-yl-1*H*-benzoimidazole

(**THIABENDAZOLE**)

2. SUCCINYL SULPHATHIAZOLE-

- It used in treatment of intestinal infection.

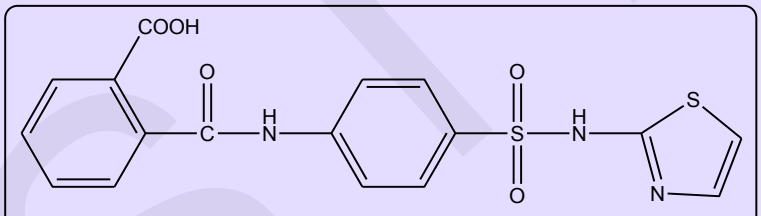


N-[4-(Thiazol-2-ylsulfamoyl)-phenyl]-succinamic acid

(SUCCINYL SULPHATHIAZOLE)

3. PHTHALYL SULPHATHIAZOLE-

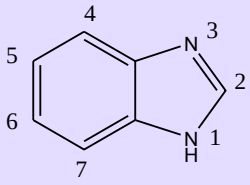
- It also used in the treatment of intestinal infection.



N-[4-(Thiazol-2-ylsulfamoyl)-phenyl]-phthalamic acid

(**PHTHALYL SULFATHIAZOLE**)

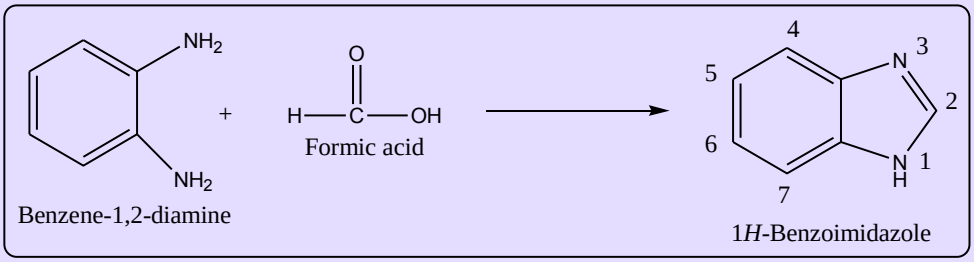
BENZIMIDAZOLE



1*H*-Benzoimidazole

PREPARATION-

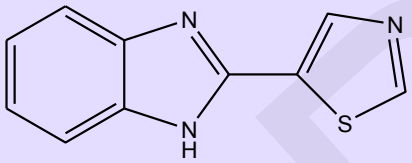
Benzimidazole can be prepared condensation of phenyl diamine and formic acid.



PHARMACEUTICAL IMPORTANCE OF BENZIMIDAZOLE-

- Benzimidazole found in only a few compound-
-

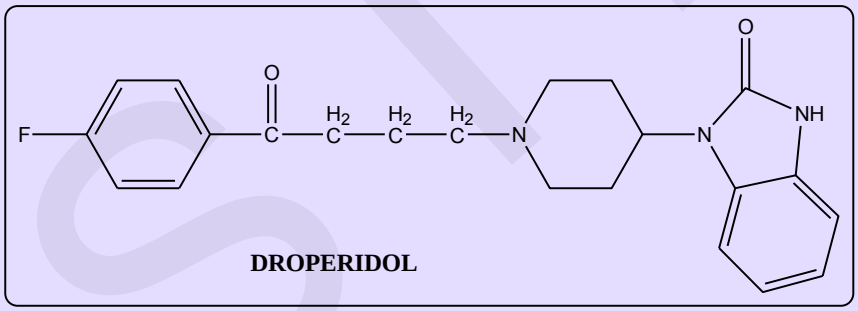
1. **THIABENDAZOLE**-It used as an anti-helminthic.



2-Thiazol-5-yl-1*H*-benzoimidazole

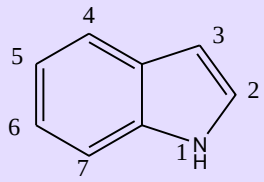
(**THIABENDAZOLE**)

2. **DROPERIDOL**-Used as anti-psychotics or antiemetic agent.



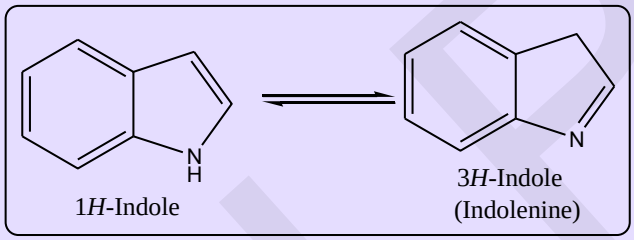
DROPERIDOL

INDOLE (1H-1-AZAINDEN)



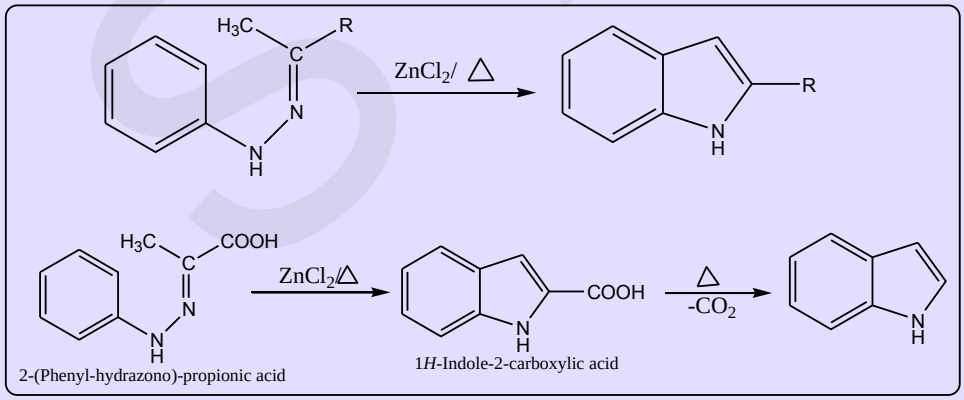
1*H*-Indole
(2,3-BENZOPYRROLE)

- Indole is made up of a benzene ring fused with a pyrrole ring.
- It exist as tautomer of indolenine.

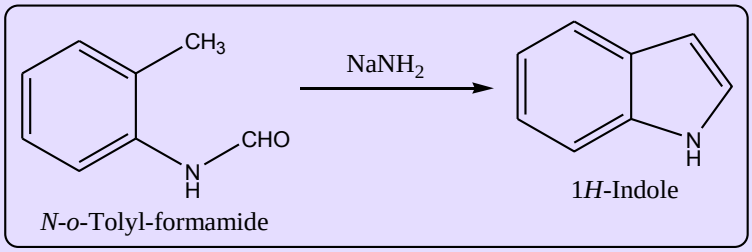


METHODS OF PREPARATION-

1. Fischer indole synthesis- in this method phenylhydrazone or derivative of an aldehyde or ketone or Ketonic acid is heated in the presence of catalyst as $ZnCl_2$, BF_3 etc.



2. **MADELUNG SYNTHESIS-**
   - N-O-tolyl formamide is heated in the presence of a base ($NaNH_2$ etc.) and in the presence of air.



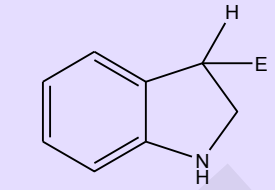
N-o-Tolyl-formamide

1*H*-Indole

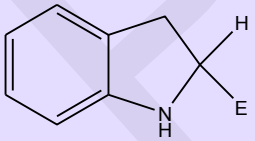
PROPERTIES AND CHEMICAL RECTION-

1. ELECTROPHILIC SUBSTITUTION REACTION-

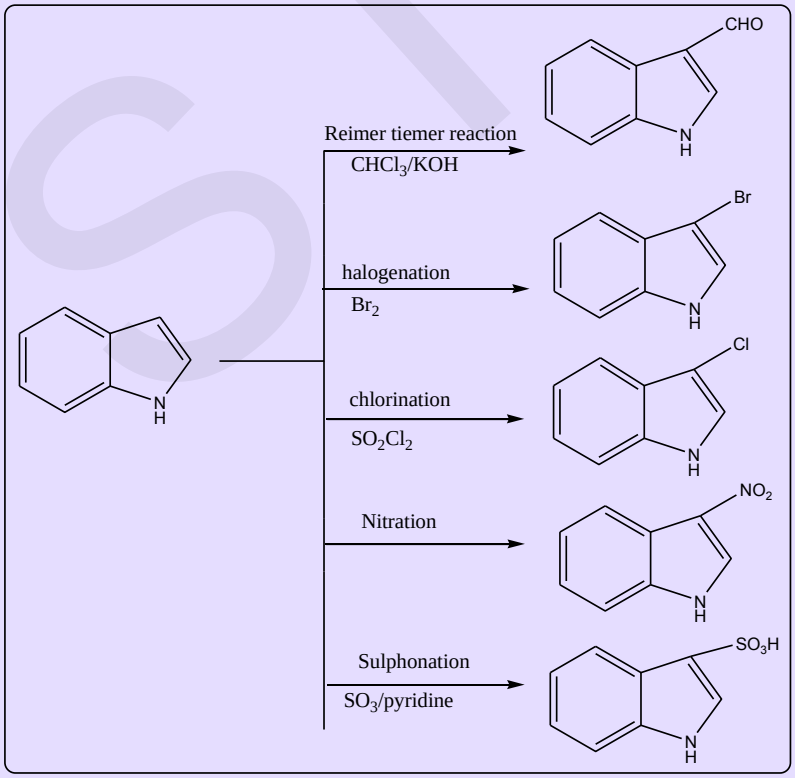
- Indole undergoes electrophilic substitution reaction at position-3 less preferably at position-2, this is due to the greater stability of the intermediate carbonium ion formed in 3-substitution than in 2-substitution.
- If both position-2 & 3 are occupied, substitution occurs at position-6.



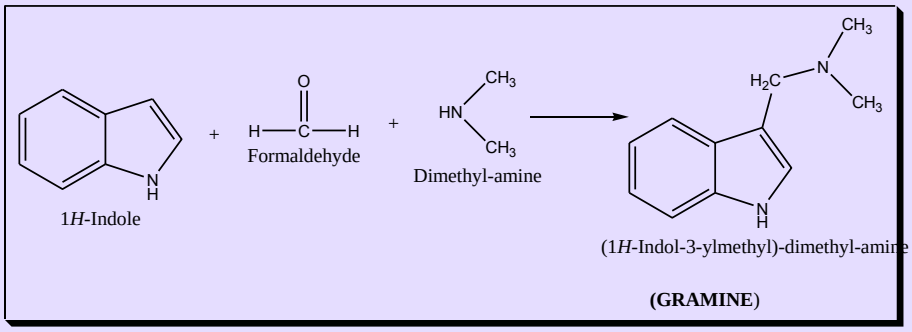
3-SUBSTITUTION



2-SUBSTITUTION



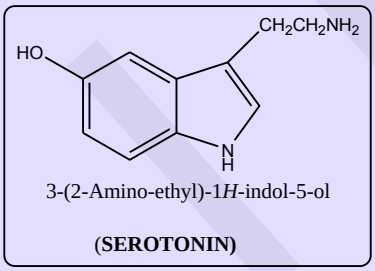
MANNICH REACTION-



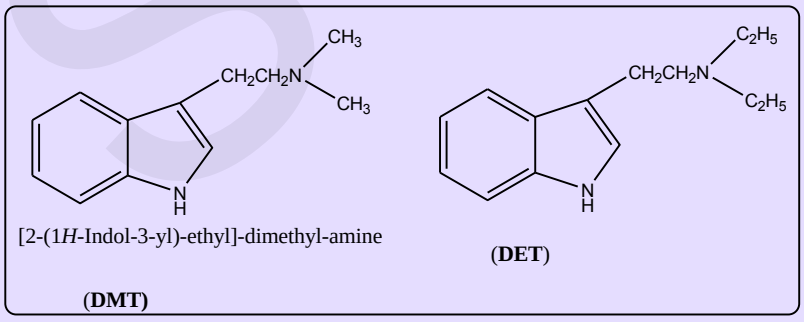
PHARMACEUTICAL IMPORTANCE-

Following pharmaceutical drug are indole derivative which have pharmaceutical importance-

1. **5-hydroxytryptamine (Serotonin or 5-HT)**
   - It produce elevated brain serotonin levels and excited behaviour.

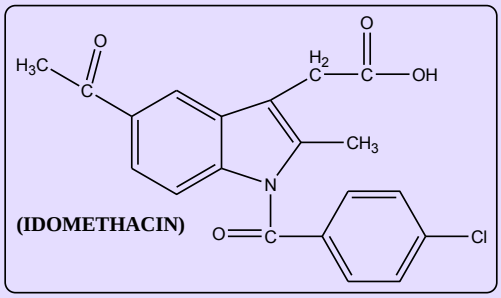


2. **Dimethyltryptamin(DMT)and diethyl-tryptamin (DET)-**



   - These compound are hallucinogenic in nature if smoked or injected.
   - These have Psychomimetic effect (onset of psychotic symptoms).

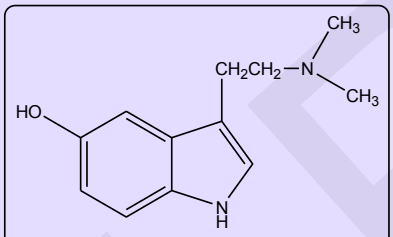
3. **INDOMETHACIN**
   - It is used as an anti-inflammatory, analgesic in rheumatoid arthritis, osteoarthritis and in gout.



(IDOMETHACIN)

4. BUFOTENINE

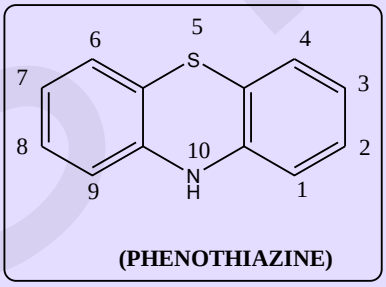
- It occurs naturally in secretion of the skin of toad and in seed of plant *Piptadenia peregrina.*
- It act as a hallucinogenic agent via injection.



3-(2-Dimethylamino-ethyl)-1*H*-indol-5-ol

(BUFOTENINE)

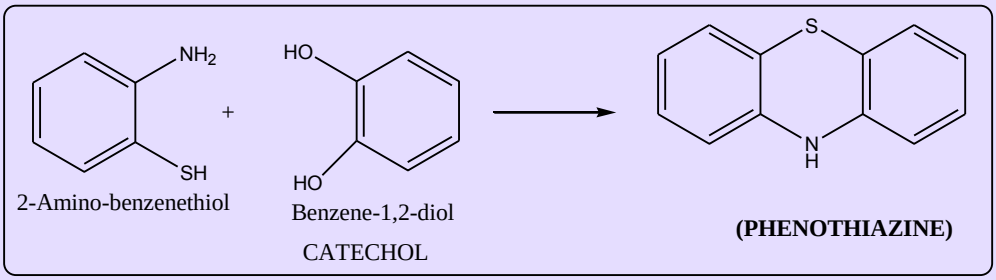
PHENOTHIAZINE



(PHENOTHIAZINE)

METHODS OF PREPARATION

1. BY HEATING AN AMINOTHIOPHENOLS WITH CATECHOLS



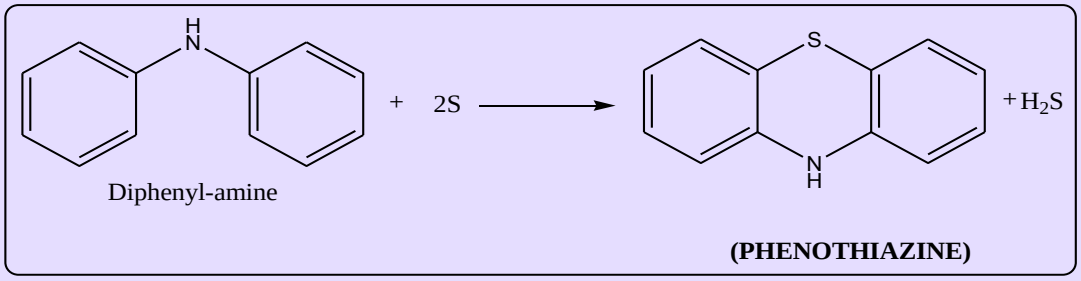
2-Amino-benzenethiol

Benzene-1,2-diol

CATECHOL

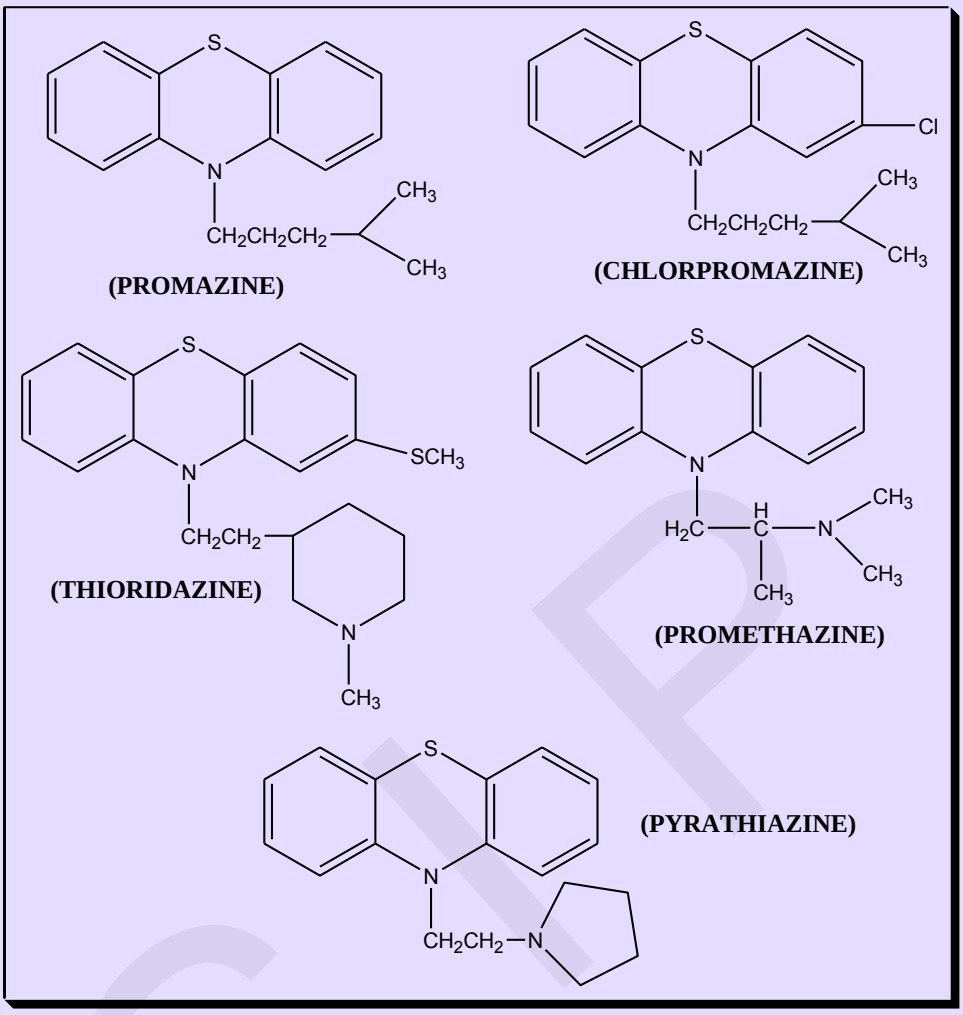
(PHENOTHIAZINE)

2. BY THE FUSION OF DIPHENYL AMINO WITH SULPHUR



PHARMACEUTICAL IMPORTANCE-

1. **PROMAZINE**
   - It can be used by oral, i.m. or i.v. and used in the management of acute neuropsychiatric.
2. **CHLORPROMAZINE**
   - It is used in the treatment of nausea and vomiting to potentiate to effect of anaesthetics, analgesic, hypnotics and sedative.
   - Also used in a variety of mental & emotional disturbance.
3. **Thioridazone-**
   - It inhibit the psychomotor function.
   - It used for the treatment of minor condition of anxiety, tension and severe psychosis.
4. **PROMETHAZINE-**
   - It used as anti-histaminic and anti-emetic effect.
5. **PYRATHIAZINE**
   - It is effecting in hay fever (allergic inflammation)
   - Used in vasomotor rhinitis, Urticaria (is a kind of skin rash notable for pale red, raised, itchy bumps) and bronchial asthma.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