Name of Unit	Synthesis, Reactions and Medicinal uses of Following Compounds/ Derivatives.
Subject /Course Name	Pharmaceutical Organic Chemistry-III
Subject/Course ID	BP401T
Class: B.Pharm. Semester	4th
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Learning Outcome of Module 4

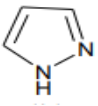
LO	Learning Outcome	Course Outcome Code
LO1.	To gain knowledge about Heterocyclic Compounds.	BP401.1
LO2.	To understand about Synthesis methods of Heterocyclic Compounds.	BP401.1
LO3.	To Understand about Reactions associated with these Heterocycles.	BP401.1
LO4.	To get the knowledge about Medicinal Compounds of these heterocycles.	BP401.3

Content Table

Topic
• Synthesis, Reactions and Medicinal uses of Following Compounds/ Derivatives. • Pyrazole • Imidazole • Oxazole • Thiazole • Pyridine, Basicity of Pyridine • Quinoline • Isoquinoline • Acridine • Indole • Pyrimidine • Purine • Azepine

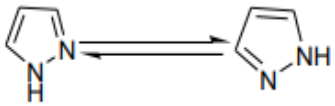
Pyrazole

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.



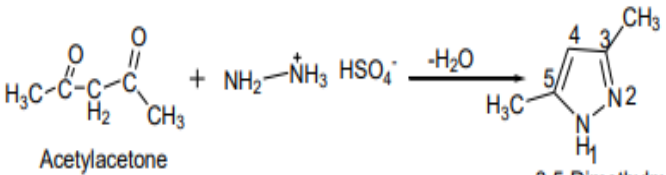
Physical Properties: -

1. Pyrazole is a colorless solid.
2. It possesses a pleasant smell.
3. Pyrazole is soluble in water.
4. Pyrazole exhibits tautomerism.
5. Pyrazole has aromatic properties.

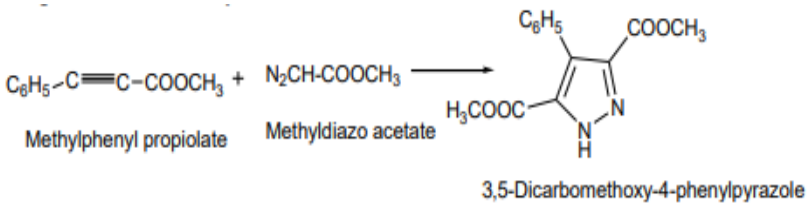


Synthesis Methods of Pyrazole :-

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

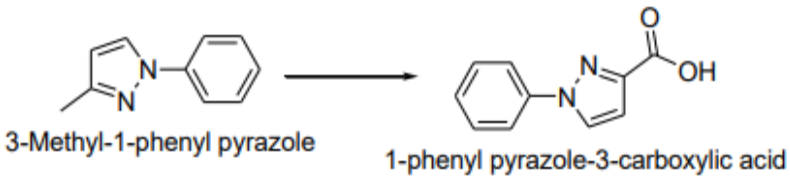


2. From 1,3-di polar compounds- Pyrazole derivatives can also be prepared by adding a diazo compound to an acetylenic derivative.

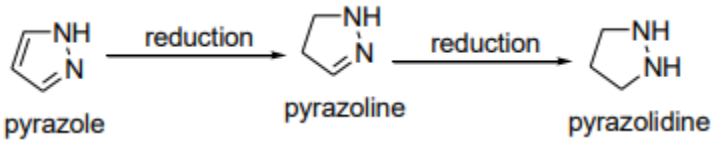


Chemical Properties: -

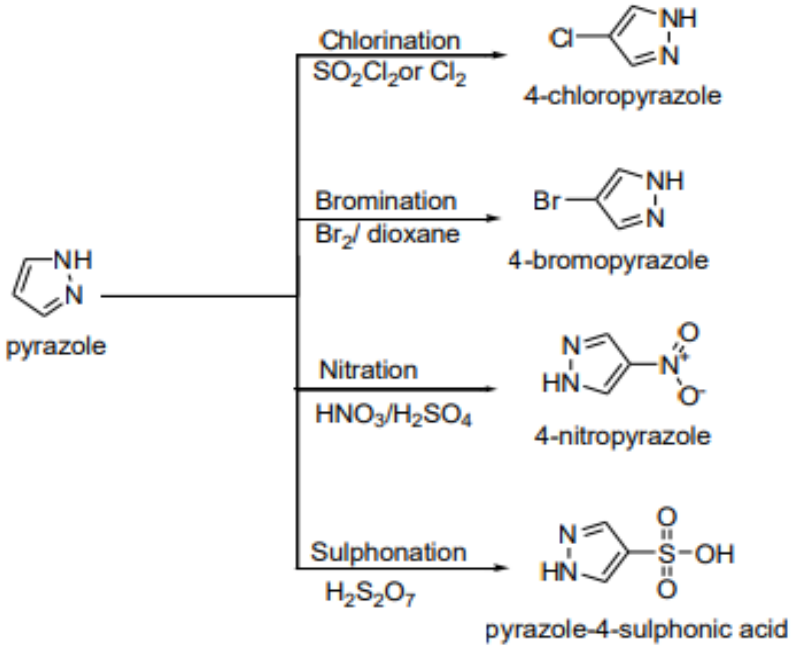
1.Oxidation: Pyrazole is resistant to oxidizing agents but the side chain may be oxidized to carboxylic acid group in presence of potassium permanganate.



2.Reduction: Pyrazole ring system can be reduced with molecular hydrogen and metal catalyst. Pyrazoline 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 substitution is favoured in neutral or basic medium but not in acidic medium.



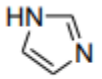
Medicinal compounds:

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

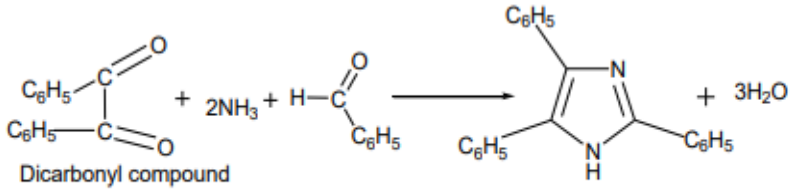
Physical Properties: -

1. Imidazole is a colorless 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 Methods of Imidazole: -

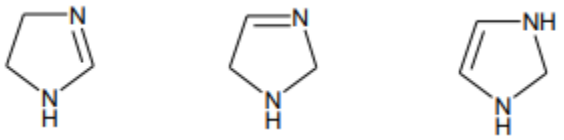
1. From dicarbonyl compounds: - Imidazoles can be prepared by condensing a dicarbonyl compound with an aldehyde in presence of ammonia.



Dicarbonyl compound

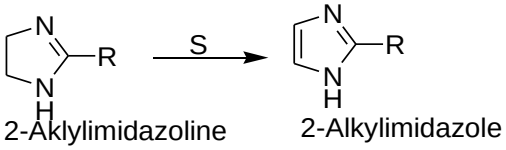
2,4,5-Triphenyl imidazole

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



2- Imidazoline 3-Imidazoline 4-Imidazoline

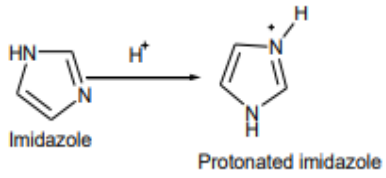
These imidazolines can be readily dehydrogenated to imidazoles in presence of sulphur.



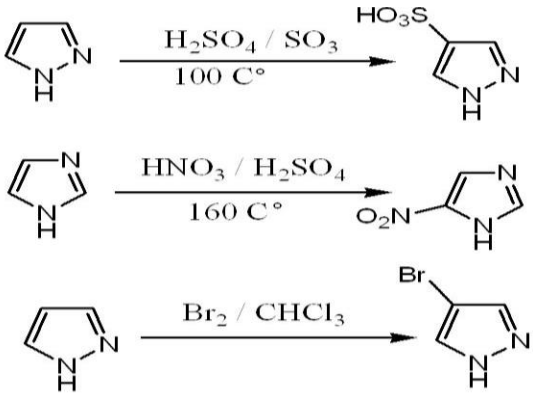
2-Aklylimidazoline 2-Alkylimidazole

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.

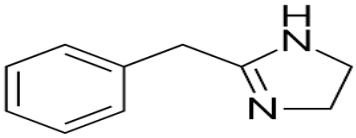


2.Electrophilic Substitution Reaction: - Imidazole is more susceptible to electrophilc attack than pyrazole, thiazole, Furan and Thiophene.

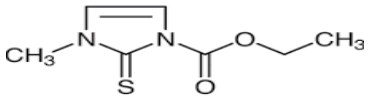


Medicinal uses of Imidazole: -

1.Tolazoline: - It is an anti-adrenergic and vasodilator. It is used to reduce pulmonary artery presuure and in the treatment of peripheral vascular disorders.



2.Carbimazole: - Carbimazole is a medicine used **to treat an overactive thyroid (hyperthyroidism)**. This is when your thyroid gland makes too many thyroid hormones. Your thyroid controls things like your heart rate and body temperature. When it makes too many hormones, you can have symptoms such as weight loss, mood swings and feeling irritable. Carbimazole helps to ease these symptoms by reducing the amount of hormones your thyroid produces.



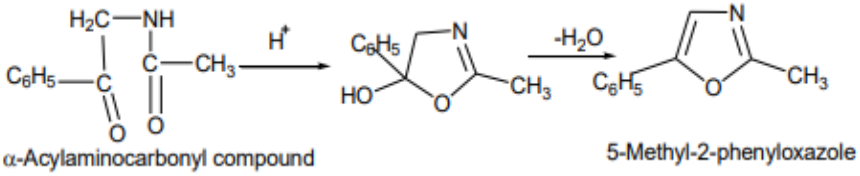
Oxazole:

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 Methods of Oxazole: -

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.



α-Acylaminocarbonyl compound

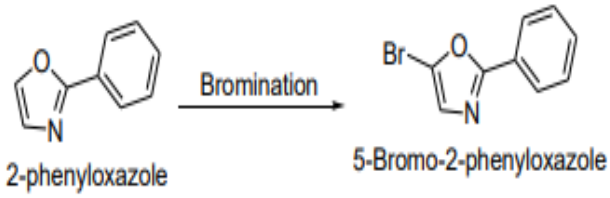
5-Methyl-2-phenyloxazole

Physical Properties:

1. Oxazole are liquids. They have pyridine like odor and boil at 69°C.
2. Oxazole are weakly basic in nature.

Chemical Reactions: -

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.

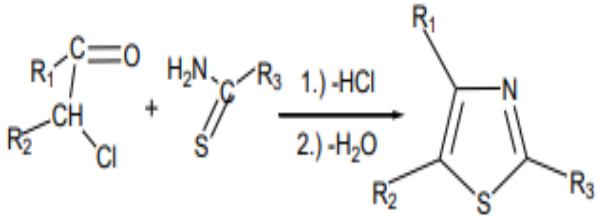
Thiazole

Physical Properties: -

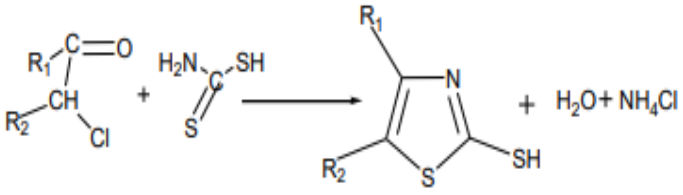
1. Thiazole is a colorless liquid.
2. It has the characteristic odor like pyridine and is miscible with water.
3. It is weakly basic and behaves as a tertiary base.

Synthesis Methods of Thiazole: -

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



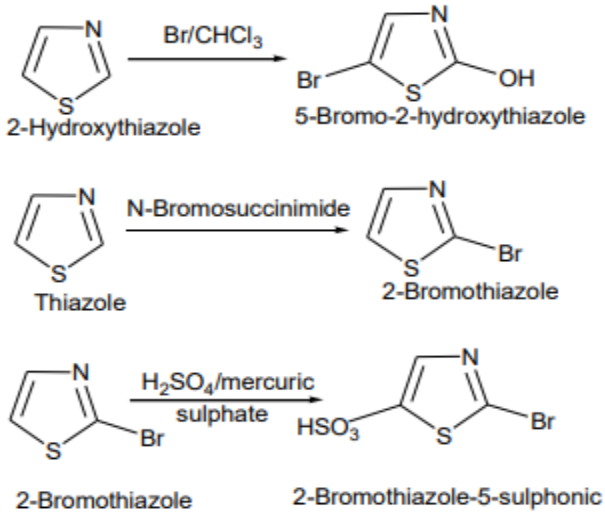
2.Condensation of α-chloroketones with ammonium dithiocarbonate: -Thiazoles may also be prepared by the condensation of α-chloroketones with ammonium dithiocarbonate.



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.



Medicinal Uses: -

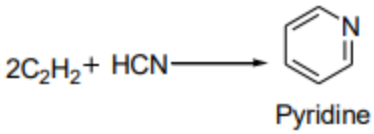
Thiazoles include mainly dyes and fungicides. Another widely used thiazole derivative is the non-steroidal anti-inflammatory.

PYRIDINE

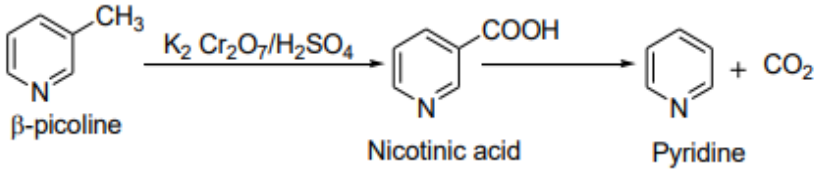
Pyridine is a six membered heterocyclic ring system containing nitrogen as heteroatom. Pyridine is a liquid of characteristic odor.

Synthesis Methods of Pyridine: -

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, neutralized 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.

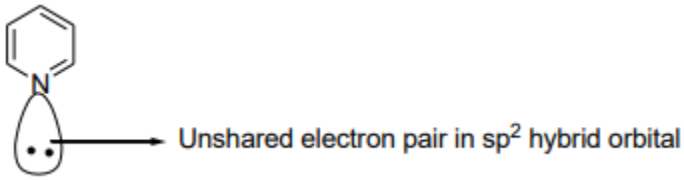


3.From Picoline:- On oxidation with potassium dichromate and sulphuric acid β-picoline changes into nicotinic acid. This on decarboxylation with calcium oxide gives rise to pyridine.



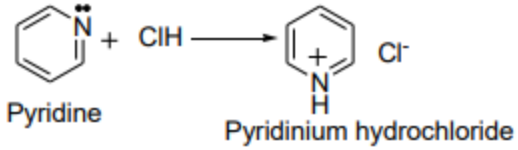
Structure of Pyridine: -

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.



Chemical 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 sp2 hybrid orbital instead of sp3 hybrid orbital. Consequently, the lone pair is more tightly held and is less available for protonation due to more S character of pyridine nitrogen.

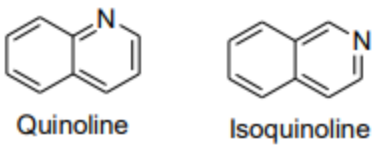


Medicinal Uses: -

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.



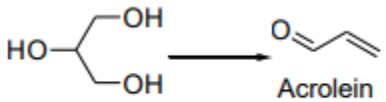
Quinoline Isoquinoline

Synthesis Methods of Quinoline and Isoquinoline: -

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

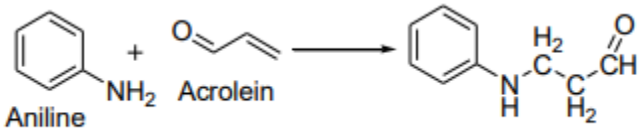
a. Quinoline is prepared by the reaction of aniline with glycerol, conc. Sulphuric acid, nitrobenzene and ferrous sulphate. This reaction is known as **Skraup synthesis**.

1. Glycerol on dehydration with hot H_2SO_4 gives acrolein.



Glycerol Acrolein

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

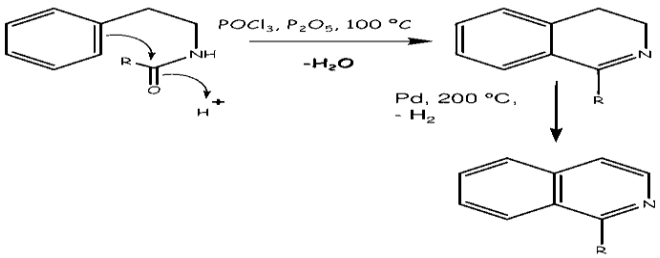


Aniline Acrolein

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.

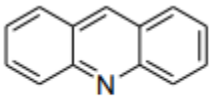


Medicinal Uses: -

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.

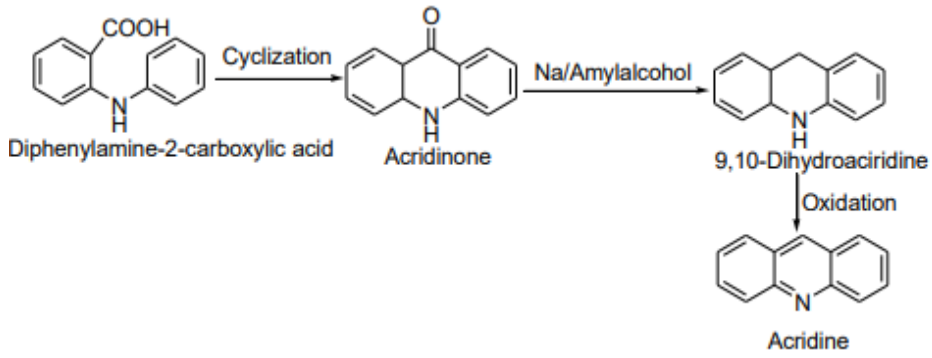


Acridine

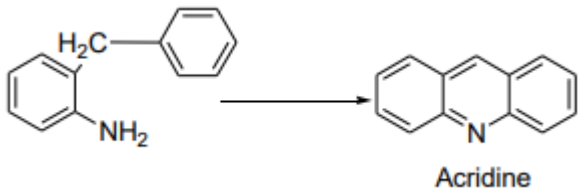
Acridine is colourless solid. It occurs in anthracene fraction of coal tar.

Synthesis Methods of Acridine: -

1. Oxidation of dihydroacridine with oxidizing agent.



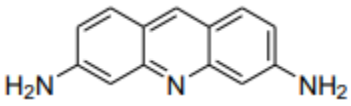
2. Acridine can also be prepared by passing o-aminodiphenylmethane through a red hot tube.



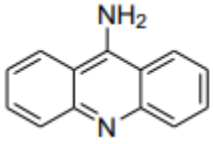
Medicinal Uses: -

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

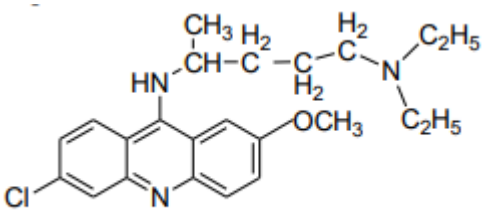
1. Proflavine: Chemically proflavine is 3,6-diaminoacridine. It is effective against many gram positive bacteria hence it is used as a disinfectant and antiseptic.



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.

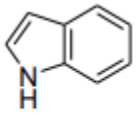


3. Quinacrine: Chemically quinacrine is N-(6-chloro-2-methoxy-9-Acridinyl)-N,N diethylpentanediamine. Quinacrine was formerly used for the treatment of malaria but it has been replaced by chloroquine.



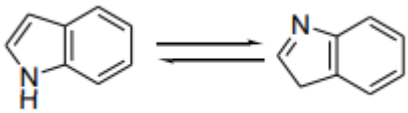
INDOLE

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

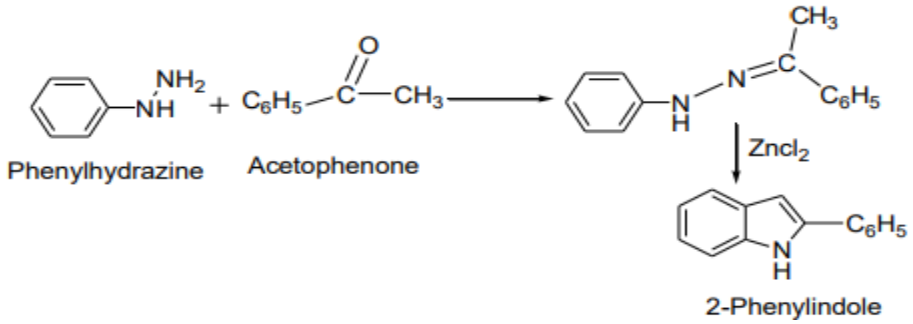


Physical Properties: -

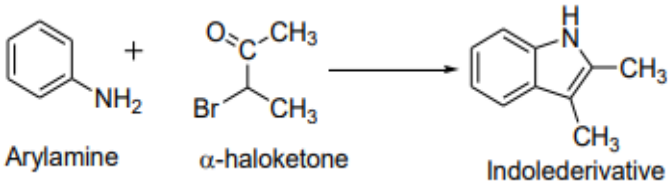
1. Indole is colorless solid.
2. It has pleasant odor.
3. It behaves as a weak acid and a weak base.

Synthesis Methods of Indole: -

1.Fischer -Indole synthesis: - In this method phenylhydrazone of aldehyde or ketone is cyclized with acid catalyst.

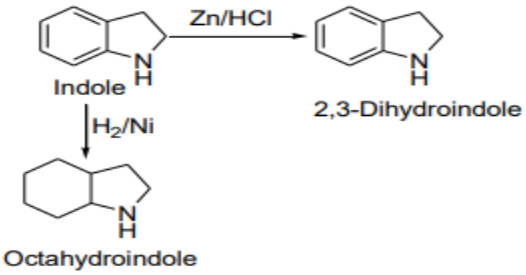


2.Bischler Synthesis: - In this method Indole derivatives can be prepared by heating aryl amine with haloketones.

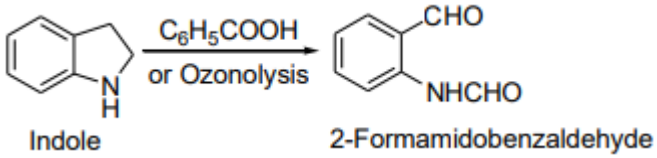


Chemical Reaction: -

1.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.



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



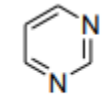
Medicinal Uses: -

1.It is used in cancer prevention.

2.It is used in tumors inside respiratory tract.

Pyrimidine

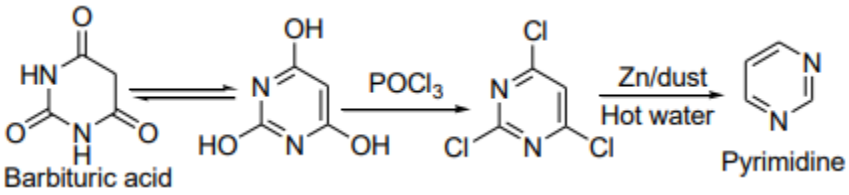
Pyrimidines are the derivatives of pyrimidine. Pyrimidine is a six membered heterocyclic ring system consisting of two nitrogen atoms at 1 and 3 positions.



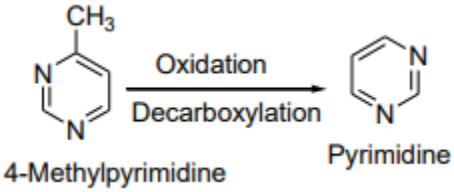
Pyrimidine

Synthesis Methods of Pyrimidine: -

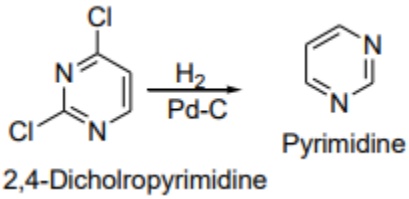
1. From Barbituric Acid: - Pyrimidine is prepared from barbituric acid by the following reactions:-



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



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



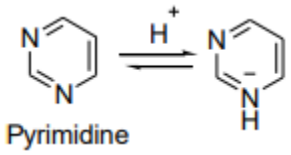
Physical Properties: -

1.Pyrimidine is a colorless solid. It is weakly basic.

2.Pyrimidine has a dipole moment of 2.4D.

Chemical Properties: -

1.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.



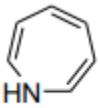
Pyrimidine

Medicinal uses : -1. Pyrimidine derivatives of Sulpha drugs are used in treatment of UTI meningitis and patients allergic to penicillin for eg. Sulphadiazine, sulphadoxine and sulphamerzine.

2. Pyrimidine also have **antifungal properties**. Flucytosine is fluorinated pyrimidine used in treatment of systemic fungal infections.

Azepines:

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



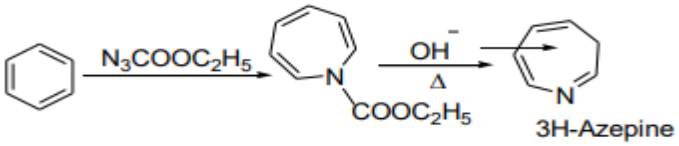
1H-Azepine

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.

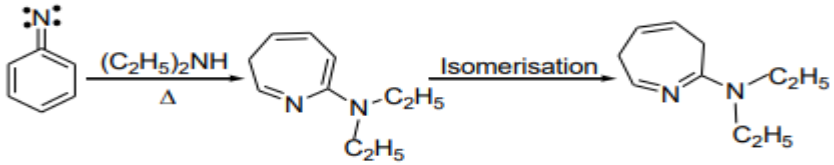
1. Azepines are not planar compounds.
2. They do not comply Huckel rule of π-electrons. Hence they are non-aromatic.
3. They are highly reactive.

Synthesis Methods of Azepine: -

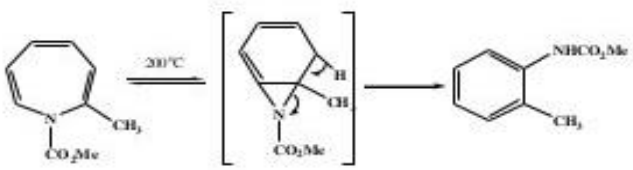
1. From Benzene: - Benzene on treating with ethoxy carbonyl nitrene gives Nethoxycarbonyl 1H-azepine which on heating with alkali followed by isomerisation yields 3H-azepine. This reaction is an example of valence bond isomerisation.



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



Chemical Reactions: - 1. Aromatization: -



Medicinal uses: -Important drugs from azepine category include

1.Imipramine (antidepressant)

2.Diazepam (tranquillizer)

3.Emocapril (ACE-inhibitor/antihypertensive)

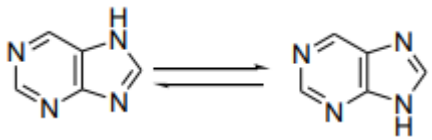
4.Omapatrilat (anti-hypertensive)

5. Quetiapine (anti-psychotic)

6.Tianeptine (anti-depressant)

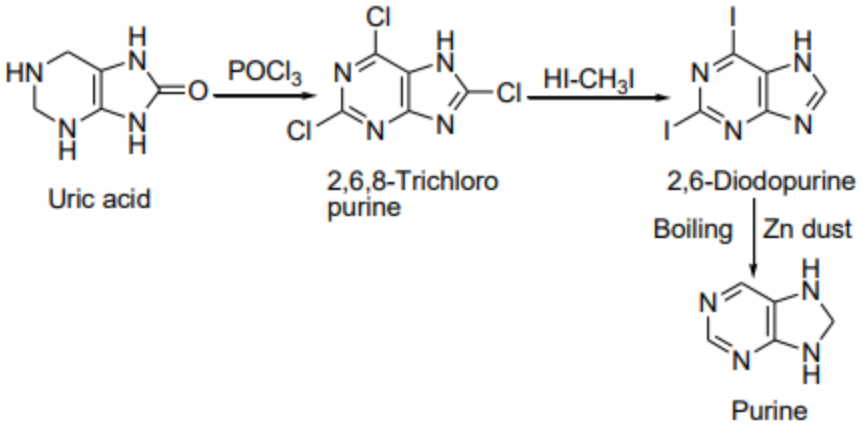
PURINES

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:



Preparation Methods of Purines: -

1.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:- Purine analogs are having **antibacterial, antifungal, antitumor, antiviral, and anti-HIV activity**.

Important drugs from the purine category include **caffeine (CNS stimulant), 6-mercaptopurine (anti-cancer), azithromycin.** Drugs having isostere of purine include **sildenafil (erectile dysfunction), allopurinol (anti-gout), tubercidin (anti-cancer).**

Question carrying (2 marks)

1. Why pyridine is more basic than pyrrole?
2. Why pyridine is less reactive than benzene and other five membered heterocyclic compound.
3. Why pyridine is weaker base than aliphatic tertiary amines?
4. Why imidazole is more basic than pyrazole?
5. Is pyridine aromatic?
6. Write the structure of Acridine.
7. Give the reaction of Bischler-Napieralski for Isoquionline.
8. What do you meant by Condensed Five and Six membered heterocyclics? Give some example.
9. Write medicinal uses of Quinoline.
10. Write medicinal uses of Isoquinoline.
11. Explain basicity of Pyridine.
12. Give any two synthesis of acridine.
13. What happens when oxazole is treated with base?
14. Why Isoquinoline is more basic than Quionline?
15. Why Electrophilic Substitution reactions of indole takes place at position 3?
16. Draw the structure of 1,2- Oxazole and Isoquionline.

17. Enlist two chemical properties of Oxazole.
18. Give an example of Electrophilic substitution reactions of pyridine.
19. Define Fischer-Indole Synthesis.
20. Pyrrole is less aromatic than pyridine. Why?

Questions carrying (5 or 10 marks)

1. Describe Skraup synthesis of Quinoline with its mechanism.
2. Write Nucleophilic and Electrophilic Substitution reactions of Oxazole.
3. Give chemical reactions of thiazole.
4. Give Electrophilic Substitution reactions of indole.
5. Describe Fischer- Indole Synthesis with its mechanism.
6. What are Heterocyclic Compounds? How they are Classified? Give one method of synthesis each of following:

1) Indole 2) Pyridine 3) Pyrazole

7. Give the Synthesis methods of Imidazole.