Unit-4

Pharmaceutical Organic Chemistry-III

B.Pharma 4st Sem Notes

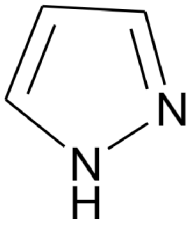
UNIT- IV

- **Synthesis, reactions and medicinal uses of following compounds/derivatives Pyrazole, Imidazole, Oxazole and Thiazole.**
- **Pyridine, Quinoline, Isoquinoline, Acridine and Indole. Basicity of pyridine Synthesis and medicinal uses of Pyrimidine, Purine, azepines and their derivatives**

Synthesis, reactions and medicinal uses of following compounds/derivatives of Pyrazole, Imidazole, Oxazole and Thiazole.

Pyrazole:

- Pyrazoles are the derivatives of a five-membered heterocyclic ring system called pyrazole. Pyrazole consists of two nitrogen atoms at 1 and 2 positions of the cyclic system.

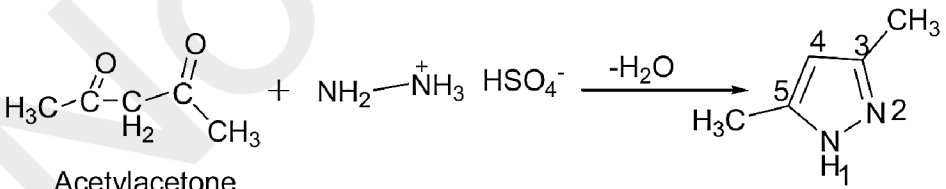


Physical Properties:

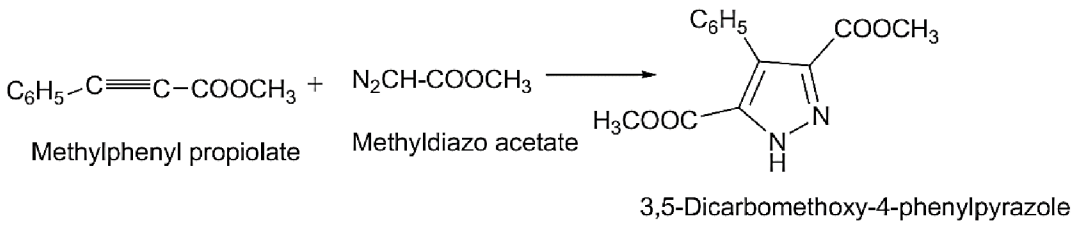
- Pyrazole is a colourless solid.
- It possesses a pleasant smell.
- Pyrazole is soluble in water.
- Pyrazole exhibits tautomerism.
- Pyrazole has aromatic properties.

Synthesis

- From 1,3-dicarbonyl compounds- 1,3-Dicarbonylcompounds react with hydrazine or hudroxylamine and gives pyrazoles.

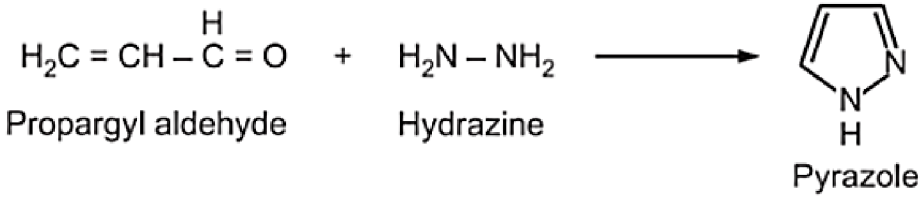


- From 1,3-di polar compounds- Pyrazole derivatives can also be prepared by adding a diazo compound to an acetylenic derivative.



From hydrazine and propargyl aldehyde:

In the reaction between hydrazine and propargyl aldehyde, pyrazole is formed.



Propargyl aldehyde Hydrazine Pyrazole

Reactions:

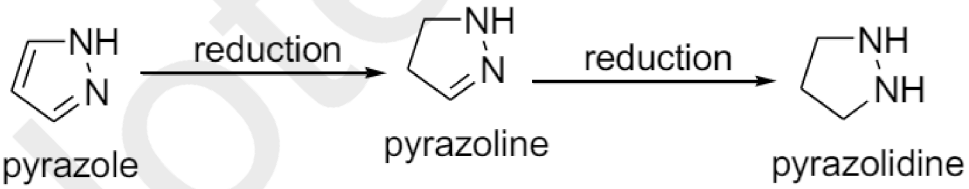
1. Oxidation:

- Pyrazole is resistant to oxidizing agents but the side chain may be oxidized to carboxylic acid group in presence of potassium permanganate.

3-Methyl-1-phenyl pyrazole 1-phenyl pyrazole-3-carboxylic acid

2. Reduction:

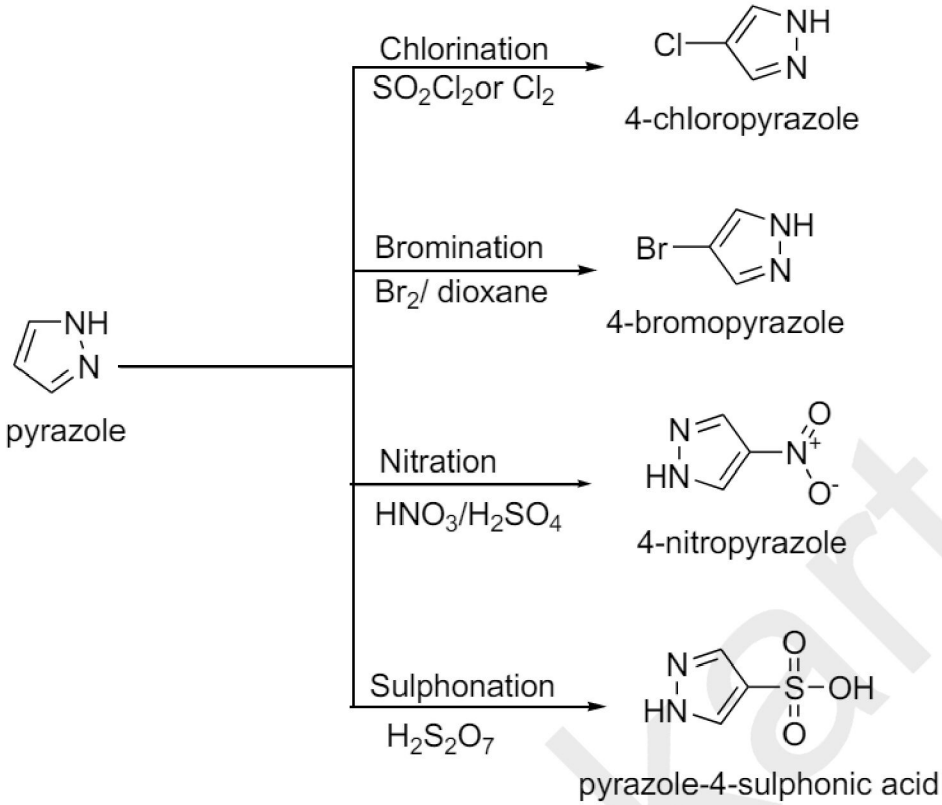
- Pyrazole ring system can be reduced with molecular hydrogen and metal catalyst. Pyrazolene and pyrazolidine are stronger bases than Pyrazole.



pyrazole pyrazoline pyrazolidine

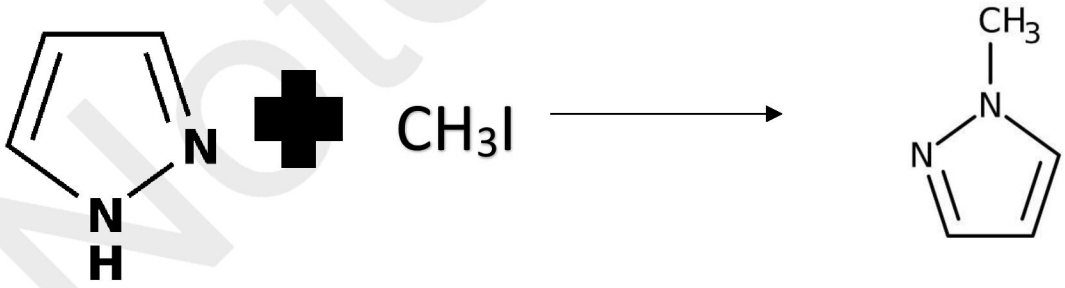
3.Electrophilic aromatic substitutions:

- Pyrazole is an aromatic compound.
- It readily undergoes electrophilic substitution at position 4 through the intermediate formation of arsenium ion.
- The electrophilic substitutiou is favoured in neutral or basic medium but not in acidic medium.



4. Alkylation:

- Pyrazole reacts with methyl iodide and yields N-methyl pyrazole.

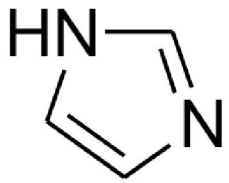


Medicinal Uses:

- Pyrazole are used as analgesics, antipyretics, anti-inflammatory (e.g., antipyrine, phenylbutazone, celecoxib), antibacterial, tranquilizers, anti-cancers, and diabetes medication.

Imidazole:

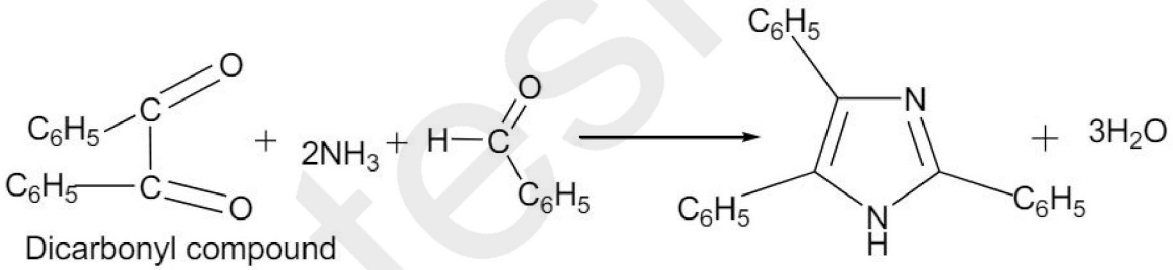
- Imidazoles are the derivatives of imidazole.
- Imidazole is a five-membered heterocyclic compound possessing of two nitrogen atoms at 1 and 3 positions.
- Imidazole is isomeric with Pyrazole and occurs in purine nucleus and in histidine.



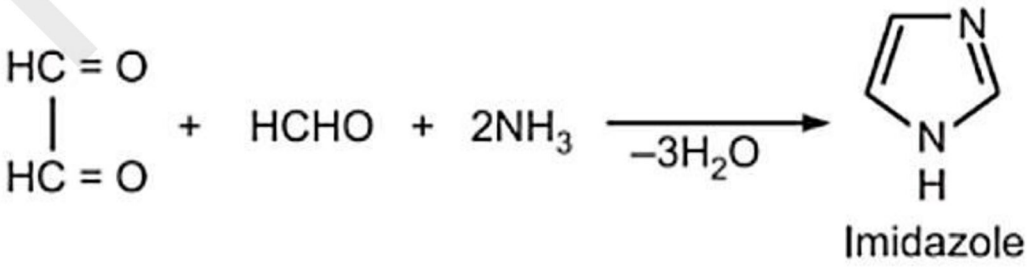
Imidazole

Synthesis:

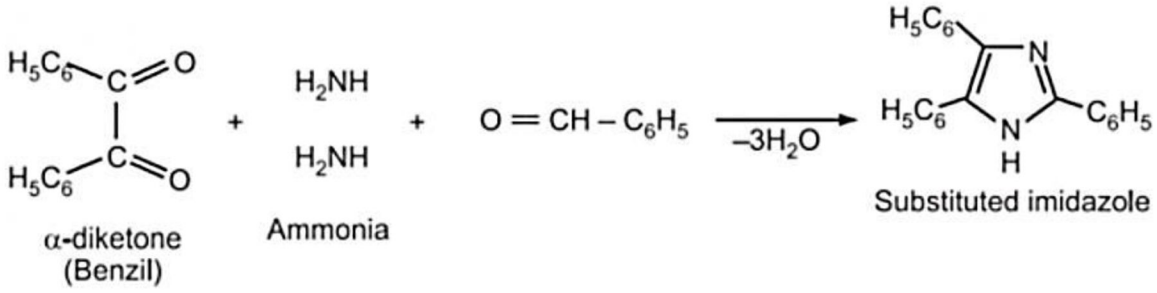
1. From dicarbonyl compounds: Imidazoles can be prepared by condensing a dicarbonyl compound with an aldehyde in presence of ammonia.



2. Debus method - According to the Debus Method published in 1858, glyoxal, formaldehyde, and ammonia produce imidazole (glyoxaline). 2- and 3-mono- and 4,3-disubstituted imidazoles are available in this product.



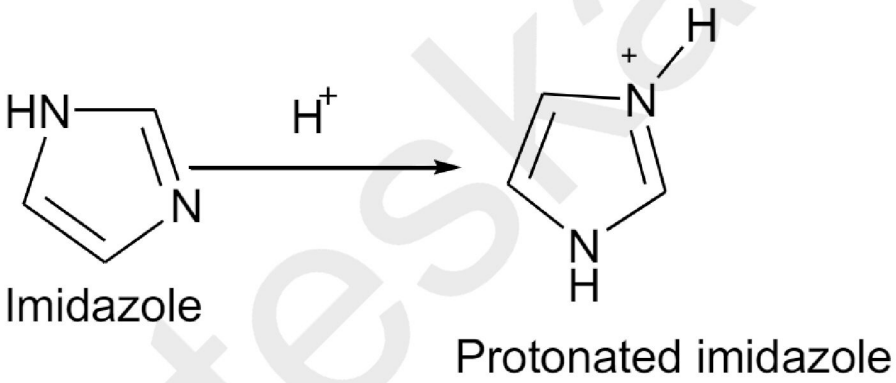
3. Radiszewski synthesis - By combining glyoxal with an aldehyde (e.g., benzaldehyde), benzaldehyde is formed. Formamide can replace ammonia.



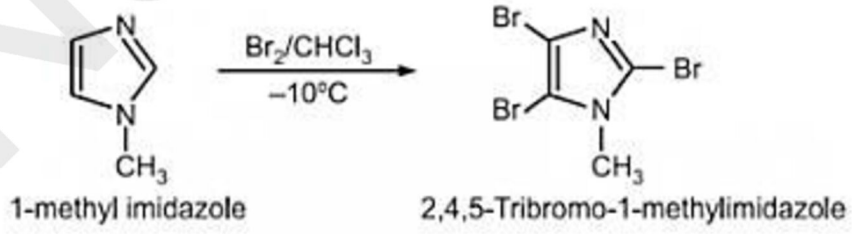
Chemical Reaction:

1. Basicity:

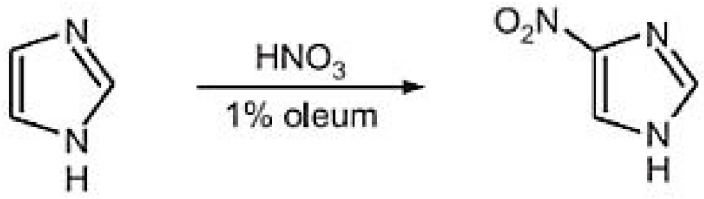
- Imidazole is a weak base forms salts with acids. It is more basic than Pyrazole, pyrrole and pyridine. Imidazole also has acidic properties the hydrogen atom of -NH can be displaced by metal. It is more acidic than pyrrole and pyridine.



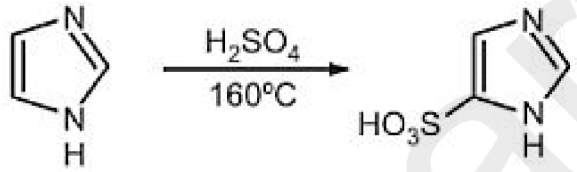
Halogenation:



Nitration:



Sulfonation:

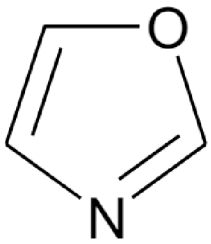


Medicinal Uses

- Imidazole has many medicinal uses, including antibacterial, anti-inflammatory, antidiabetic, antiparasitic, antituberculosis, antifungal, antioxidant, antitumor, antimalarial, and anticancer properties.

Oxazole:

- Oxazole is a heterocyclic aromatic organic compound with a five-membered ring containing one nitrogen and one oxygen atom separated by one carbon.

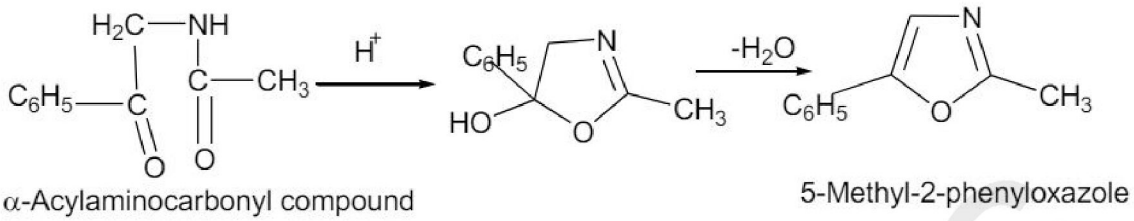


oxazole

Synthesis:

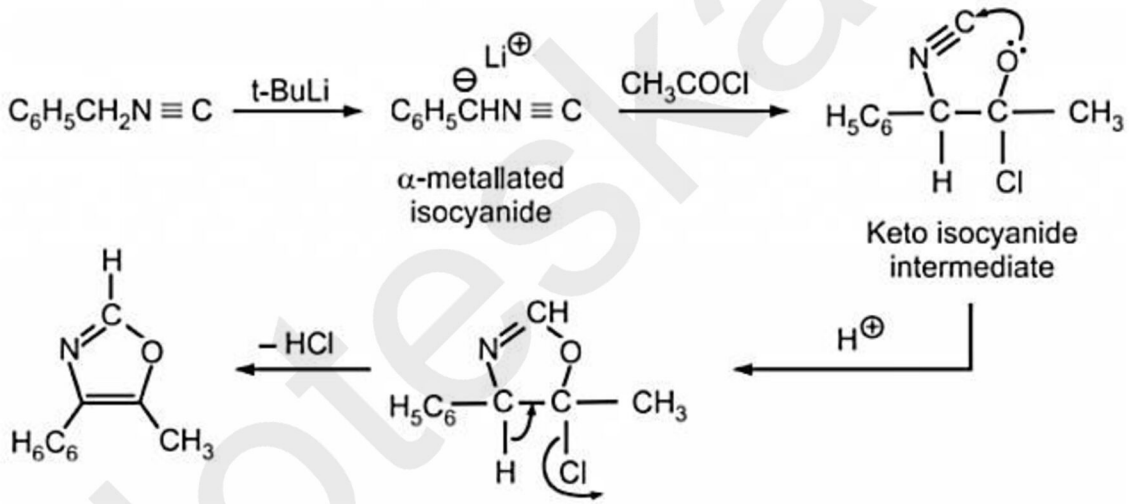
1. From α-acylamino carbonyl compound:-

- Oxazole is prepared by refluxing αacylamino carbonyl compound with acid or phosphorous pentaoxide. This is the most common method to prepare oxazoles which involve cyclization and dehydration in presence of phosphorous pentaoxide or strong mineral acid.

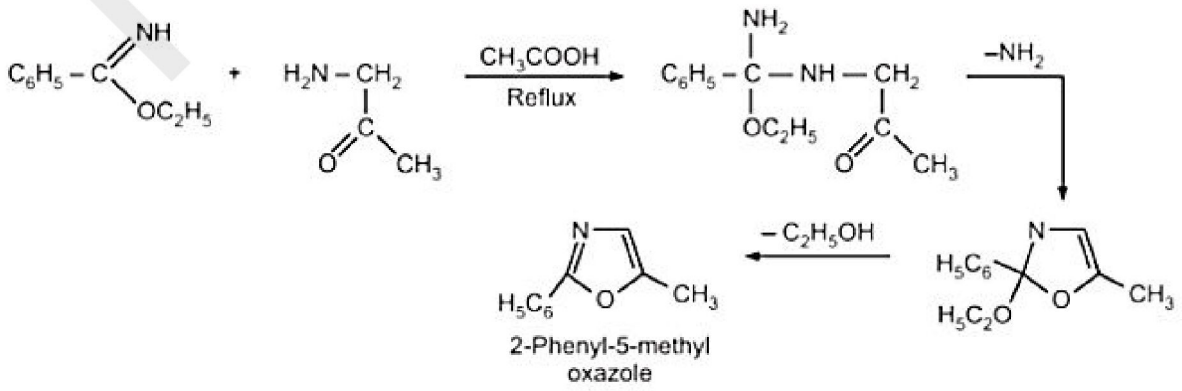


2. From isocyanides with acid chlorides –

- Anhydrous hydrogen fluoride, polyphosphoric acid, or phosgene are usually used to induce cyclization, while dehydrating agents, such as H2SO4, PCl3, POCl3, or SOCl2, are frequently used to induce dehydration.



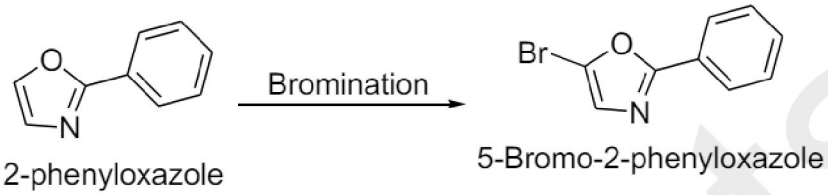
From α - aminocarbonyl compounds –



Reactions:

1. Electrophilic Substitution:-

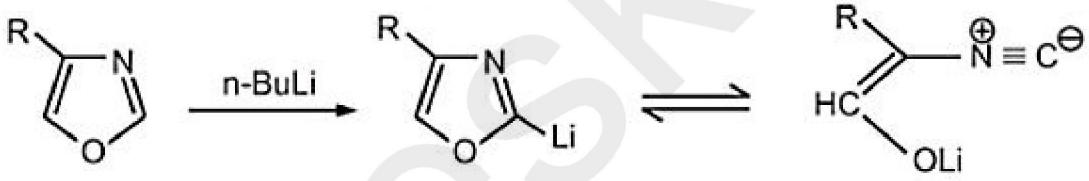
- Oxazole undergoes electrophilic aromatic substitution reactions. The preferred attack is at position-5. These reactions occur more readily when the oxazole ring is activated by electron-donating group. Oxazole is more reactive with electrophiles than thiazole but less than imidazole.



2-phenyloxazole 5-Bromo-2-phenyloxazole

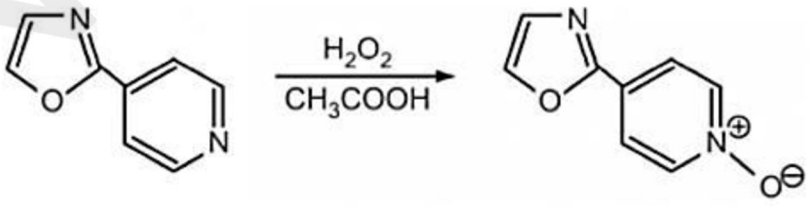
2. Metallation –

- The most electron-deficient C2-atom in the carbon chain is attacked by lithium first. Due to their instability, these 2-lithia-oxazoles break down into open-chain isocyanides.



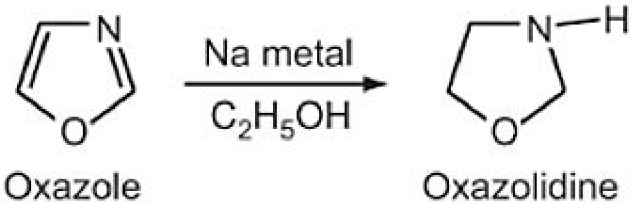
3. Oxidation –

- By using cold potassium permanganate, chrome acid, and ozone, oxidizing agents can open the oxazole ring. Hydrogen peroxide generally does not affect oxazole. N-oxides can be formed from substituted oxazole.



4. Reduction –

- The oxidation of oxazole is relatively easy. The oxidation of oxyazoles is relatively easy. Open-chain products result from reduction and cleavage of the ring caused by other reducing agents.



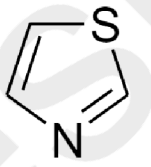
Oxazole Oxazolidine

Medicinal Uses:

- Oxazoles have been claimed as stimulants of cognitive function, adrenergic antagonists, fungicides, anthelmintic agents, antihypertensive agents, and antiulcer agents.
- They are also reported to show activity as pesticides, agrochemical fungicides, and insecticides.

Thiazole:

- Thiazoles are five membered heterocyclic compounds consisting of nitrogen and sulphur heteroatoms.
- The numbering in thiazole starts from the sulphur atom.

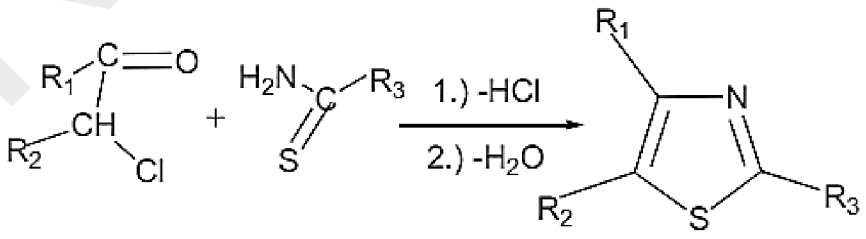


Thiazole

Synthesis:

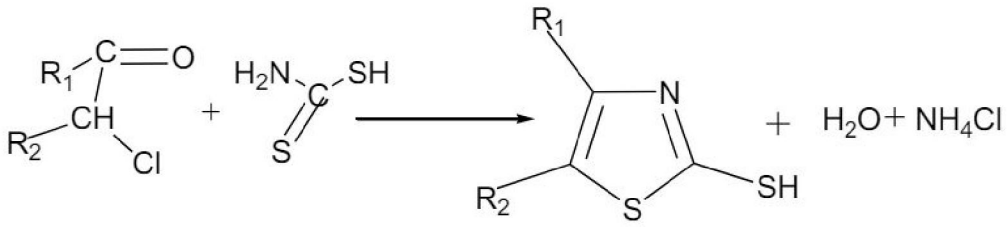
1. Condensation of α-chlorocarbonyl compounds with thioamides:-

- Thiazoles are synthesized by condensing α-chlorocarbonyl compounds with thioamides.



2. Condensation of α-chloroketones with ammonium dithiocarbonate:-

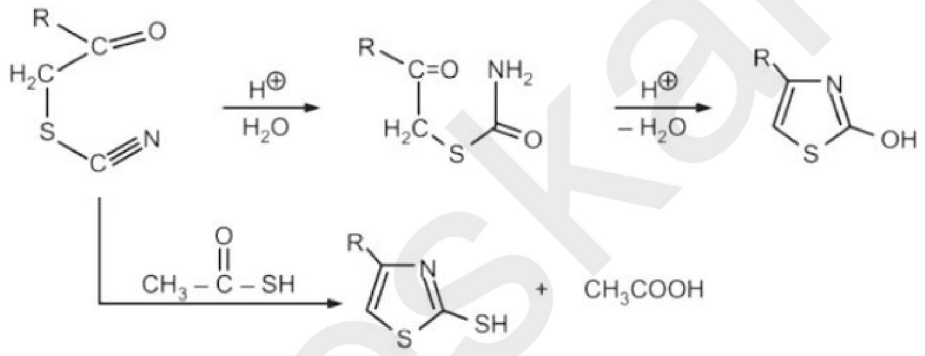
- Thiazoles may also be prepared by the condensation of α-chloroketones with ammonium dithiocarbonate.



2-Mercaptothiazole

3. Tcherniac's synthesis –

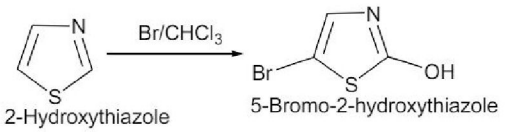
- The 2-substituted thiazoles are synthesized by hydrolyzing *-thiocyanic ketones with acid or treating them with sulfur compounds.



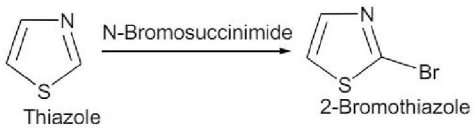
Reactions:

Electrophilic substitution reactions:-

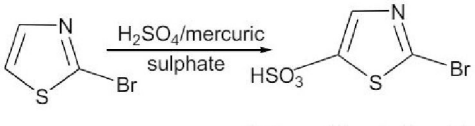
- Thiazole undergoes electrophilic substitution reactions. The reactivity of thiazole is intermediate to pyridine and thiophene.
- It is resistant to substitution reactions but if an electron donating group is present at positions 2, thiazole readily undergoes the following substitution reactions.



2-Hydroxythiazole 5-Bromo-2-hydroxythiazole



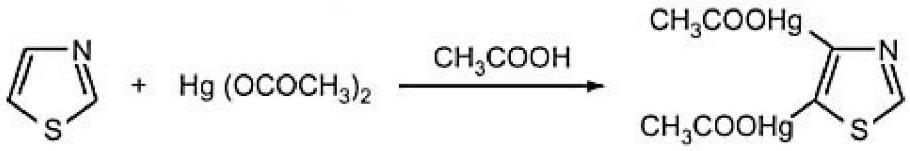
Thiazole 2-Bromothiazole



2-Bromothiazole 2-Bromothiazole-5-sulphonic acid

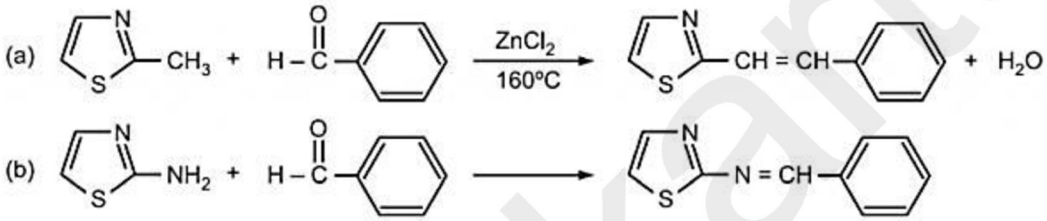
Mercuration –

- In the presence of mercury acetate, thiazole tends to be mercurated in C5 > C4 > C2 order.



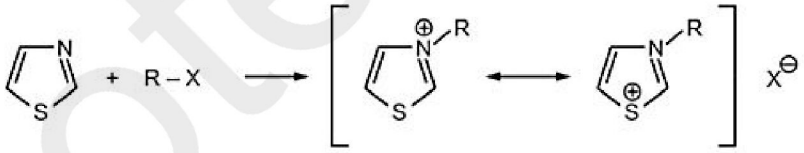
Condensation reaction –

- To generate heterocycles, 2-methylthiazole and 2-aminothiazole undergo condensation reactions with aromatic aldehydes.



N – alkylation –

- Thiazolium cations are formed by the reaction between thiazoles and alkyl halides. Almost all of the positive charge is located on sulfur atoms in this cation, which is resonance stabilized.

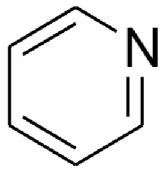


Medicinal Uses:

- Thiazoles include mainly dyes and fungicides. Another widely used thiazole derivative is the non-steroidal anti-inflammatory.

Pyridine:

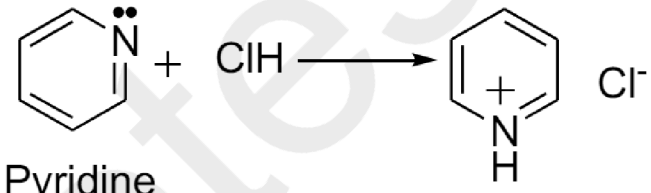
- Pyridine is a six membered heterocyclic ring system containing nitrogen as heteroatom. Pyridine is a liquid of characteristic odour.



Pyridine

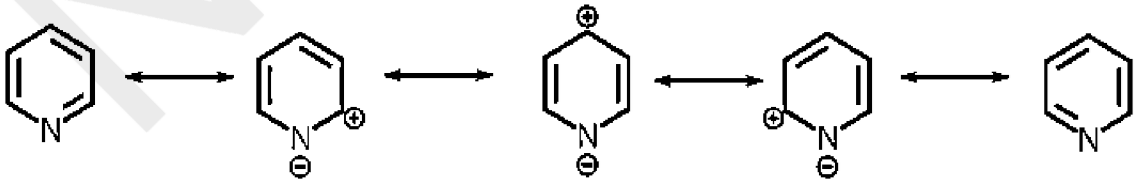
Basicity:-

- Pyridine is more basic than pyrrole because in Pyridine the non bonding electrons on N atom is in the same plane of pyridine hybridized orbitals plane, so it is not participating in resonance phenomenon, due to this the lone pair of electrons on Nitrogen are readily available for acid-base reaction.
- Nitrogen atom of pyrrole has lone pair of electrons perpendicular to pyrrole hybridized orbitals plane, here the lone pair of electron participate in resonance phenomenon, due to this the lone pair of electron on N is not readily available for acid-base reaction. Pyridine is less basic than aliphatic amines.



Pyridine Pyridinium hydrochloride

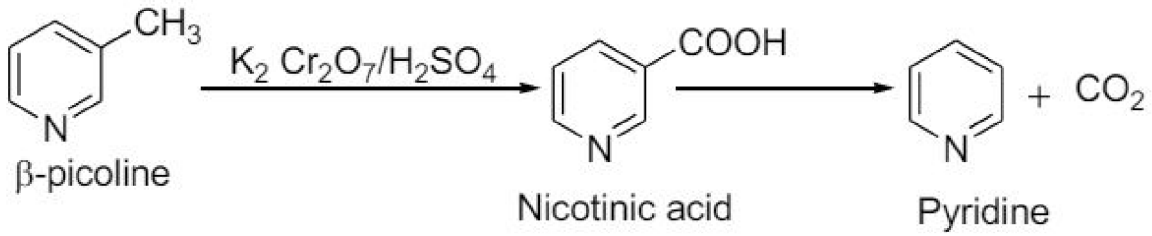
Resonance Structure:



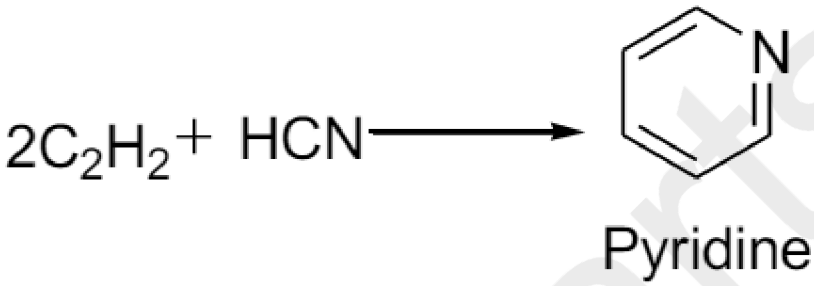
Resonance energy of pyridine is about 125 KJ mol^{-1}

Preparation:

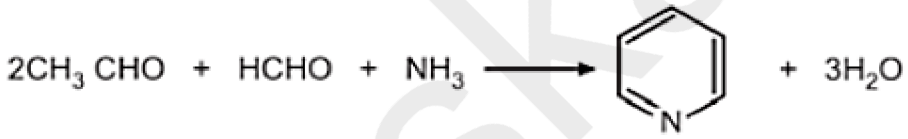
1. From picoline:- On oxidation with potassium dichromate and sulphuric acid β-picoline changes into nicotinic acid. This on decarboxylation with calcium oxide gives rise to pyridine.



Pyridine is prepared by passing a mixture of acetylene and HCN through a red hot tube.

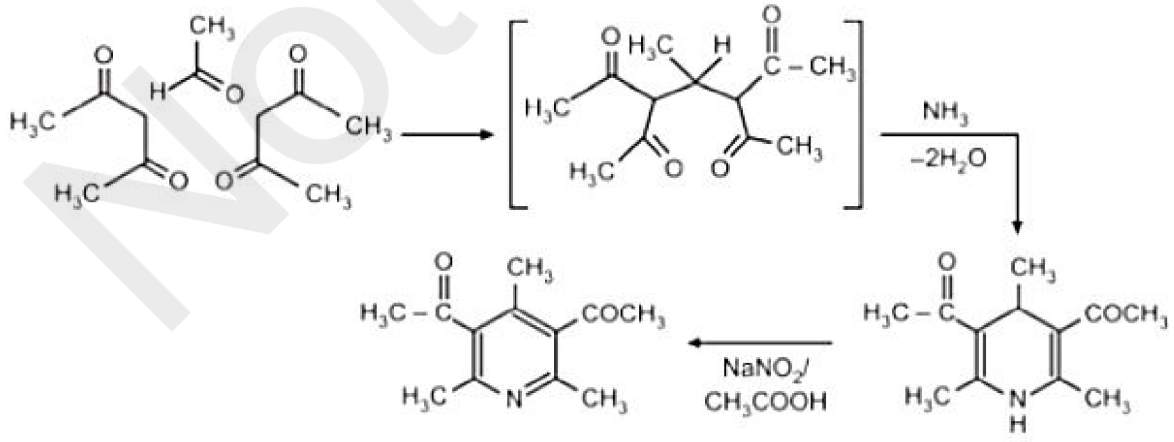


Acetaldehyde and formaldehyde are combined with ammonia to make pyridine.



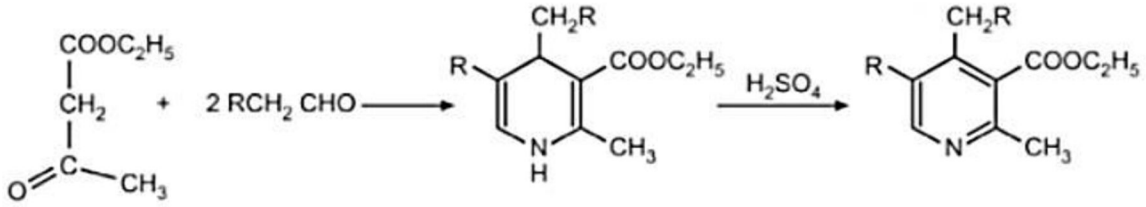
2. Hantzsch synthesis –

- A tricarbonyl compound, an aldehyde, and ammonia are combined in an efficient reaction.



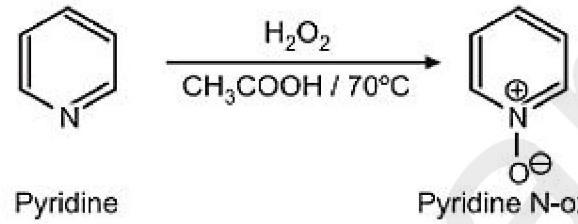
3. Guareschi Thorpe synthesis –

- Aldehydes are condensed into substituted pyridine when they combine with keto ester.

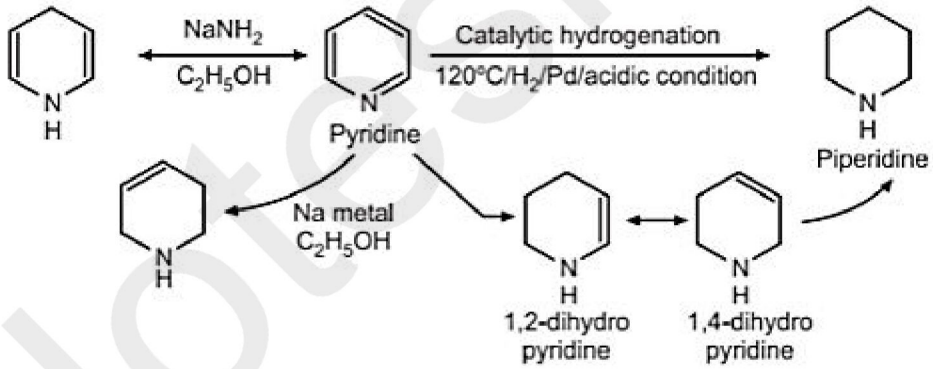


Reactions:

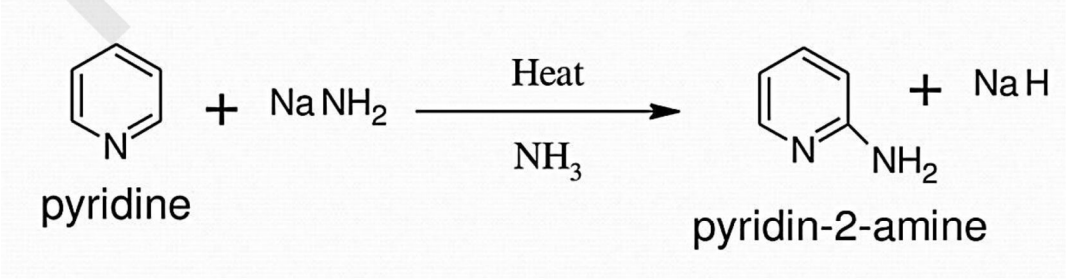
- **Oxidation -** In contrast to this, the N-atom in its pyridine ring is highly electron-rich, which makes it easily susceptible to oxidation by hydrogen peroxide or other peracids.



- **Reduction -** Nucleophilic reducing agents can reduce pyridine since it easily reacts with nucleophiles.



- **Amination:** Pyridine reacts with sodamide to give 2-aminopyridine. It is called chichibabin reaction.



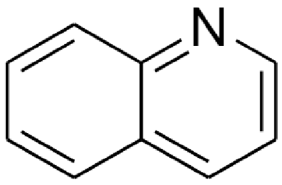
Medicinal Uses:

- Pyridine can also be found in medication that's used to treat cancer.

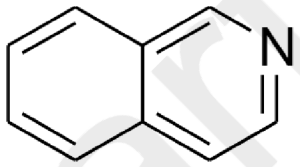
- Pyridine derivatives have many medicinal uses, including:
  - antimicrobial, antiviral, anticancer, antioxidant, antihypertensive, antidiabetic, antimalarial, anti-inflammatory, psychopharmacological antagonists, and antiamebic agents.

Quinoline and Isoquinoline:

- Quinoline and isoquinoline are condensed heterocyclic systems. They are also known as benzopyridines because they have fused benzene and pyridine rings. They are aromatic compounds.



Quinoline

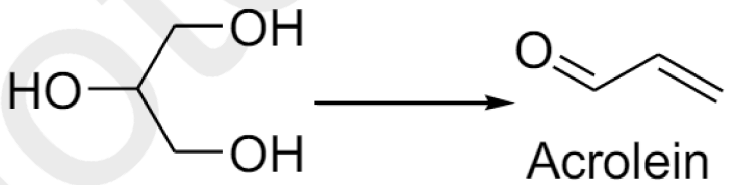


Isoquinoline

Preparation: Naturally quinoline and isoquinoline are available in coal tar, bone oil and alkaloids. Synthetically they are prepared by the following methods:

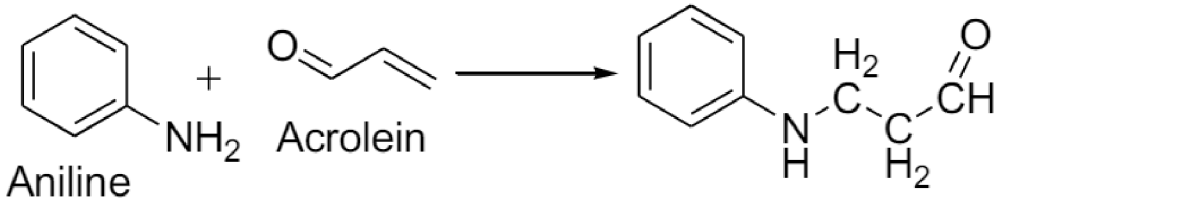
a. Quinoline is prepared by the reaction of aniline with glycerol, conc. Sulphuric acid, nitrobenzene and ferrous sulphate. This reaction is known as Skraup synthesis.

1. Glycerol on dehydration with hot H2SO4 gives acrolein.



Glycerol Acrolein

2.Nucleophilic addition of aniline to acrolein form β-phenylamino propionaldehyde.



Aniline Acrolein β-Phenylamino propionaldehyde

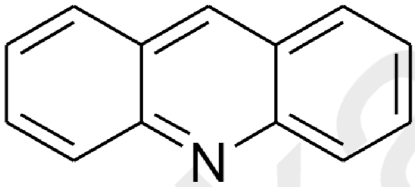
b. Isoquinoline is prepared by Bischler-Napieralski synthesis:- In Bischler-Napieralski synthesis β-phenylethylamine is allowed to undergo cyclodehydration on heating with phosphoryl chloride to form substituted isoquinoline.

Medicinal Uses:

- It is used for the suppression and treatment of malaria by interfering with DNA. It is used as an anthelmintic drug. It is used as high boiling basic solvent in organic reaction. It is used in manufacturing of pharmaceutical dyes.

Acridine:

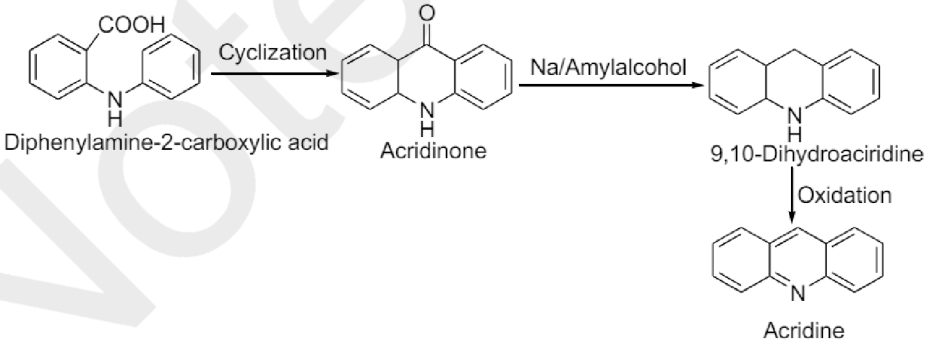
- Acridine is a condensed heterocyclic system. It is a tertiary base. Acridine is also known as benzoquinoline or dibenzpyridine.
- Acridine is colourless solid. It occurs in anthracene fraction of coal tar.



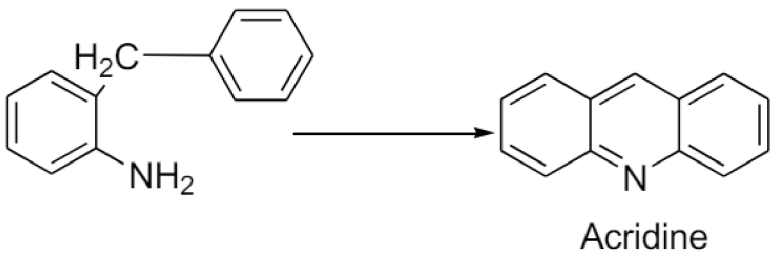
Acridine

Preparation:

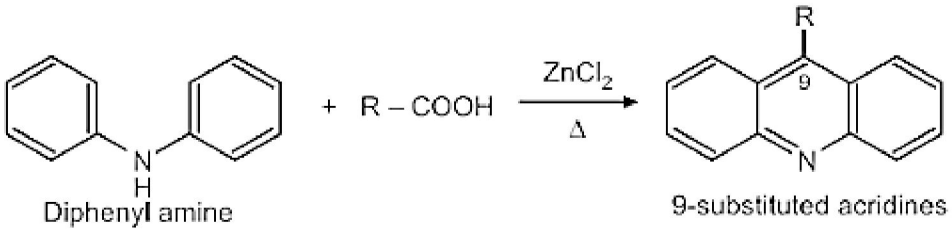
1. Oxidation of dihydroacridine with oxidizing agent.



2. Acridine can also be prepared by passing o-aminodiphenylmethane through a red hot tube.

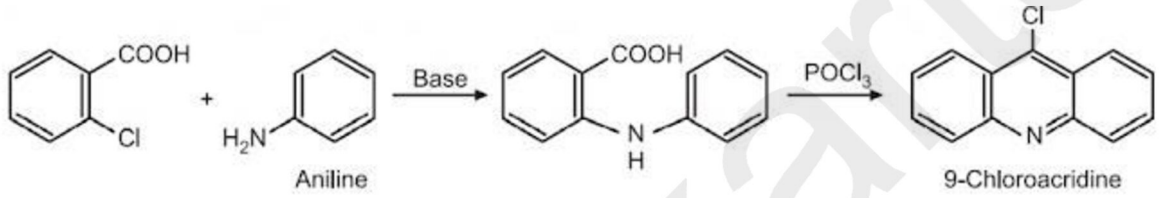


3. Bernthsen acridine synthesis - In the presence of zinc chloride, diphenylamine condenses with carboxylic acids to form acridines.

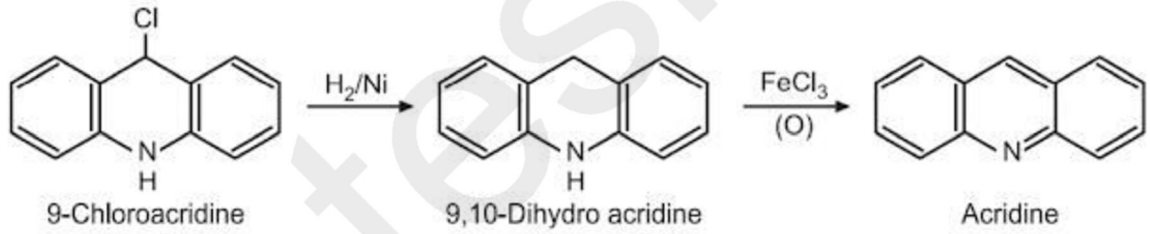


4. From o-chlorobenzene acid –

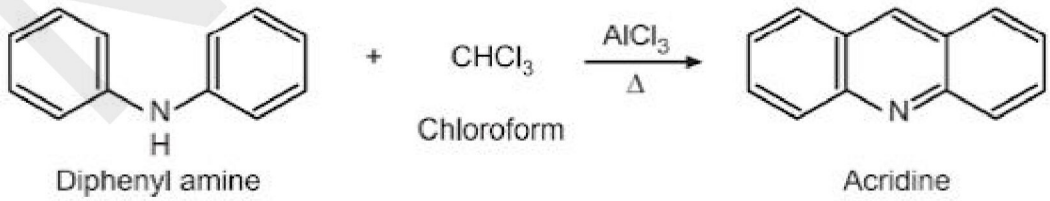
- A diphenylamine-2-carboxylic acid is formed by condensing aniline and o-chlorobenzene acid. Using POCl3 as a catalyst, this acid gives 9-chloroacridine.



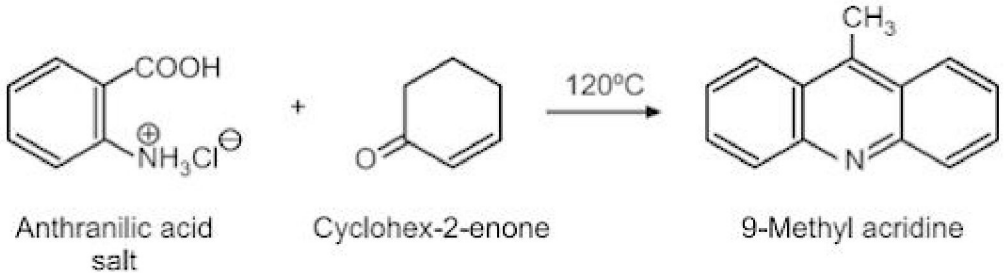
- Acridine is formed after the hydrogenation of 9-chloroacridine is followed by the oxidation of the chloride with ferric chloride.



- Condensation of diphenylamine with chloroform along with alkyl chloride gives acridine.



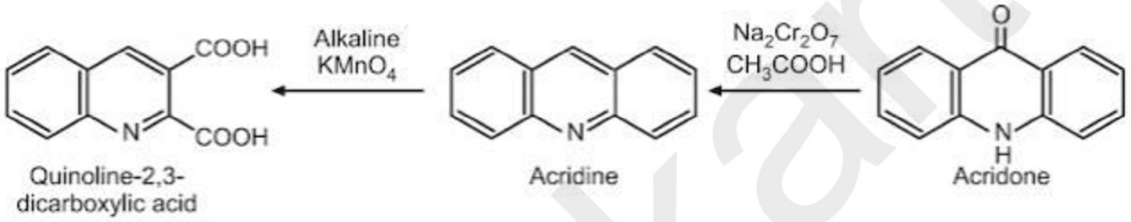
5. Friedlander synthesis - At 120°C, cyclohexane-2-enone is treated with salt of anthranilic acid to produce 9-methyl acridine.



Anthranilic acid salt | Cyclohex-2-enone | 9-Methyl acridine

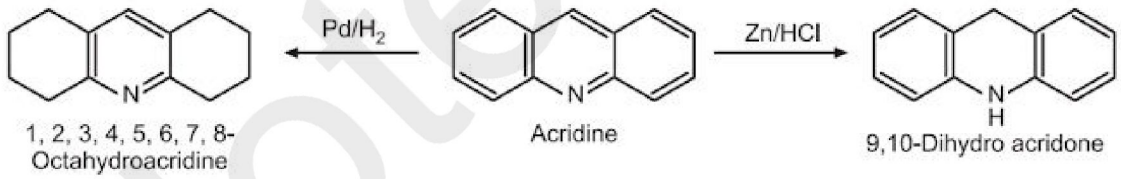
Chemical Reactions:

- **Oxidation -** During dichromate oxidation in acetic acid, acridine becomes acridone. Quinoline -2, 3-dicarboxylic acid is formed by oxidative ring cleavage carried out by KMnO4 in alkaline media.



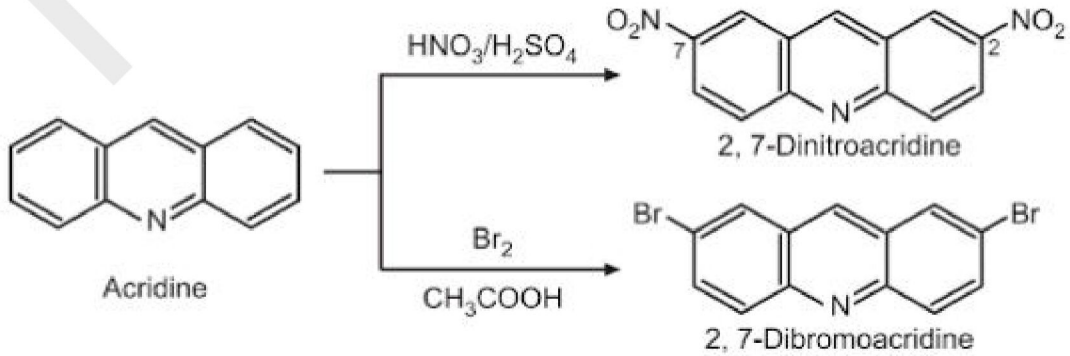
Quinoline-2,3-dicarboxylic acid | Acridine | Acridone

- **Reduction -** By catalytic hydrogenation, the benzene rings in acridine can be selectively reduced while the pyridine ring can be selectively reduced by zinc/hydrochloride to give 9, 10-dihydroacridine.



1, 2, 3, 4, 5, 6, 7, 8-Octahydroacridine | Acridine | 9,10-Dihydro acridone

- **Electrophilic substitution -** A benzenoid ring is attacked by the electrophile preferably in the 2- or 7-position, resulting in di-substitution. For example,



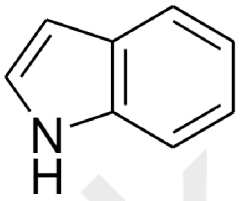
Acridine | 2, 7-Dinitroacridine | 2, 7-Dibromoacridine

Medicinal Uses

- Acridine is a key component in many drugs on the market. There are a number of drugs that may be considered anaesthetics: bucricaine (anesthetic), quinacrine (or mepacrine: antimalaria), 9-ammoacridine (disinfectant), proflavin (antibacterial), nitracine (anti-cancer), acriflavine (antiseptic), etc.

Indole.

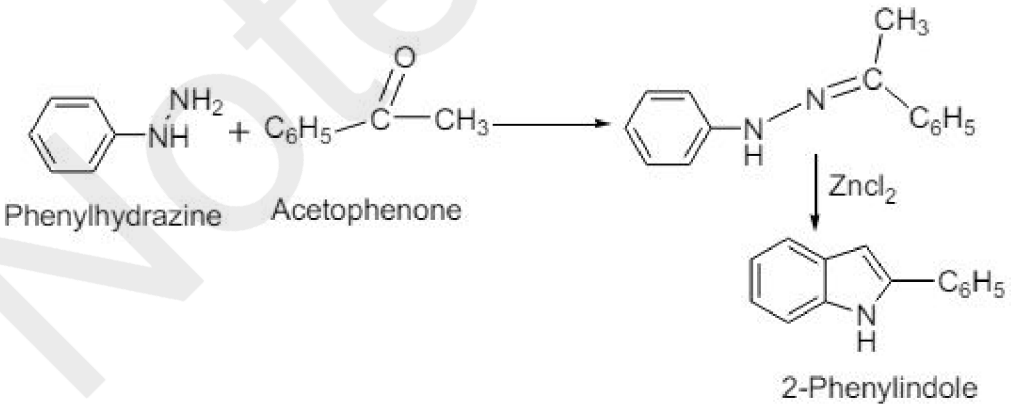
- Bayer first synthesized Indole in 1866. Indole consists of a pyrrole moiety which is fused to benzene ring. The two rings are flat and associate with Pi-delocalized electrons. Therefore Indole exhibits aromatic properties. The IUPAC name of Indole is 1H-benzopyrrole.



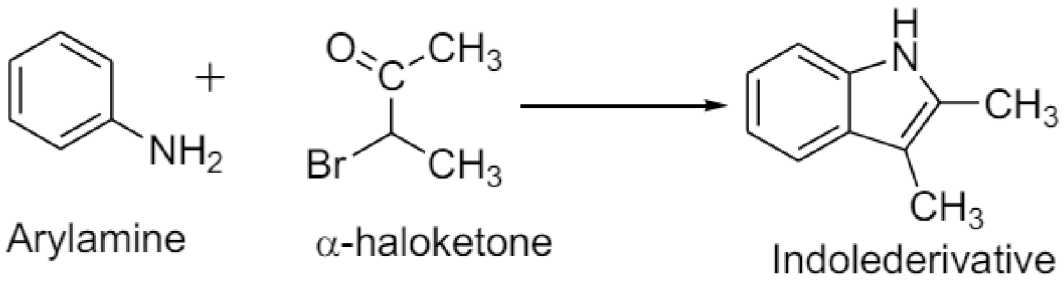
Indole

Synthesis:

- **Fischer -Indole synthesis:** In this method phenylhydrazoneof aldehyde or ketone is cyclized with acid catalyst.

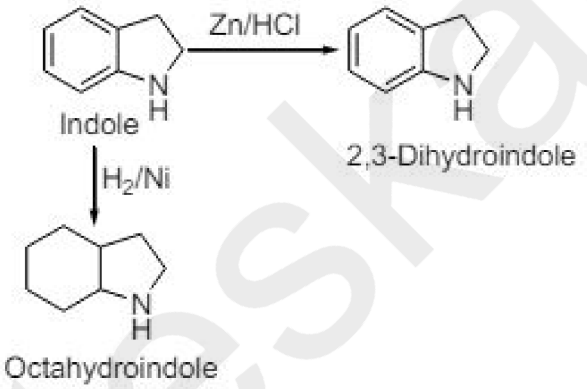


- **Bischler synthesis:** In this method Indole derivatives can be prepared by heating aryl amine with haloketones.

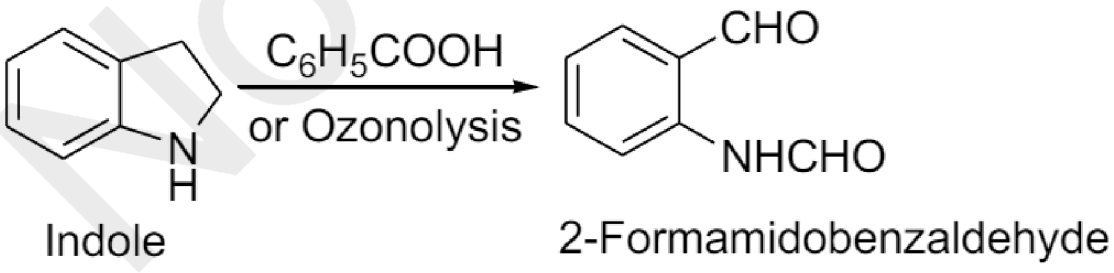


Chemical reaction:

- **Reduction:** Electrolytic reduction or metal and acid reduction of Indole gives 2,3-dihydroindole. Catalytic reduction of Indole with molecular hydrogen and metal gives octahydroindole.



- **Oxidation:** In presence of peroxy acid or ozone Indole is oxidized to form 2-formamidobenzaldehyde by opening the heterocyclic ring.



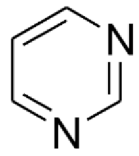
Medicinal Uses:

- It is used in cancer prevention.
- It is used in tumors inside respiratory tract.

- **Synthesis and medicinal uses of Pyrimidine, Purine, azepines and their derivatives**

Pyrimidine:

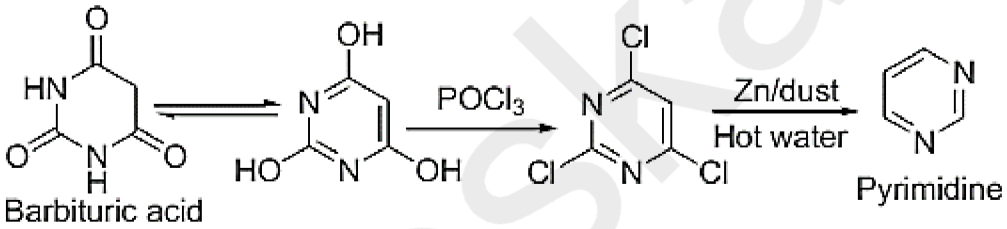
- Pyrimidines are the derivatives of pyrimidine. Pyrimidine is a six membered heterocyclic ring system consisting of two nitrogen atoms at 1 and 3 positions.



Pyrimidine

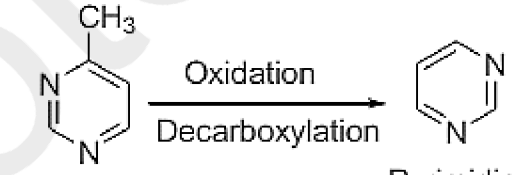
Synthesis:

1. From barbituric acid:- Pyrimidine is prepared from barbituric acid by the following reactions:-



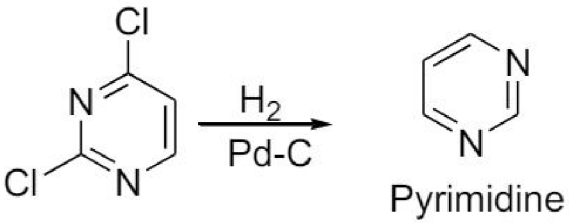
Barbituric acid Pyrimidine

2. From alkylpyrimidines:- Alkylpyrimidines on oxidation followed by decarboxylation yield pyrimidine.



4-Methylpyrimidine Pyrimidine

3. From chloropyrimidines:- Catalytic reductive dechlorination of 2,4-dichloropyrimidine yields pyrimidine.



2,4-Dicholropyrimidine Pyrimidine

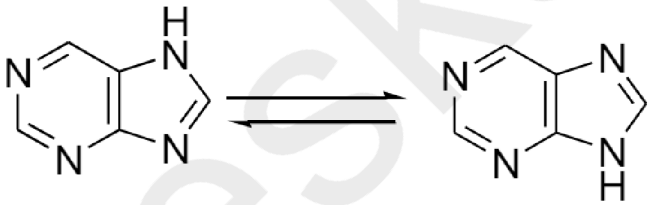
Medicinal Uses:

Pyrimidine derivatives have a broad variety of pharmaceutical applications. They are used as:

- **Antiviral** agents: They inhibit the replication of viruses.
- **Anticancer** agents: They interfere with the growth of cancer cells.
- **Antifungal** agents: They prevent the growth of fungi.
- **Antimalarial** agents: They are used in the treatment of malaria.
- **Sedatives and Hypnotics**: They are used to reduce excitement or irritability and induce sleep.
- **Anticonvulsant**: They prevent or reduce the severity of epileptic fits or other convulsions.
- **Anthelmintic**: They are used to destroy parasitic worms.
- **Antithyroid**: They are used to treat overactive thyroid.

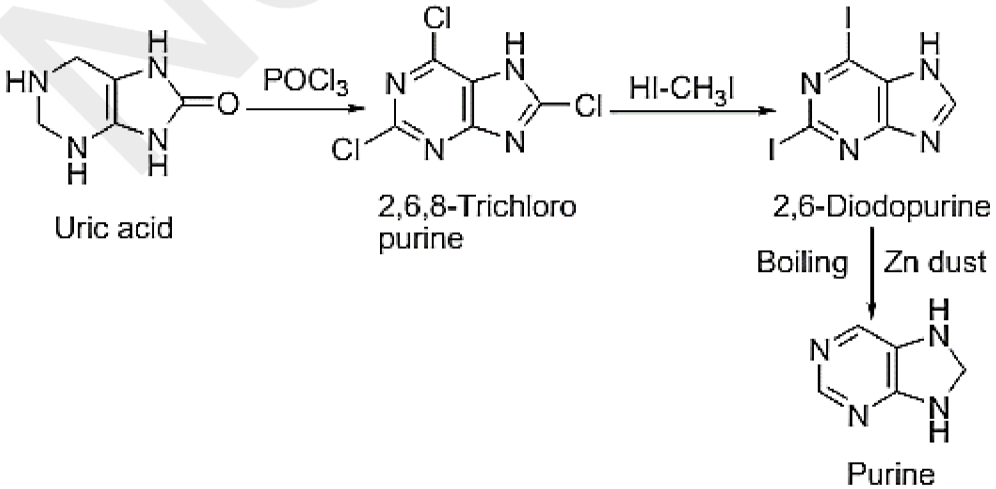
Purine:

- Purines are the cyclic compounds having two urea residues. It consists of a pyrimidine ring fused with an imidazole ring. It structure is given as follows:-



Synthesis:

Fischer method:- This is the oldest method for synthesis of purines like adenine and guanine. This method involves conversion of uric acid into 2,6,8-trichloropurine by reaction with PoCl3. Excess of chlorine atoms are removed by reduction with HI to form the required purine.



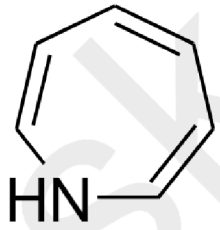
Medicinal Uses:

They are used as:

- **Antibacterial** and **Antifungal** agents: They inhibit the growth of bacteria and fungi.
- **Antitumor** and **Antiviral** agents: They inhibit the growth of tumors and replication of viruses.
- **Anti-HIV** activities: They inhibit the replication of HIV.
- Some of the most popular medicines in the purine category include **caffeine** (a CNS stimulation drug), **6-mercaptopurine** (an anti-cancer drug), and **azithromycin**.

Azepines:

- Azepines are unsaturated seven membered heterocyclic compounds containing nitrogen atom as heteroatom.



1H-Azepine

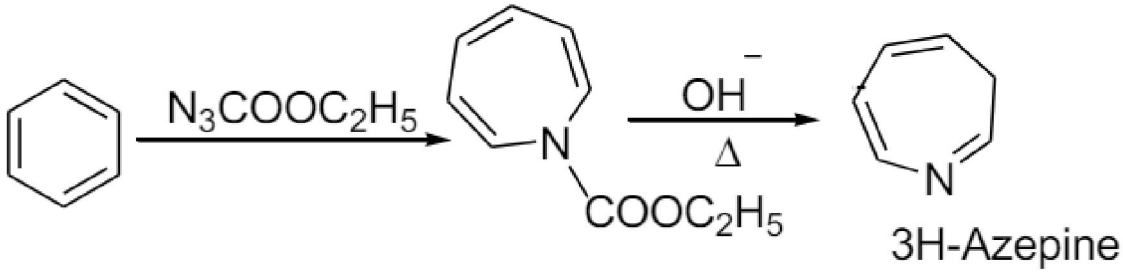
Four tautomeric azepines were identified. They are 1H, 2H, 3H and 4H-azepine. The numbering commences from the nitrogen atom. All azepines only 3H-azepine was isolated because of its high stability. 1H-azepine is unstable and immediately rearranges to 3Hazepine.

1. Azepines are not planar compounds.
2. They do not comply Huckel rule of π-electrons. Hence they are non-aromatic.
3. They are highly reactive.

Synthesis:-

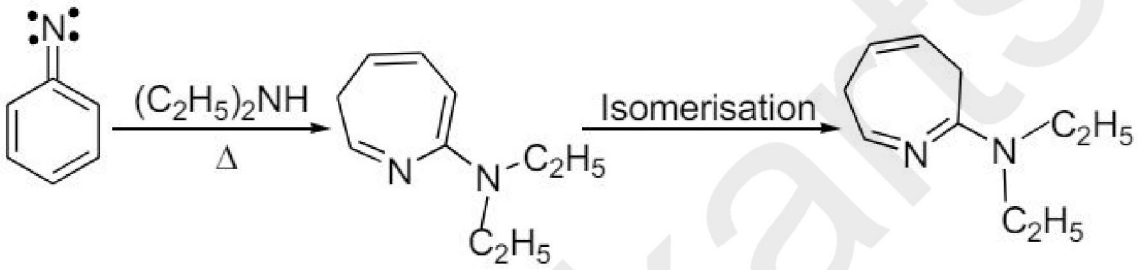
1. From benzene:-

- Benzene on treating with ethoxy carbonyl nitrene gives Nethoxycarbonyl 1H-azepine which on heating with alkali followed by isomerisation yields 3H-azepine.
- This reaction is an example of valence bond isomerisation.



2. From phenylazide:-

- Phenylazide on decomposition in presence of primary and secondary amines yields 3H-azepine derivative.



Medicinal Uses:

They are used as:

- **Antidepressants**: They are used to treat depression.
- **Tranquilizers**: They are used to reduce tension or anxiety.
- **ACE-inhibitors** and **Antihypertensives**: They are used to treat high blood pressure.
- **Anti-psychotics**: They are used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought).