Module-4 Learning Material

Learning Material

Course: B. Pharmacy 4th Sem

MODULE-4: SYNTHESIS, REACTIONS AND MEDICINAL USES OF FOLLOWING COMPOUNDS/ DERIVATIVES

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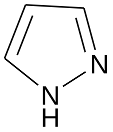
PYRAZOLE: Pyrazoles are the derivatives of a five-membered heterocyclic ring system called pyrazole. Pyrazole consists of two nitrogen atoms at 1 and 2 positions of the cyclic system.



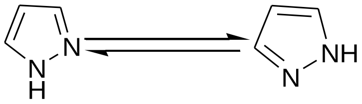
Physical Properties: 1. Pyrazole is a colourless solid.

2. It possesses a pleasant smell.

3. Pyrazole is soluble in water.

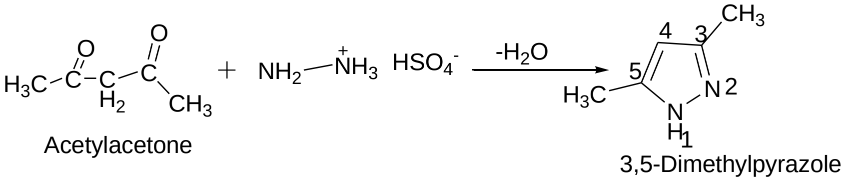
4. Pyrazole exhibits tautomerism.

5. Pyrazole has aromatic properties.

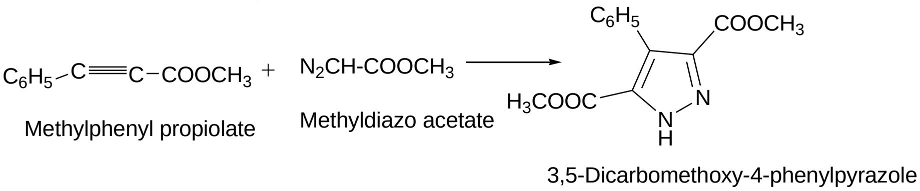


Synthesis

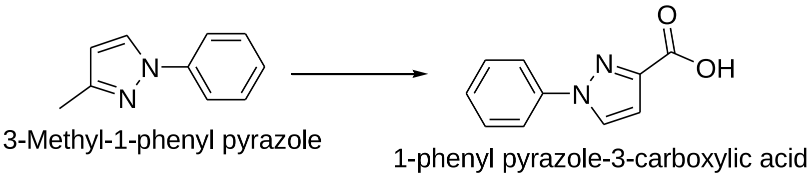
1. **From 1,3-dicarbonyl compounds-** 1,3-Dicarbonylcompounds react with hydrazine or hudroxylamine and gives pyrazoles.



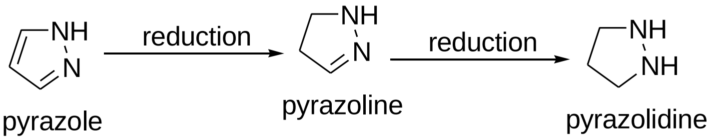
2. **From 1,3-di polar compounds-** Pyrazole derivatives can also be prepared by adding a diazo compound to an acetylenic derivative.



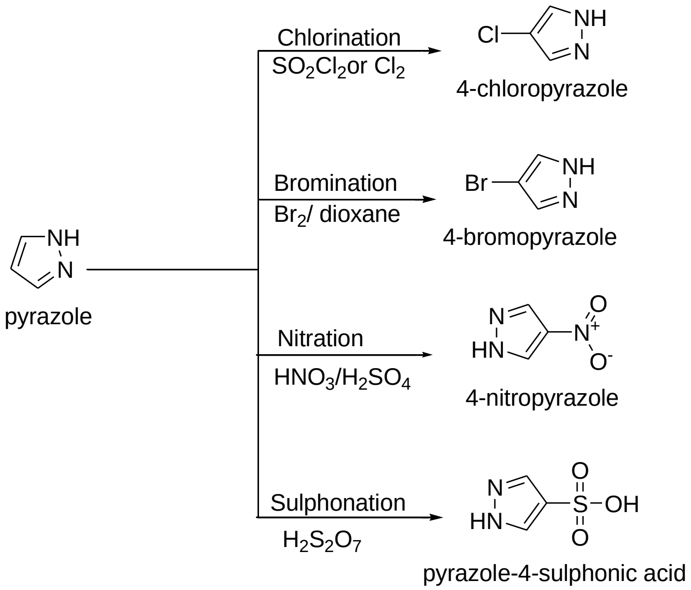
Chemical Properties: 1. Oxidation: Pyrazole is resistant to oxidizing agents but the side chain may be oxidized to carboxylic acid group in presence of potassium permanganate.



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



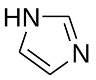
3.Electrophilic aromatic substitutions: Pyrazole is an aromatic compound. It readily undergoes electrophilic substitution at position 4 through the intermediate formation of arsenium ion. The electrophilic substitutiou is favoured in neutral or basic medium but not in acidic medium.



Medicinal compounds: 1. Analgin- Analgin is a pyrazoline derivative. It is an analgesic agent. It is also used as antipyretic.

2.Phenazone- Phenazone is 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one. It is used orally as an analgesic and antipyretic.

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.



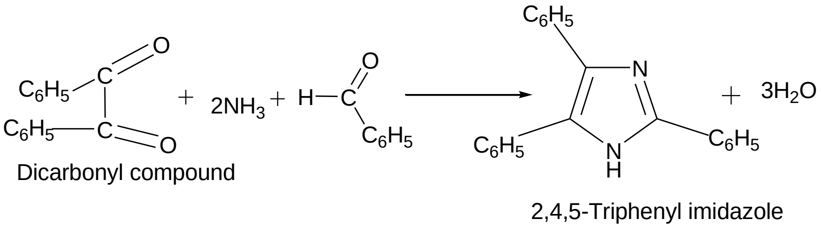
Imidazole

Physical Properties: 1. Imidazole is a colourless solid.

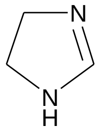
2. It exhibits amphoteric properties. It is more basic than Pyrazole and pyridine. It also contains pyrrole type of amino nitrogen in the ring structure and shows acidic properties.

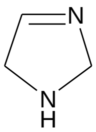
Synthesis:

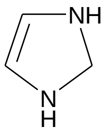
1. **From dicarbonyl compounds:** Imidazoles can be prepared by condensing a dicarbonyl compound with an aldehyde in presence of ammonia.



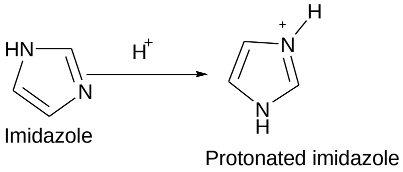
2. **By dehydrogenation of Imidazolines:** Imidazolines are the dihydrogenated derivatives of Imidazoles.TheseImidazolines can be readily dehydrogenated to imidazoles in presence of sulphur.


2- Imidazole

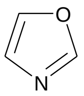

3- Imidazole


4-Imidazole

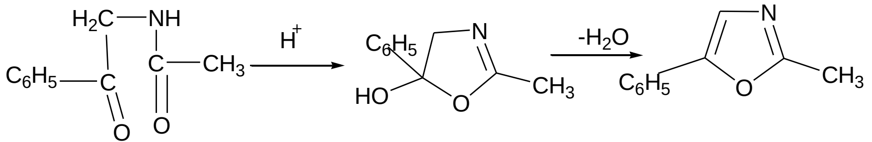
Chemical Reaction: 1. Basicity: Imidazole is a weak base forms salts with acids. It is more basic than Pyrazole, pyrrole and pyridine. Imidazole also has acidic properties the hydrogen atom of -NH can be displaced by metal. It is more acidic than pyrrole and pyridine.



OXAZOLE:- A group of 5-membered cyclic compounds composed of oxygen and nitrogen as heteroatoms are oxazoles. In oxazoles the oxygen and nitrogen atoms are separated by one carbon atom.


oxazole

Synthesis:- 1. From α-acylamino carbonyl compound:- Oxazole is prepared by refluxing α-acylamino 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.



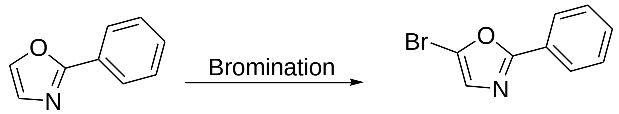
α-Acylaminocarbonyl compound

5-Methyl-2-phenyloxazole

Physical Properties: 1. Oxazole are liquids. They have pyridine like odour and boil at 69^{o}C.

2. Oxazole are weakly basic in nature.

Chemical 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.

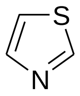


2-phenyloxazole

5-Bromo-2-phenyloxazole

Medicinal uses: Oxazole show broad biological activities like antibacterial, antifungal, antiviral, antitubercular, anticancer and anti-inflammatory.

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



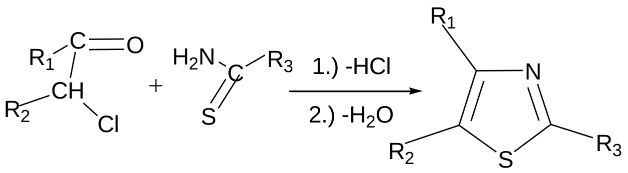
Thiazole

Physical Properties:- 1. Thiazole is a colourless liquid.

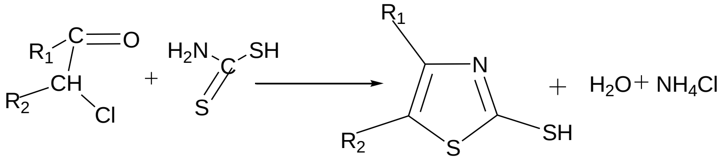
2. It has the characteristic odour like pyridine and is miscible with water.

3. It is weakly basic and behaves as a tertiary base.

Synthesis:-1. Condensation of α-chlorocarbonyl compounds with thioamides:- Thiazoles are synthesized by condensing α-chlorocarbonyl compounds with thioamides.

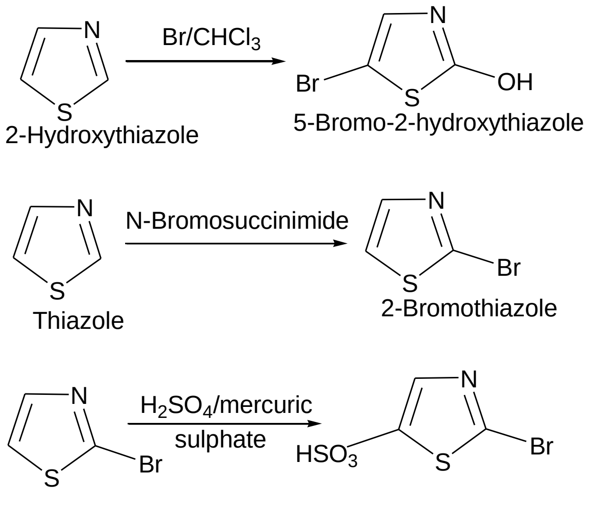


2.Condensation of α-chloroketones with ammonium dithiocarbonate:- Thiazoles may also be prepared by the condensation of α-chloroketones with ammonium dithiocarbonate.



2-Mercaptothiazole

Chemical Properties:- 1. 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.



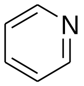
2-Hydroxythiazole 5-Bromo-2-hydroxythiazole

Thiazole 2-Bromothiazole

2-Bromothiazole 2-Bromothiazole-5-sulphonic acid

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

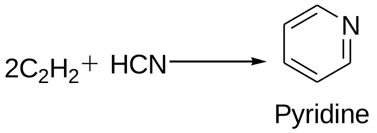
PYRIDINE:- Pyridine is a six membered heterocyclic ring system containing nitrogen as heteroatom. Pyridine is a liquid of characteristic odour.



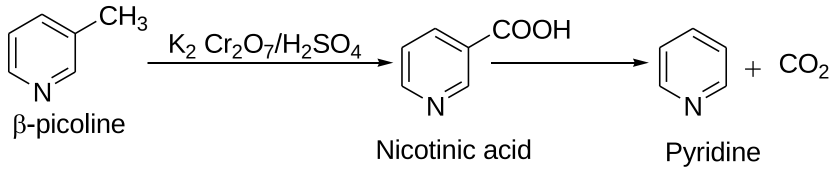
Pyridine

Preparation:- 1. Pyridine is present in light oil fraction of coal tar distillation. The light oil fraction is treated with dilute sulphuric acid. This dissolves basic substances including pyridine. The acid layer is isolated, neutralised and fractionated several times to get pure pyridine.

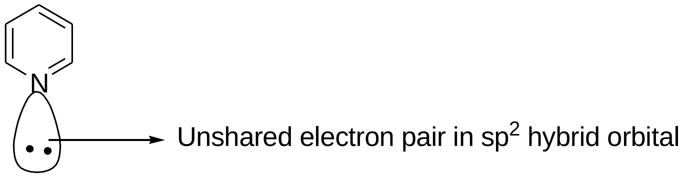
2. Pyridine is prepared by passing a mixture of acetylene and HCN through a red hot tube.



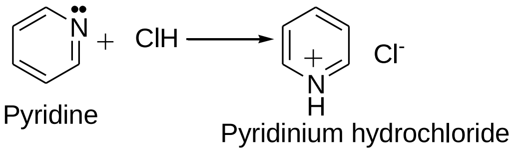
3.**From picoline**:- On oxidation with potassium dichromate and sulphuric acid β-picoline changes into nicotinic acid. This on decarboxylation with calcium oxide gives rise to pyridine.



Structure of Pyridine: Pyridine has a cyclic, planar structure. In pyridine the aromatic sextet is complete without using the nitrogen lone pair of electrons. This unshared electron pair occupies an sp^2 orbital.

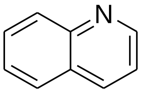


Properties:- 1. Basicity:- Pyridine is basic in nature and reacts with acids to forms salts. The basicity of pyridine is due to the availability of lone pair of electrons on nitrogen atom. Pyridine is a much weaker base than alkylamines because the lone pair of electrons of nitrogen are present in sp^2 hybrid orbital instead of sp^3 hybrid orbital. Consequently, the lone pair is more tightly held and is less available for protonation due to more S character of pyridine nitrogen.

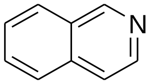


Medicinal Uses:- Used in antitubercular drug, normal functioning of skin, intestinal tract and nervous system.

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

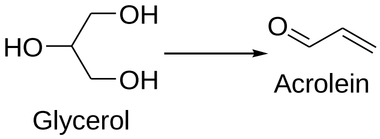


Isoquinoline

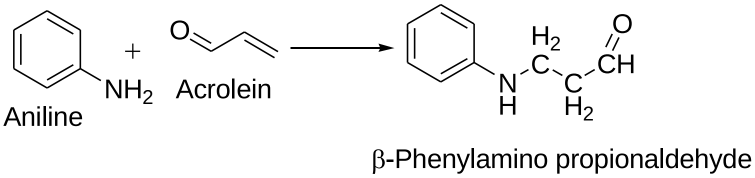
Preparation: Naturally quinoline and isoquinoline are available in coal tar, bone oil and alkaloids. Synthetically they are prepared by the following methods:

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 H_2SO_4 gives acrolein.



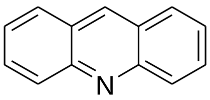
2.Nucleophilic addition of aniline to acrolein form β-phenylamino propionaldehyde.



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.

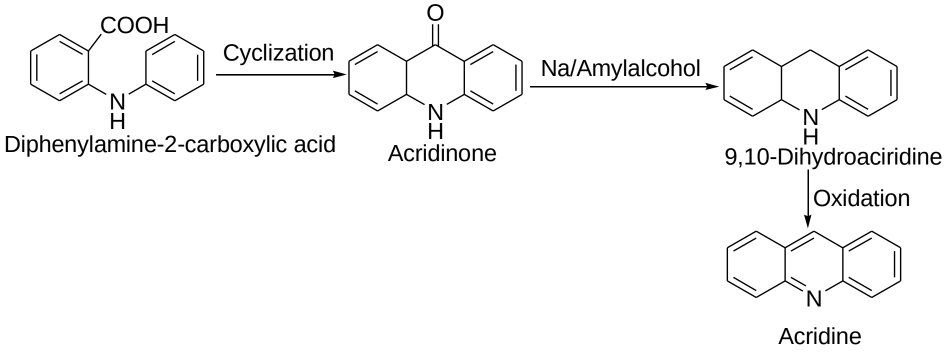
ACRIDINE: Acridine is a condensed heterocyclic system. It is a tertiary base. Acridine is also known as benzoquinoline or dibenzpyridine.



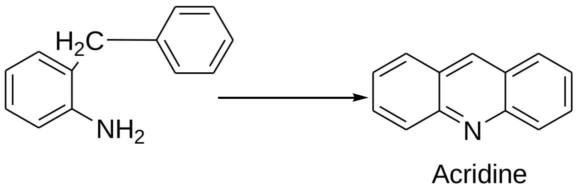
Acridine

Acridine is colourless solid. It occurs in anthracene fraction of coal tar.

Preparation: 1. Oxidation of dihydroacridine with oxidizing agent.

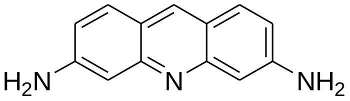


2. Acridine can also be prepared by passing o-aminodiphenylmethane through a red hot tube.

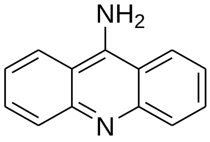


Acridine is a potent substance of a number of dyes and antiseptic. Acridine ring system is present in dyes and pharmaceutical substances.

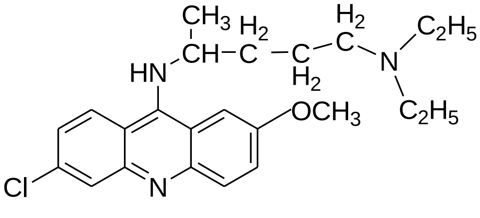
1. **Proflavine:** Chemically proflavine is 3,6-diaminoacridine. It is effective against many gram positive bacteria hence it is used as a disinfectant and antiseptic.



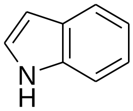
2. **Aminacrine:** Chemically aminacrine is 9-amino Acridine. It is effective against many gram positive bacteria hence it is used as a antiseptic and disinfectant.



3. **Quinacrine:** Chemically quinacrine is N-(6-chloro-2-methoxy-9-Acridinyl)-N,N-diethylpentanediamine. Quinacrine was formerly used for the treatment of malaria but it has been replaced by chloroquine.

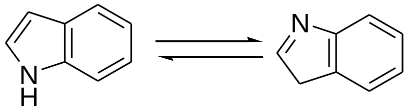


INDOLE: Bayer first synthesized Indole in 1866. Indole consists of a pyrrole moiety which is fused to benzene ring. The two rings are flat and associate with Pi-delocalized electrons. Therefore Indole exhibits aromatic properties. The IUPAC name of Indole is 1H-benzopyrrole.



Indole

Indole exhibits tautomerism. The tautomeric form of Indole are

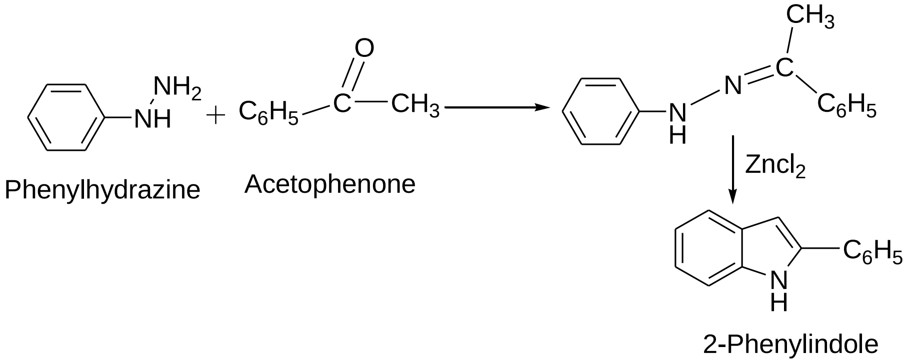


Physical properties: 1. Indole is colourless solid.

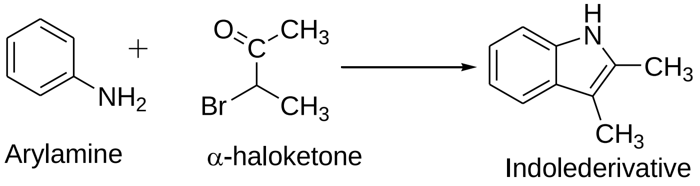
2. It has pleasant odour.

3. It behaves as a weak acid and a weak base.

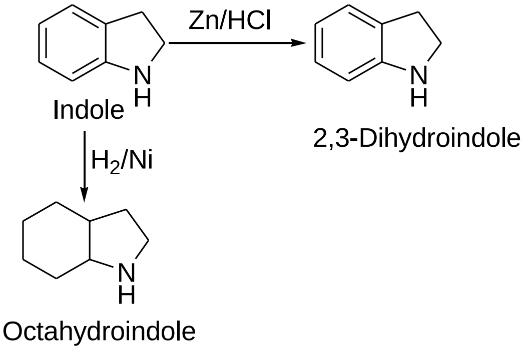
Synthesis: Fischer -Indole synthesis: In this method phenylhydrazoneof aldehyde or ketone is cyclized with acid catalyst.



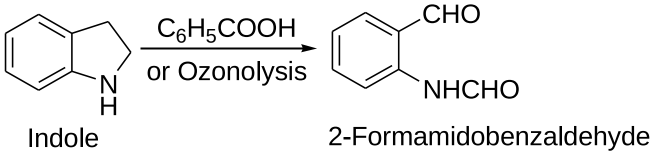
Bischler synthesis: In this method Indole derivatives can be prepared by heating aryl amine with haloketones.



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.



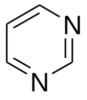
Oxidation: In presence of peroxy acid or ozone Indole is oxidized to form 2-formamidobenzaldehyde by opening the heterocyclic ring.



Uses: It is used in cancer prevention.

It is used in tumors inside respiratory tract.

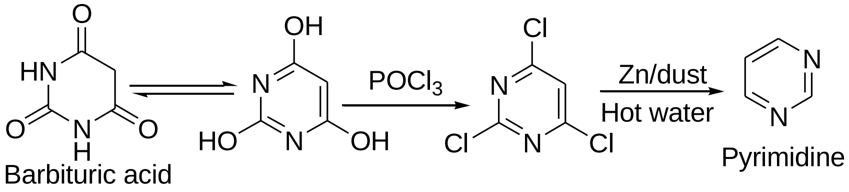
PYRIMIDINE:- Pyrimidines are the derivatives of pyrimidine. Pyrimidine is a six membered heterocyclic ring system consisting of two nitrogen atoms at 1 and 3 positions**.**



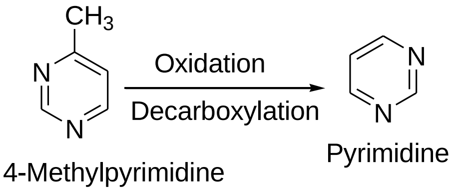
Pyrimidine

Synthesis:-

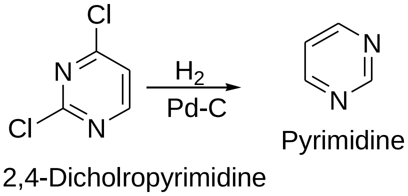
1. **From barbituric acid:-** Pyrimidine is prepared from barbituric acid by the following reactions:-



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



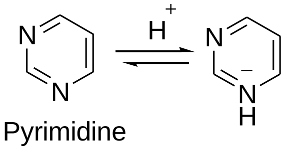
3. **From chloropyrimidines:-** Catalytic reductive dechlorination of 2,4-dichloropyrimidine yields pyrimidine.



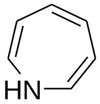
Physical Properties:- Pyrimidine is a colourless solid.
It is weakly basic.
Pyrimidine has a dipole moment of 2.4D.

Chemical Properties:-

Basicity:- Pyrimidine is weakly basic than pyridine due to the electron withdrawing effect of the second nitrogen atom present in pyrimidine. Pyrimidine is protonated in acidic medium. Presence of electron releasing groups enhances the basicity.



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



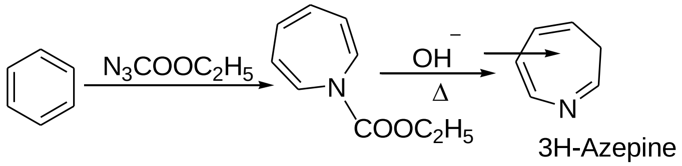
1H-Azepine

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 3H-azepine.

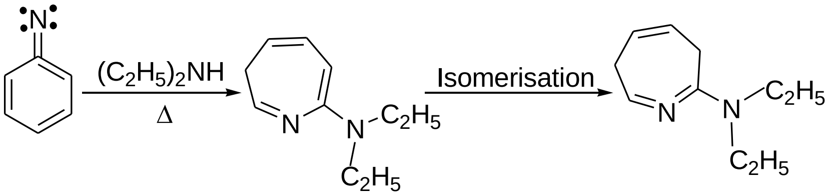
1. Azepines are not planar compounds.
2. They do not comply Huckel rule of π-electrons. Hence they are non-aromatic.
3. They are highly reactive.

Synthesis:-

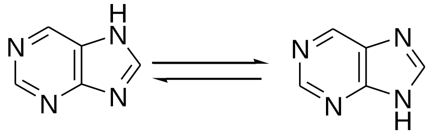
1. **From benzene:-** Benzene on treating with ethoxy carbonyl nitrene gives N-ethoxycarbonyl 1H-azepine which on heating with alkali followed by isomerisation yields 3H-azepine. This reaction is an example of valence bond isomerisation.



2. **From phenylazide:-** Phenylazide on decomposition in presence of primary and secondary amines yields 3H-azepine derivative.



PURINES:- 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:-



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 $PoCl_3$. Excess of chlorine atoms are removed by reduction with HI to form the required purine.