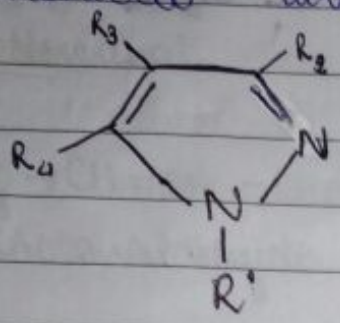
Unit-4

Heterocyclic compound-II

Pyrazole:

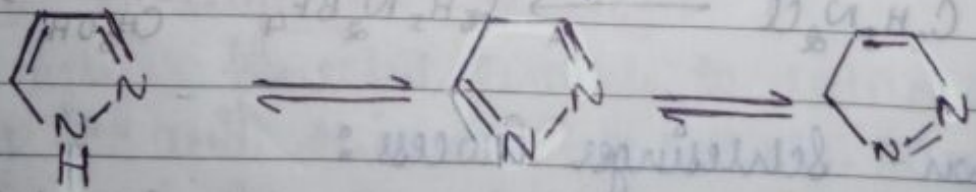
Pyrazole is a 5-membered heterocyclic compound which contains 2 Nitrogen molecules. It is an important organic compound in pharmaceutical & agrochemical industries.



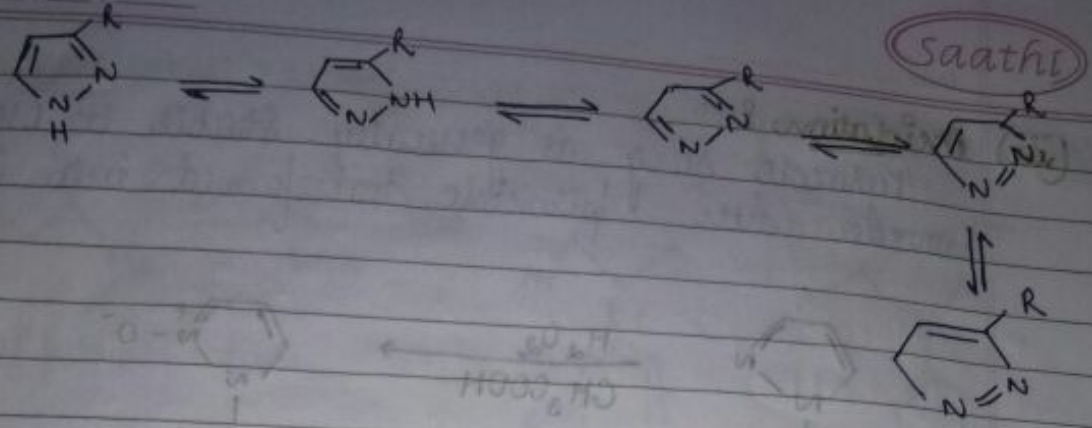
Chemistry -

Pyrazole molecules are aromatic in nature because their planar conjugated ring structure have 6 delocalised π-electron.

Pyrazoles, just like other nitrogen-containing heterocycles, have different tautomeric structures. Three tautomeric forms can be written for unsubstituted pyrazole.



Pyrazole derivatives in which the two neighbour Carbon atoms of the nitrogen atoms on the ring carry different substituents have five tautomeric structures.



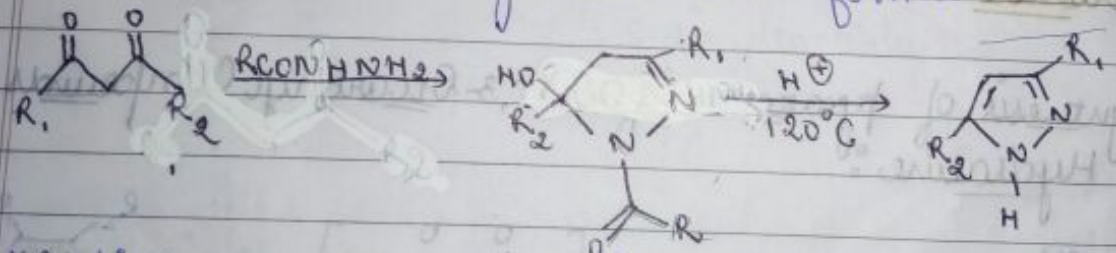
Properties - [Physical]:

- It is a crystalline solid having pyridine-like odour & bitter taste.
- It's melting point is 70°C.
- It's boiling point is 187°C.
- It is soluble in water & organic solvents.

[Chemical]:

(i) Ring opening Reaction:

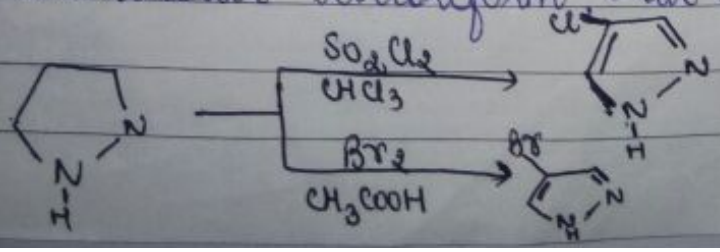
When pyrazolium salts are treated with caustic alkalis, disubstituted hydrazines are formed.



1,3-diakenes — 4,5-dihydro-5-hydroxy pyrazole — Pyrazole

(ii) Halogenation:

Pyrazole can be chlorinated by chlorinating reagent such as chlorine water, chlorine in Carbontetrachloride, hypochlorous acid, chlorine in acetic acid & Sulfuryl chloride in chloroform. Pyrazole is brominated by bromine in chloroform ~~bromine~~ bromine in acetic acid.



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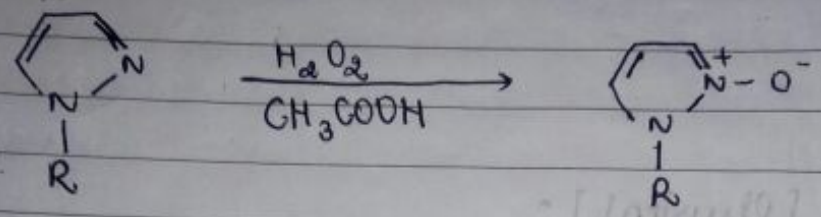
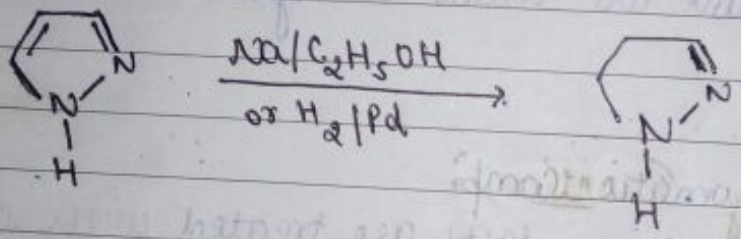
(iii) Oxidation :

Pyrazole ring is generally stable to oxidation, however with peroxide transformed into its 2-oxide.



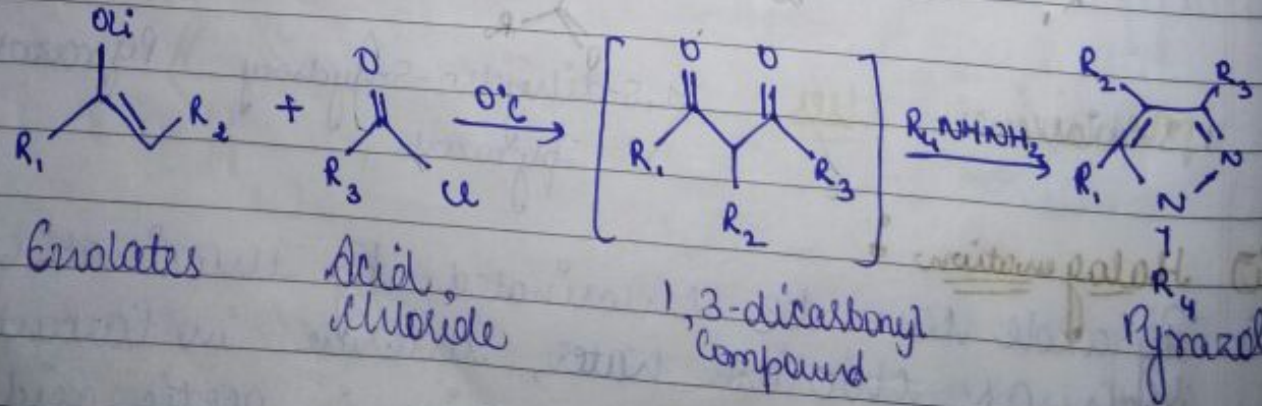
(iv) Reduction :

The reduction of pyrazoles with sodium & alcohol or by catalytic hydrogenation over palladium results in 2- pyrazolines.



Syntsesis-

(1) Synthesis of pyrazole from 1,3-Dicarbonyl Compounds & Hydrazine :



Enolates Acid chloride 1,3-dicarbonyl Compound Pyrazole

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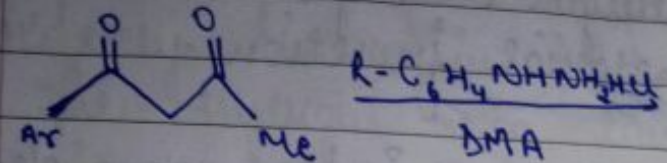
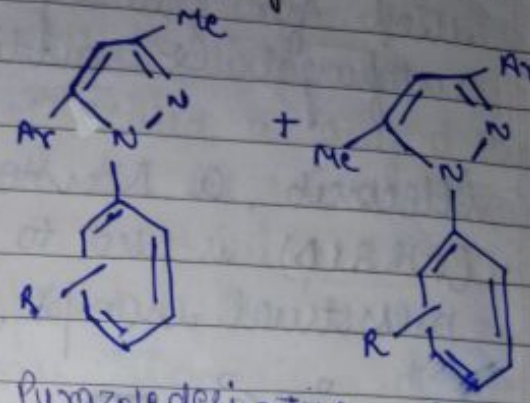
(ii) Cyclocondensation Reaction b/w arylhydrazines & 1,3-Diketones

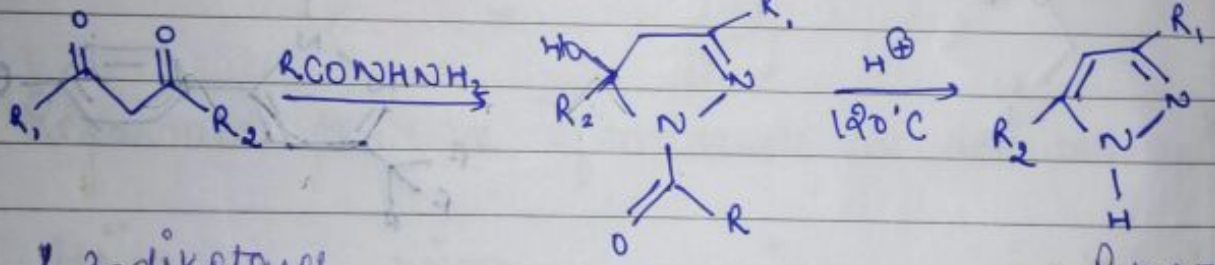


1-Arylbutane-1,3-diones



Pyrazole derivative Pyrazole isomer

(iii) On heating 1,3-diketones with acylhydrazines, 4,5-dihydro-5-hydroxy pyrazole derivative having complete regioselectivity are obtained.



1,3-diketones

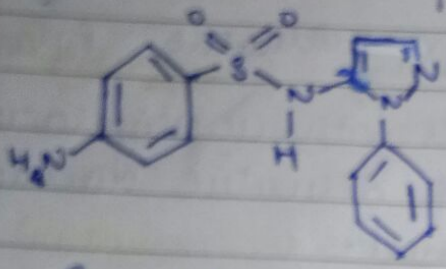
4,5-dihydro-5-hydroxy pyrazole

Pyrazole

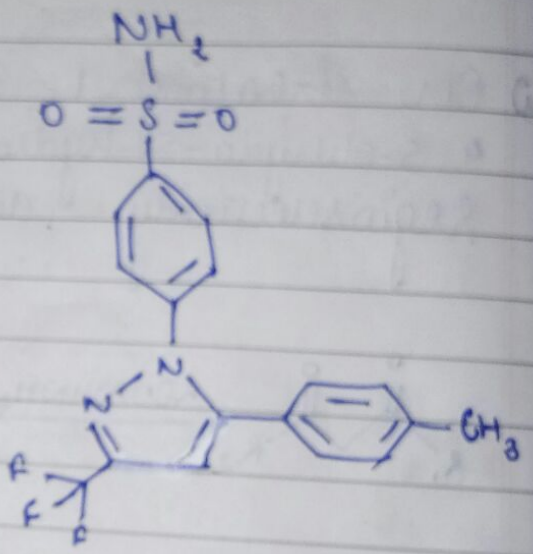
Medicinal Uses -

- It is used as analgesic, antinociceptive, anti-inflammatory, antipyretic, antiarrhythmic, tranquillising, muscle relaxing, analeptic, anticancer, anticonvulsant, monoamine oxidase inhibiting agent, antidiabetic, antifungal, antibacterial activities.

- Sulfaphenazole is a sulphonamide antibiotic which is used for treating allergies, cough as well as antifungal & antimalarial function.
- Celecoxib, a Nonsteroidal anti-inflammatory drug (NSAID) is used to treat arthritis, pain, menstrual cramps, & colonic polyps.



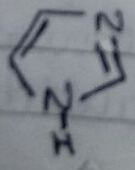
Sulfaphenazole.



Celecoxib

Imidazole:

Imidazole is a five-membered heterocyclic system with 3 carbon atoms & 2 nitrogen atoms at the positions 1 & 3. It is also named as 1,3-diazole.



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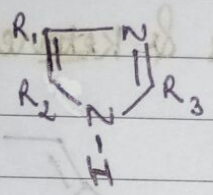
Properties - [Physical]:

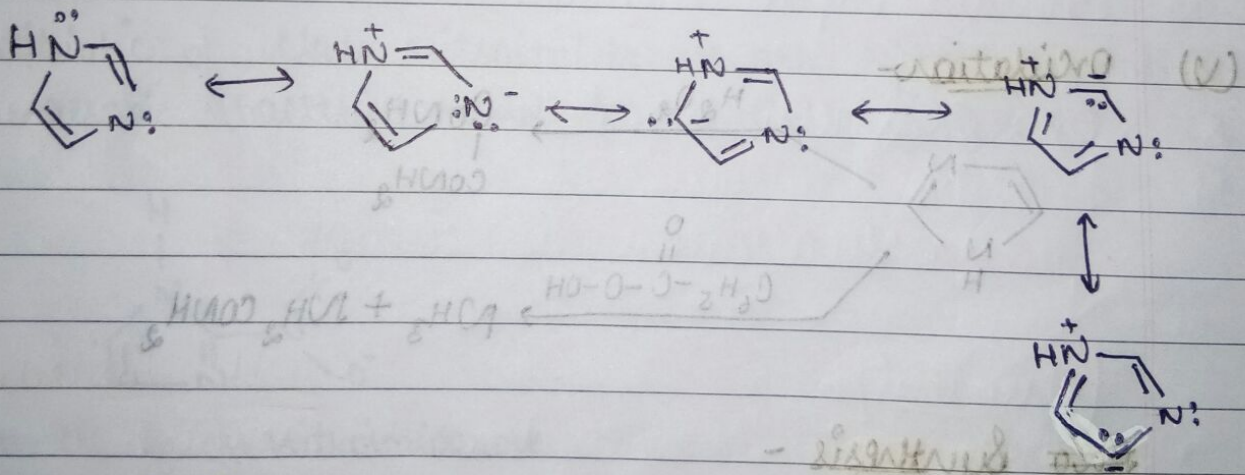
- It is highly polar compound having dipole of 3.61 D & it
- It's freely soluble in polar solvents like water.

The hydrogen atom can be located on any of the 2 nitrogen atoms, which results in its two tautomeric ~~atoms~~ forms.

The aromaticity of the compound is due to the completion of Sextet by the π-electrons, comprising of electrons pair obtained from protonated nitrogen atom, one from each of other four atoms present in the ring.

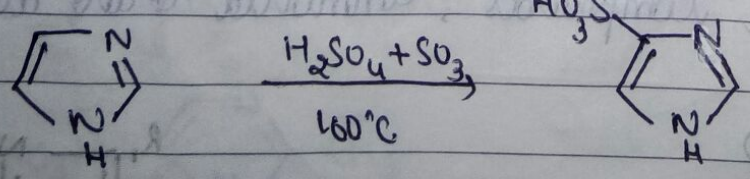


Resonance structure of imidazole are described as follows:



[Chemical]:

(i) Sulfonation -



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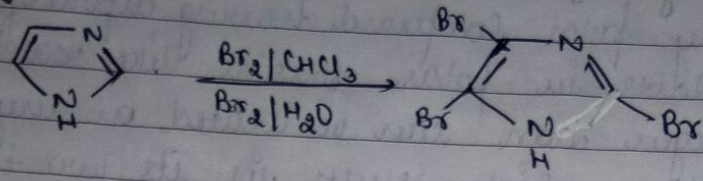
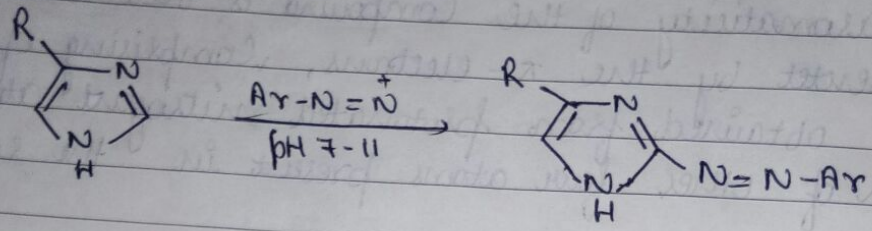
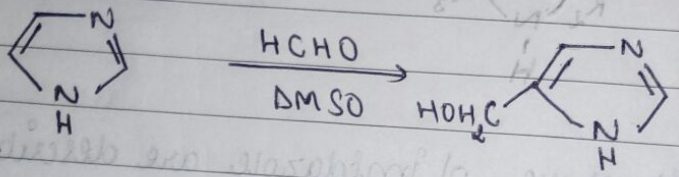
(iii) Halogenation -



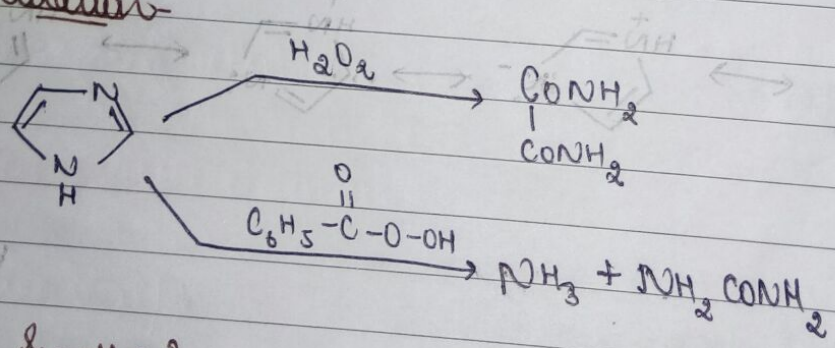
(iii) Diazo coupling -



(iv) Reaction with aldehydes & ketones -

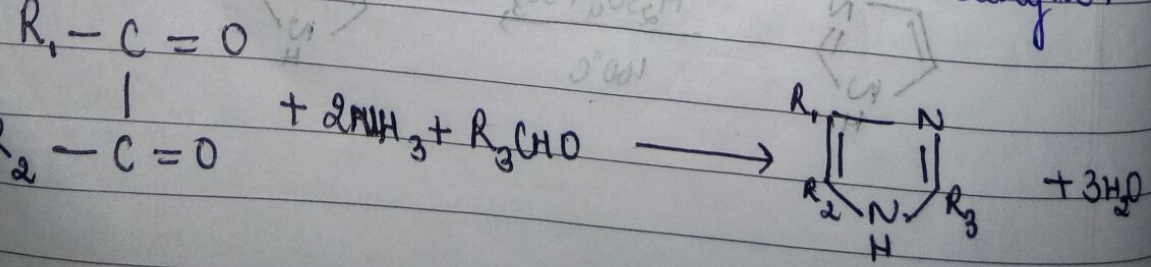


(v) Oxidation -



~~Mec~~ Synthesis -

(i) Generally, imidazole can be prepared by reacting α-dicarbonyl compounds, ammonia & an aldehyde.



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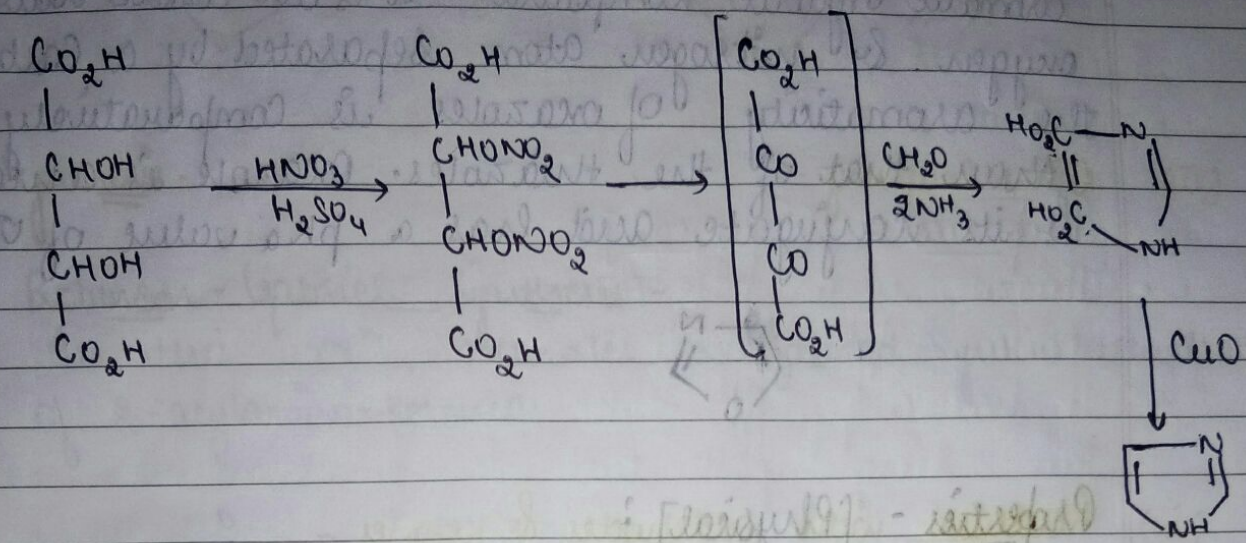
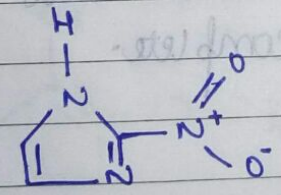
i) Reaction between glyoxal, ammonia, formaldehyde yields imidazole.



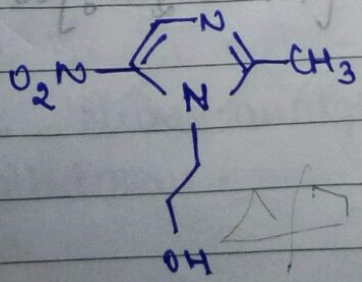
Medicinal Uses -

- Derivatives of imidazole are potent antifungal agents & are ~~the~~ also used to treat mycotic infection of skin.
- Antibiotic of class nitroimidazole are used to combat anaerobic bacterial and parasitic infections.



nitroimidazole.

- Metronidazole is used to treat bacterial infections of the skin, vagina, stomach, joints or respiratory tract.



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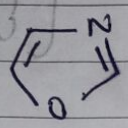
Oxazole:

(mp)

Oxazole is the parent compound for various heterocyclic aromatic organic compounds. It is an azole having an oxygen & nitrogen atom separated by a carbon. The aromaticity of oxazoles is comparatively less than that of the thiazoles. Oxazole is a weak base & its conjugate acid has a pK_a value of 0.8.



(i)

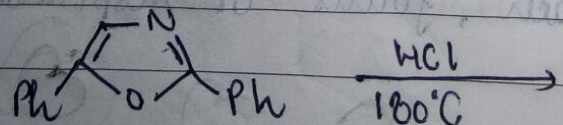
Properties - [Physical]:

- It is a liquid with boiling point of 69°C
- It has a pyridine-like colour.
- It is miscible with water & some organic solvent
- It is weakly basic but more than isoxazole. (ii)
- It is dipole moment is 1.5 D.

* Oxazole exhibits a sextet of π-electrons, but its properties establish that due to its low aromaticity the delocalisation is incomplete.

[Chemical]:

- Oxazoles are stable towards alkalis, but undergoes decomposition at high temperatures in the presence of strong acids.



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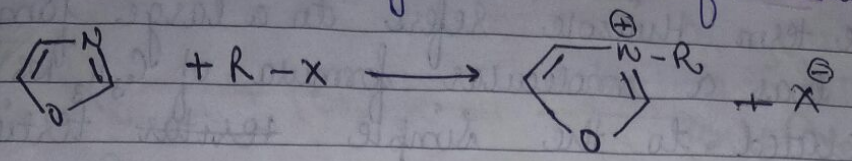
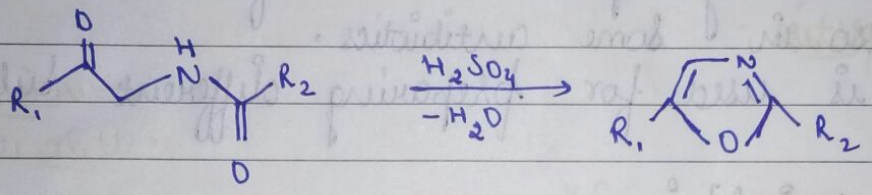
- Oxazole reacts with alkyl halides to form salts.

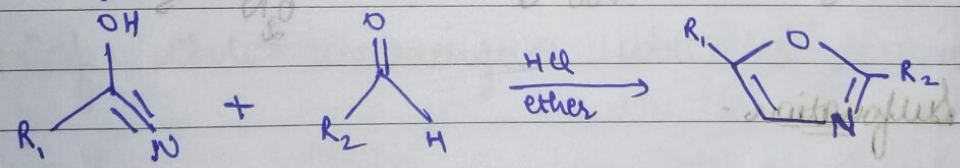


Synthesis -

(i) Robinson - Gabriel Synthesis -
In this rx^n, oxazoles are formed by the dehydration of 2-acylamino-ketones.

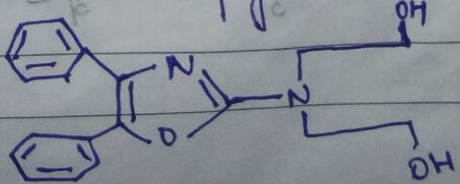


(ii) Fischer Oxazole Synthesis -
In this rx^n, discovered by Hermann Emil Fischer in 1896, oxazole is formed by reacting cyanohydrins & aldehydes in the presence of anhydrous HCl.



Medicinal Uses -

- It derivative are used in pesticide, dyes, fluorescent, brightening agent, textile auxiliaries, plastic.
- It is used as building blocks for biochemical & pharmaceutical
- Oxazole is a non-steroidal anti-inflammatory agent which shows analgesic & antipyretic activity similar to phenylbutazone.



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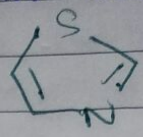
Thiazole :

The term 'thiazole' refers to a large family of derivatives. It has a molecular formula of C_3H_3NS. It can be related to the simple ~~resitar~~ tertiary aliphatic amines.

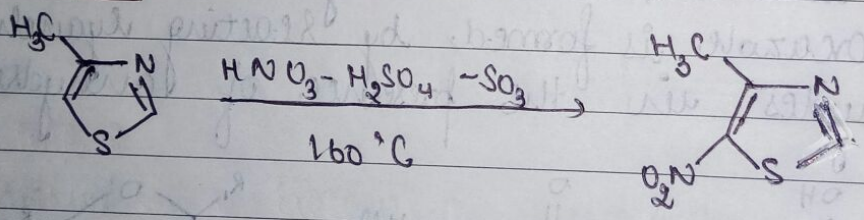


Properties - [Physical] :

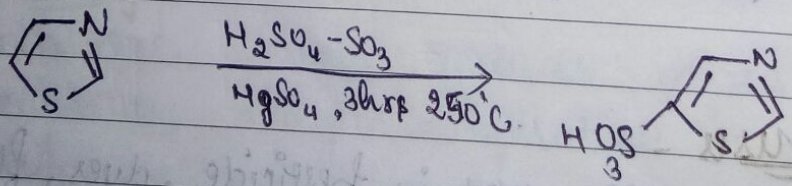
- Thiazole is a pale yellow coloured liquid with a boiling point of 117°C.
- It has a pyridine-like odour.
- This ring ~~by~~ structure is found in vitamin B, & also in some antibiotics.
- It is used for preparing different sulpha drugs.

[Chemical] :

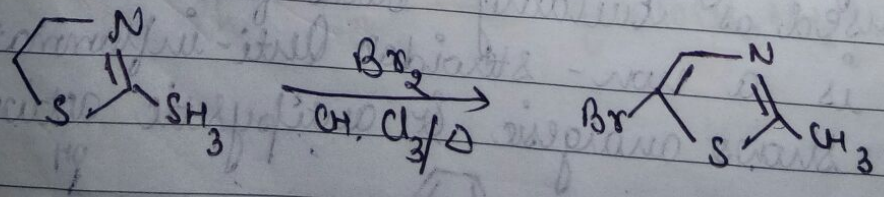
(i) Nitration -



(ii) Sulfonation -



(iii) Halogenation -



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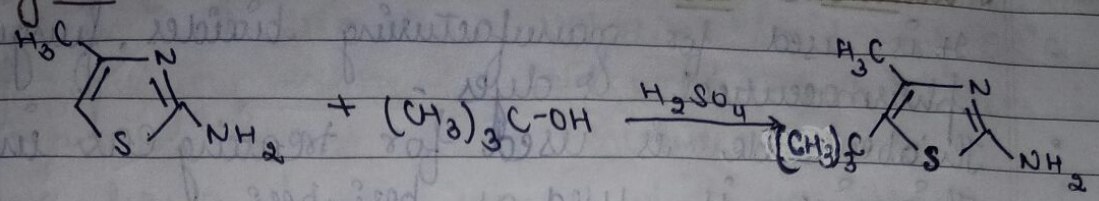
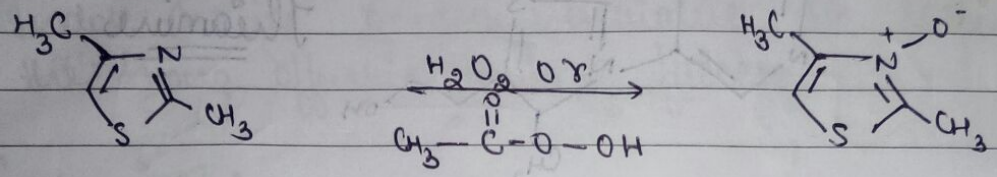
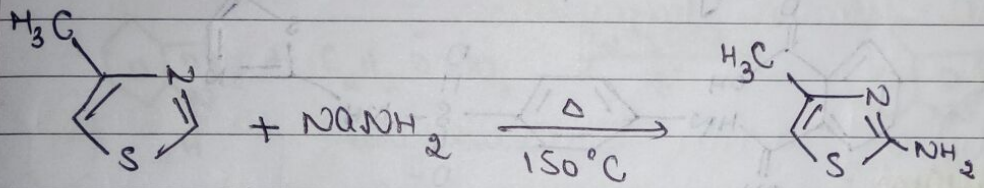
(iv) Alkylation -



(v) Oxidation -

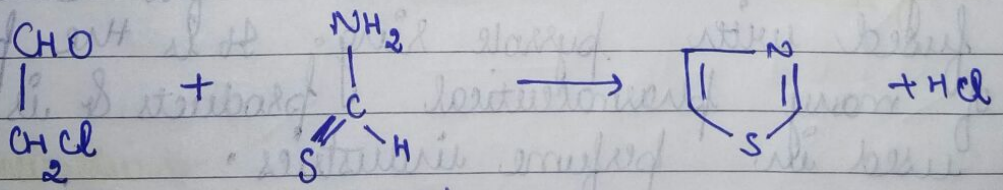


(vi) Amination -



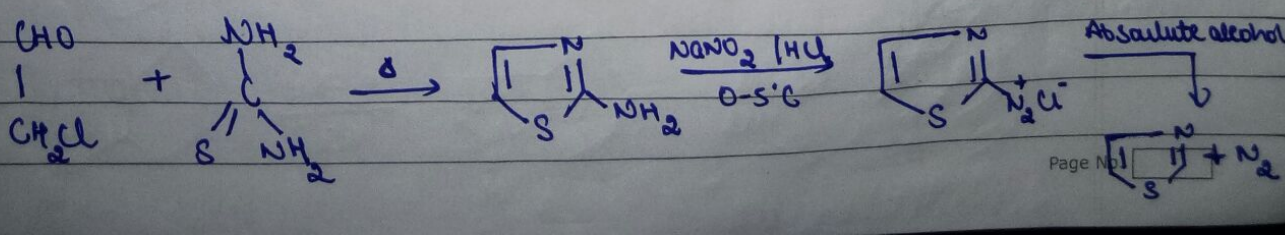
Synthesis -

(i) By the rxn of chloroacetaldehydes with thioformamide :



chloroacetaldehydes Thioformamide

(ii) By the rxn of chloroacetaldehydes with thiourea :



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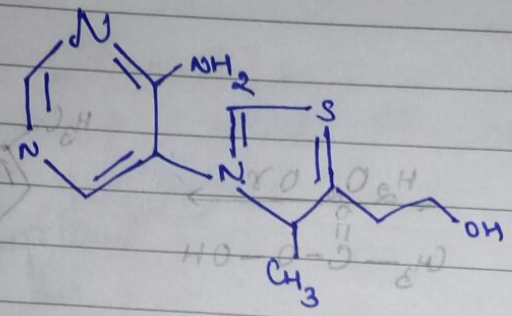
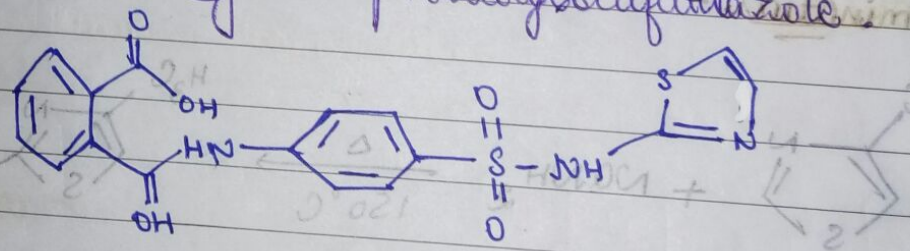
Medicinal uses -

- It is used for manufacturing biocides, fungicides, pharmaceutical & dyes.
- Thiabendazole is used for treating ear infection.
- Thiamine is used as beri-beri.



Thiamine

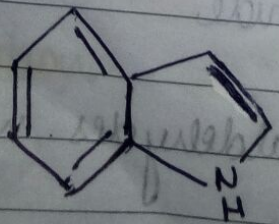
- Thiazole ring is found in the structure of many antibiotics. Eg - phthalylsulfathiazole.



Phthalylsulfathiazole

Indole : (Imp)

Indole is a heterocyclic aromatic compound with bicyclic structure. It consist of a benzene ring fused with pyrrole ring. It is the precursor of many pharmaceutical products & is also used in perfume industries.



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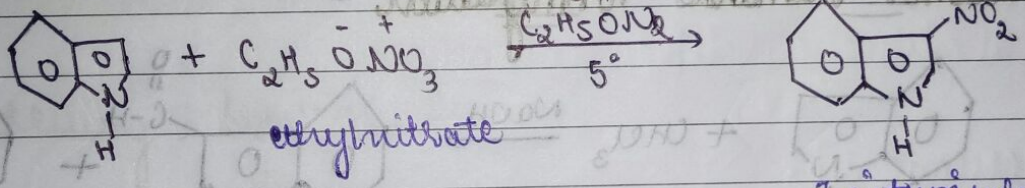
Properties - [Physical]:

- Indole is a colourless, volatile solid, mp 52°C.
- It is sparingly soluble in cold water, but dissolves in hot water & most organic solvents.
- Indole has a powerful odour which is pleasant & flowery in low concentration.
- It is commercially used as a perfume base.
- Indole & its 3-methyl derivative are responsible for the strong offensive odour of faeces.

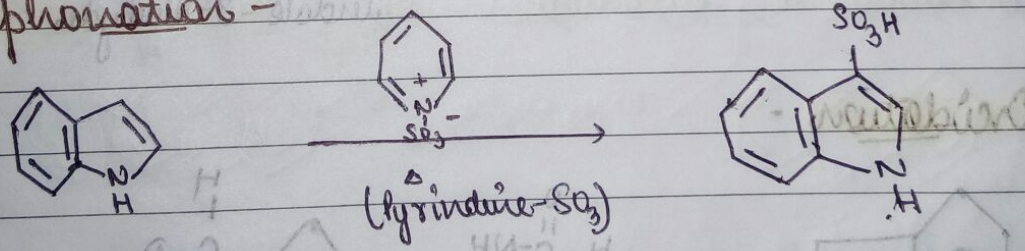
[Chemical]:

(i) Nitration -

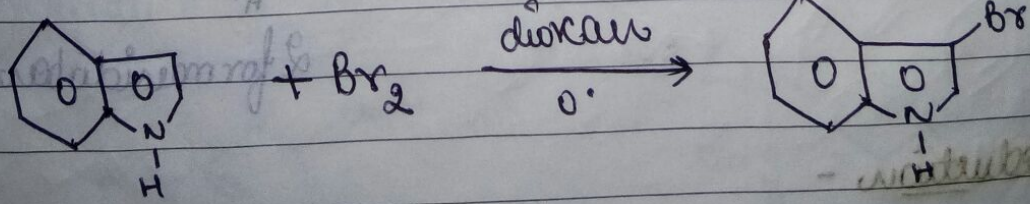


3-nitroindole.

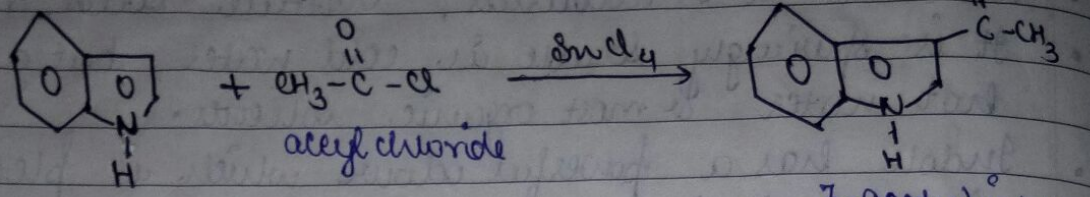
(ii) Sulphonation -



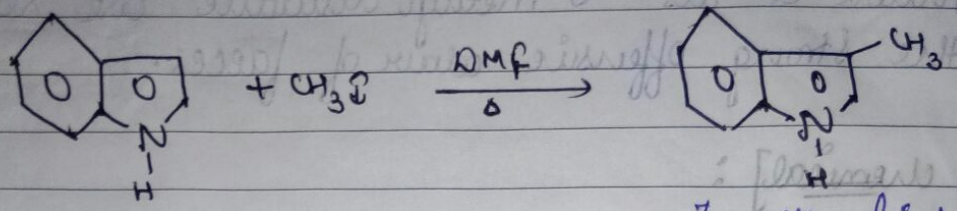
(iii) Bromination -



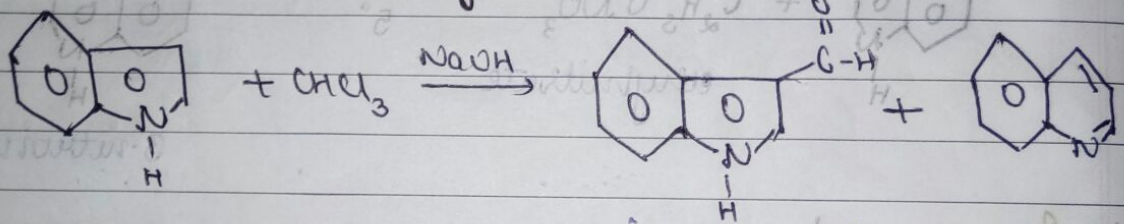
(iv) Friedel-Craft acylation -



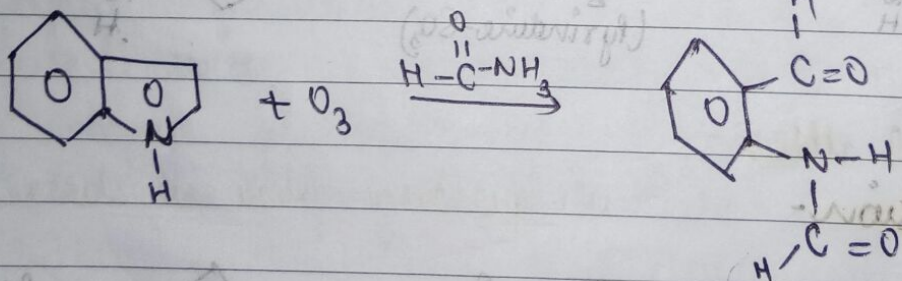
(v) Alkylation -



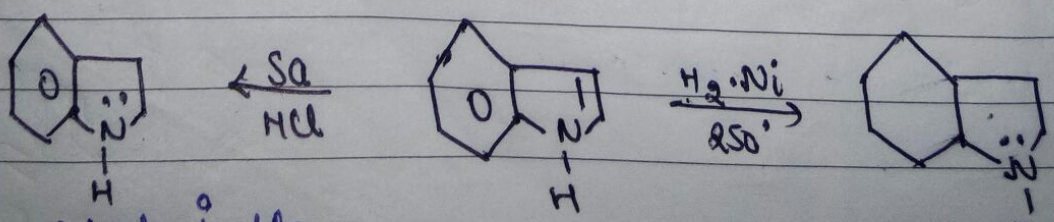
(vi) Reimer-Tiemann formylation -



(vii) Oxidation -



(viii) Reduction -



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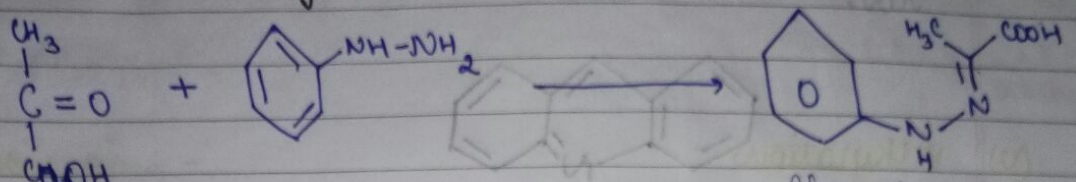
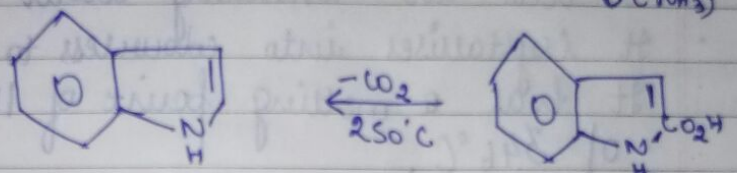
Synthesis-

(i) Fischer-Indole Synthesis:



Phenylhydrazone salt of pyruvic acid

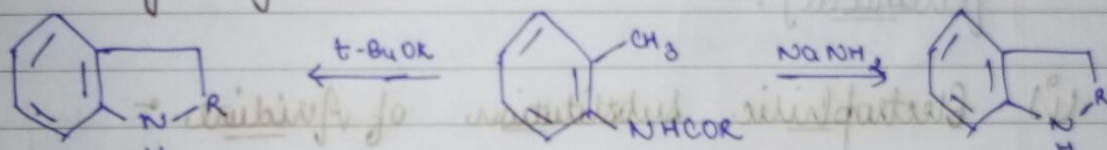
$ZnCl_2/\Delta$ ($-NH_3$)



Indole

Indole-2-Carboxylic acid

(iii) Madelung Synthesis:



(79%)

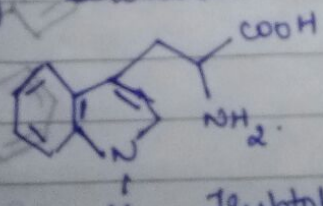
(R=H) Indole

(R=Me) Indole

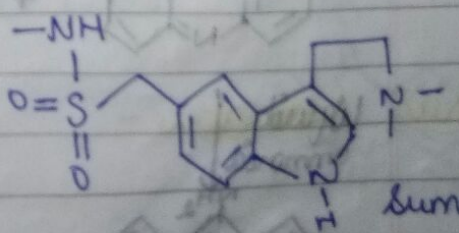
(80%)

Medicinal Uses -

- It can be produced by a variety of bacteria.
- Tryptophan is an essential amino acid & the precursor of serotonin.



Tryptophan



Sumatriptan

- Sumatriptan is used for the treatment of headache mainly associated with migraine.

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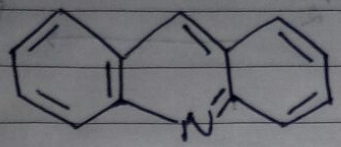
Acridine:

Acridine is an alkaloid derived from anthracene. It is Aza derivative of anthracene, like fractions of Coal Tar.

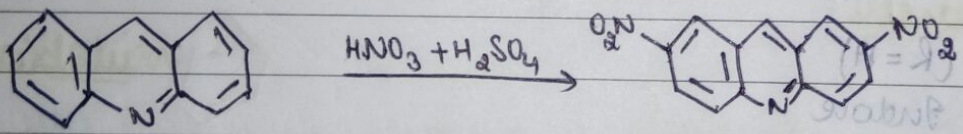


Properties - [Physical]:

- It has an irritating odour.
- It crystallises into colourless to light yellow needles.
- It has a melting point of 110°C & boiling point of 346°C.
- The solution of its salt shows blue fluorescence.
- It have a dipole moment of 2.10 D.

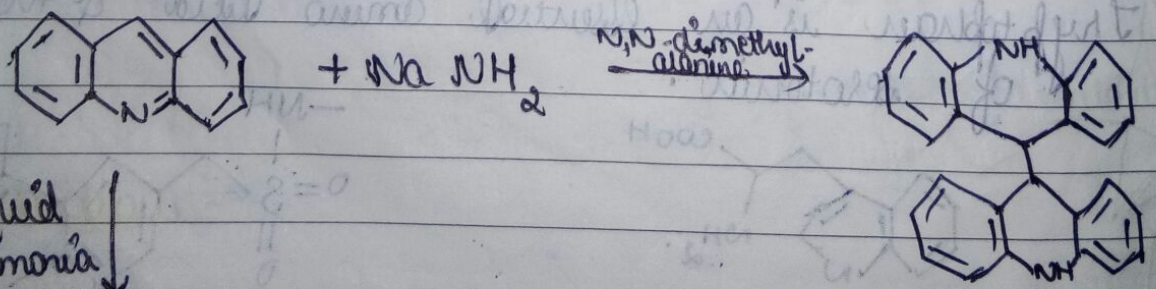
[Chemical]:

(i) Electrophilic substitution of Acridine -



Acridine → 2,7-dinitroacridine

(ii) Reactions towards nucleophiles -



9,9-biacridinyl

9-aminoacridine

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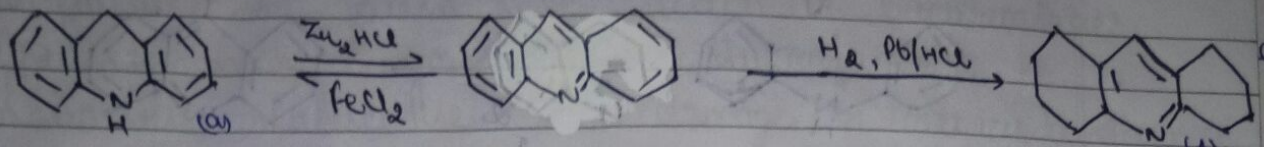
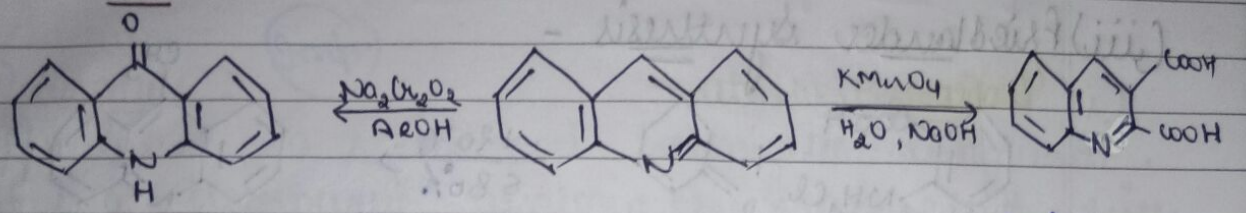
(iii) Reduction -



9,10-dihydroacridine

1,2,3,4,5,6,7,8-octahydroacridine

(iv) Oxidation -

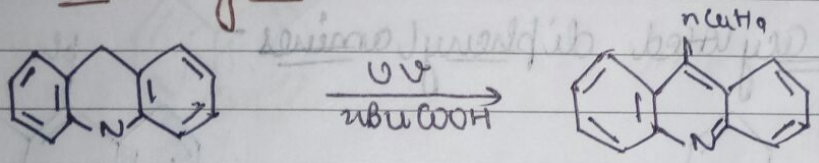


10H-acridine-9-one

Acridine

quinoline-2,3-dicarboxylic acid

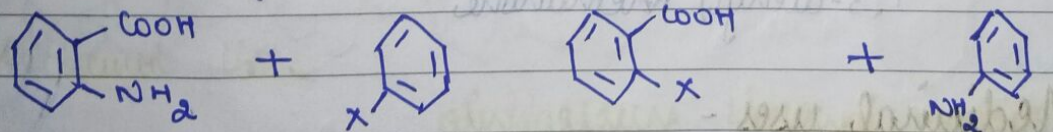
(v) Reductive alkylation -



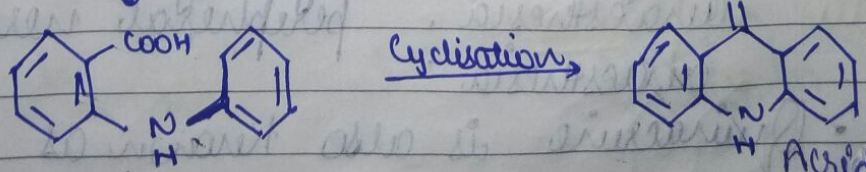
9-butylacridine

Synthesis -

(i) Ullmann synthesis -

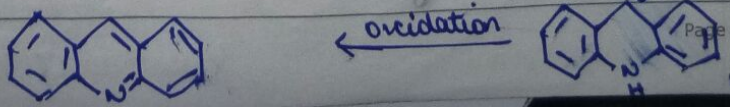


Anthranilic acid + Aryl halide + o-halobenzoic acid + Aniline



N-phenylanthranilic acid

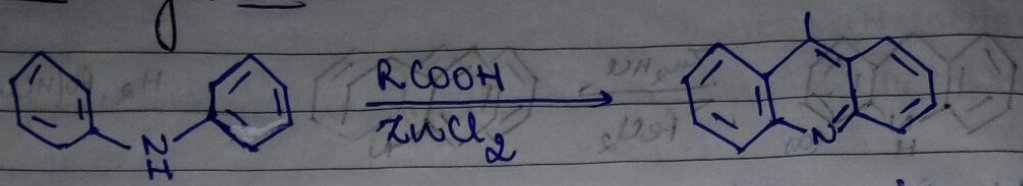
Acridone



Acridine

Acridone

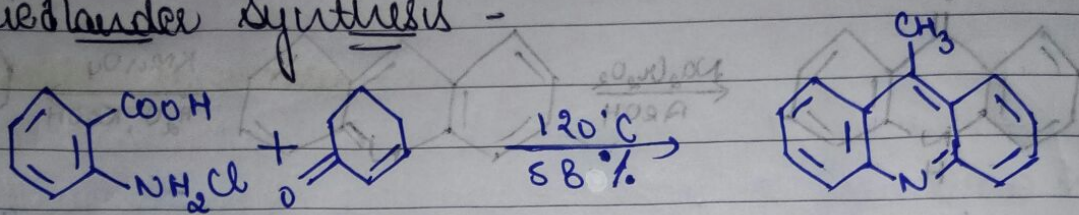
(ii) Bernthsen Synthesis-



Diphenylamine

9-substituted acridine

(iii) Friedlander Synthesis -

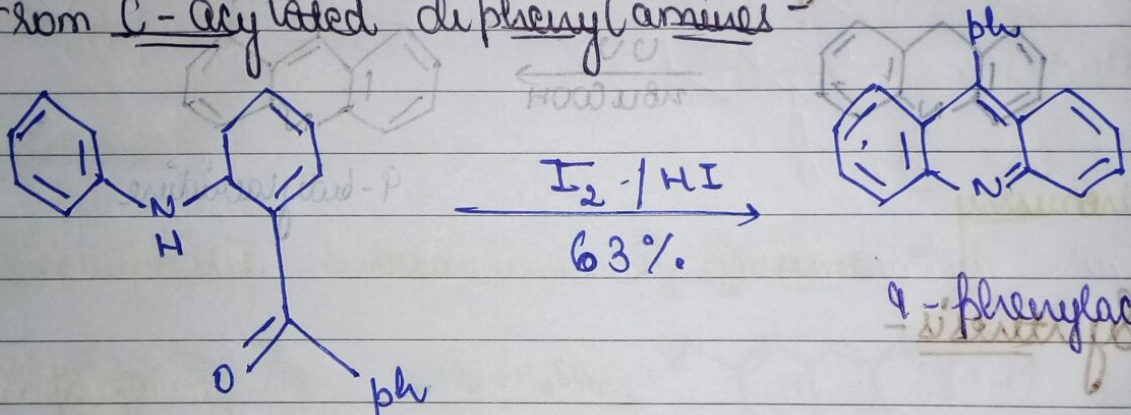


Anthranilic acid

Cyclohex-2-enone

9-methylacridine

(iv) From C-acylated diphenylamines -



9-phenylacridine

Phenyl-(6-phenylaminocyclohexa-1,3-dienyl) methanone

Medicinal uses -

- Bucricaine is used topically as surface anaesthesia of eye & given by injection as an infiltration anaesthesia, peripheral nerve block & spinal anaesthesia.
- Quinacrine is also known as mepacrine is used as gametocytocide.

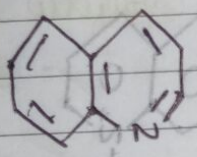
Saathi

Date ___ / ___ / _____

- 9 - Aminoacridine acts as disinfectant.
- Proflavin is found to be active as bacteriostatic against many gram positive bacteria.
- Nitracrine causes the DNA damage & acts as anticancer agent.
- Acriflavin is used as an antiseptic for skin & mucous membrane.

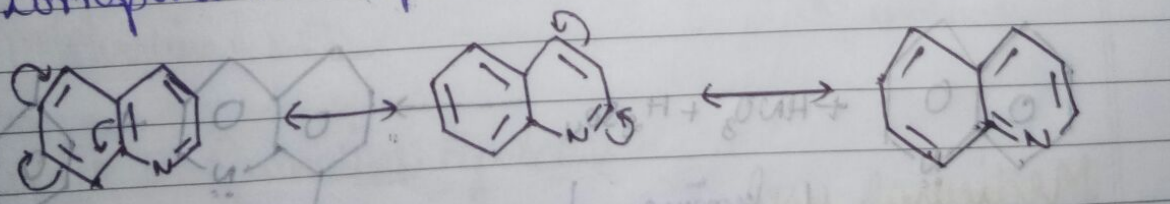
Quinoline : (Imp.)

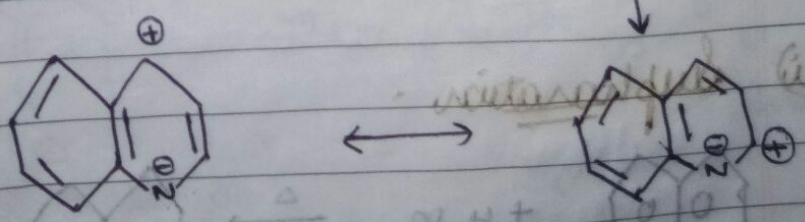
Quinoline, a 6-membered heterocyclic compound. It is a heterocyclic analogue of naphthalene which can be obtained by fusing a benzene ring to pyridine nucleus. Chemically quinoline is 2,3-benzopyridine.



Chemistry -

The resonance hybrid of quinoline is represented by the 5 canonical structures, among which 3 structures correspond to naphthalene.





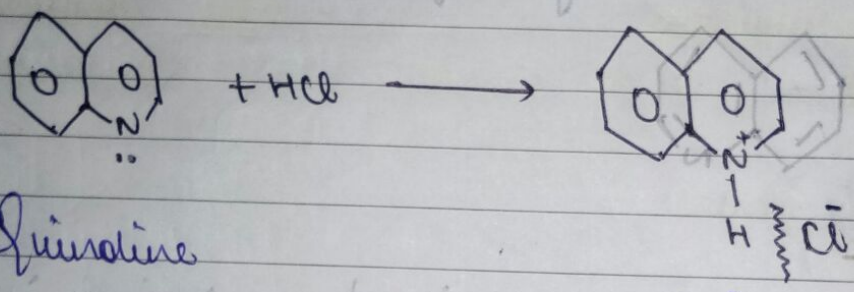
Properties - [Physical]:

- Quinoline is a colourless liquid, bp 231°C.
- It turns yellow on standing & has pyridine-like smell.
- Quinoline is miscible with most organic solvent, dissolves in water to about 0.7% at room temperature.

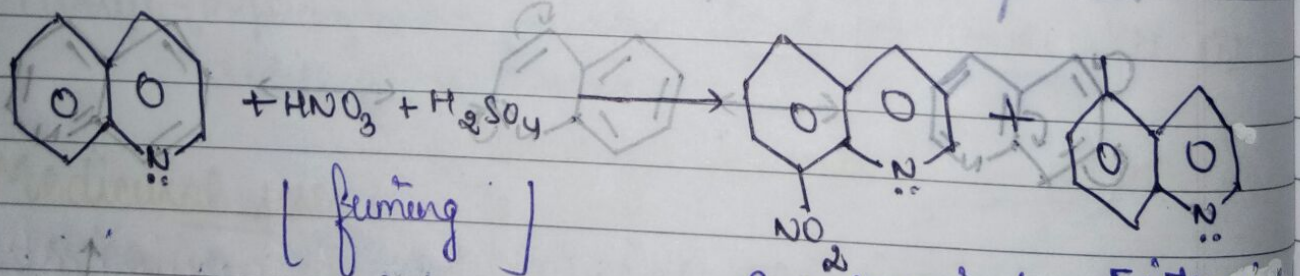
[Chemical]:

(i) Basic Character -

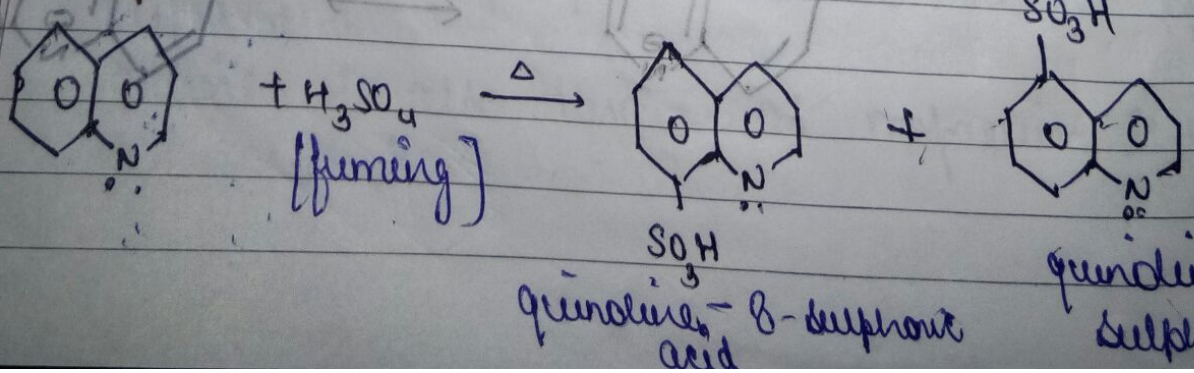
Quinoline is slightly weaker base ~~less~~ ($pK_b = 4.94$) than pyridine ($pK_a = 5.2$). It reacts with acids to yield salt which are sparingle soluble in water.



(ii) Nitration -



(iii) Sulphonation -



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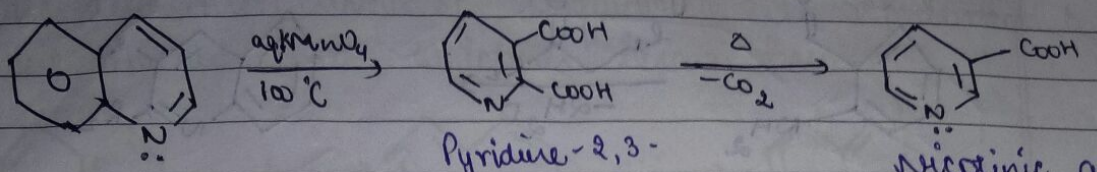
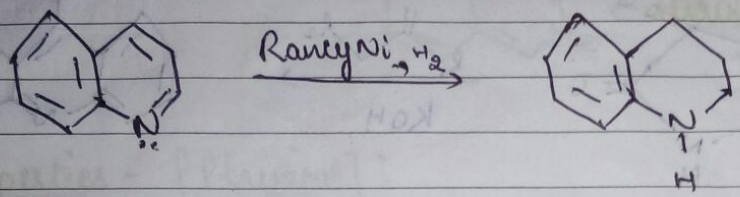
(iv) Oxidation -



Pyridine-2,3-dicarboxylic acid

Nicotinic acid

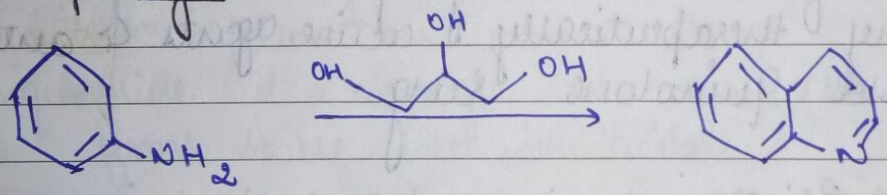
(v) Reduction -



1,2,3,4-Tetrahydroquinoline

Synthesis -

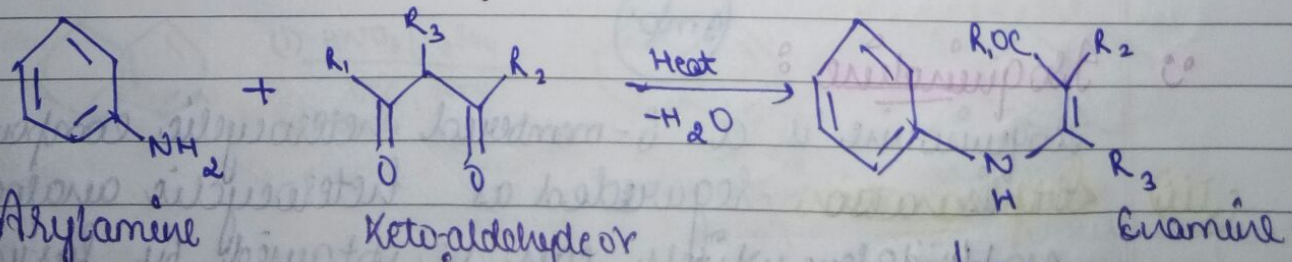
(i) Skraup Synthesis -



Aniline

Quinoline

(ii) Combe's Quinoline Synthesis -

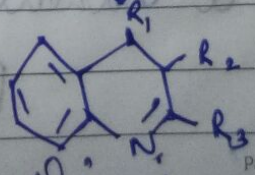


Arylamine

Keto-aldehyde or dialdehyde

Enamine

$-H_2O$ | Acid heat



Quinoline

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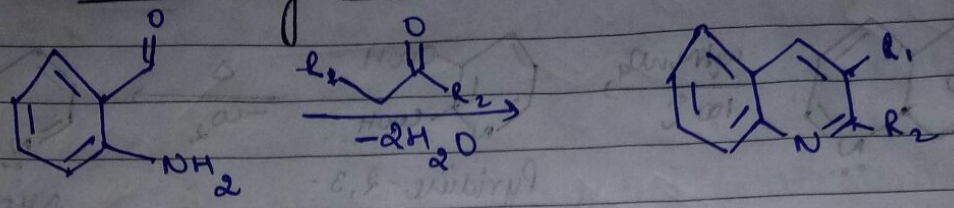
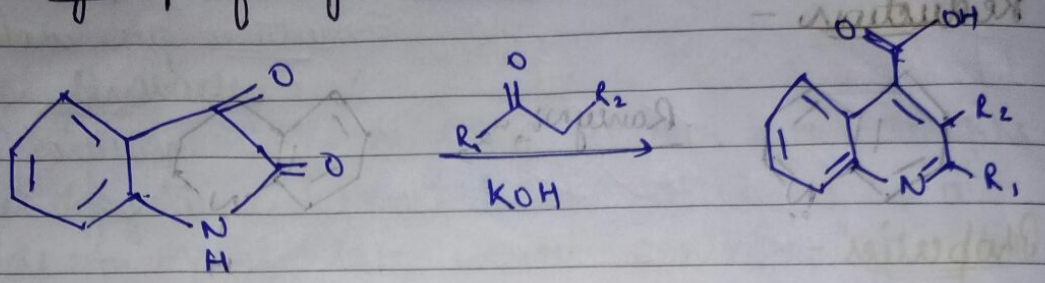
(iii) Friedlander Synthesis -



(iv) Pfitzinger / Pfitzinger - Borsche Rxn -



Medicinal uses -

- Quinoline & its derivatives are used in pharmaceutical & fertilizer industry.
- It is found in many plant derivatie like quinolones
- many therapeutically active agents & antibiotics posses quinolone ring.

Eg.

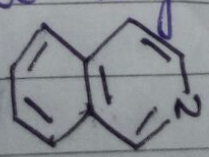
(a) Primaquine is used as antimalarial agent.

(b) Tafenoquine is used as antimalarial agent specifically used for preventing ~~repto~~ relapse of malaria

(mp)

3. Isoquinoline :

Isoquinoline is a 6-membered heterocyclic compound. It is also regarded as heterocyclic analogue of naphthalene which can be obtained by fusing a benzene ring to pyridine nucleus.



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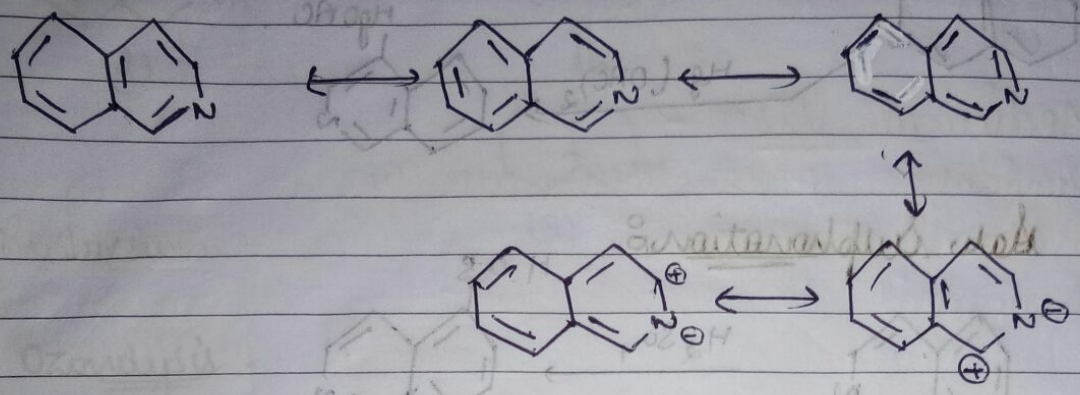
Chemistry -

The resonance hybrid of isoquinoline is represented by the 5-canonical structures shown below.



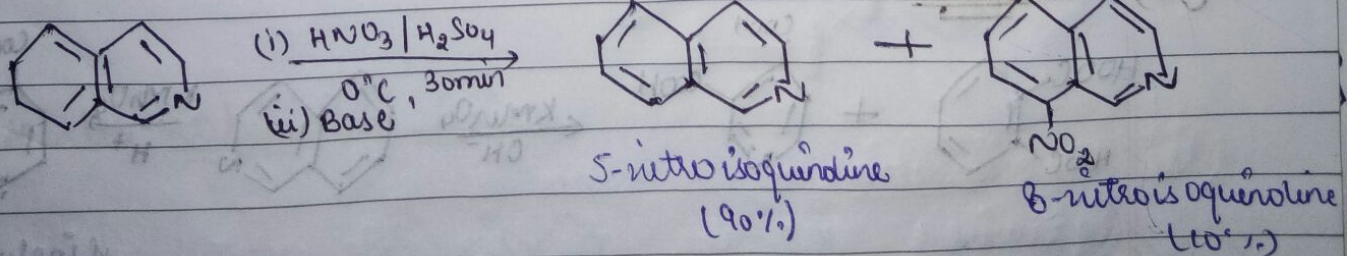
Properties - [Physical]:

- Isoquinoline is a colourless liquid with a smell like that of benzaldehyde.
- Melting point is 25°C & boiling point 243°C.
- It is volatile in steam, sparingly soluble in water, & soluble in many organic solvents.
- It turn yellow on normal storage.
- Isoquinoline is a stronger base than quinoline.
- It forms stable salts with acids.

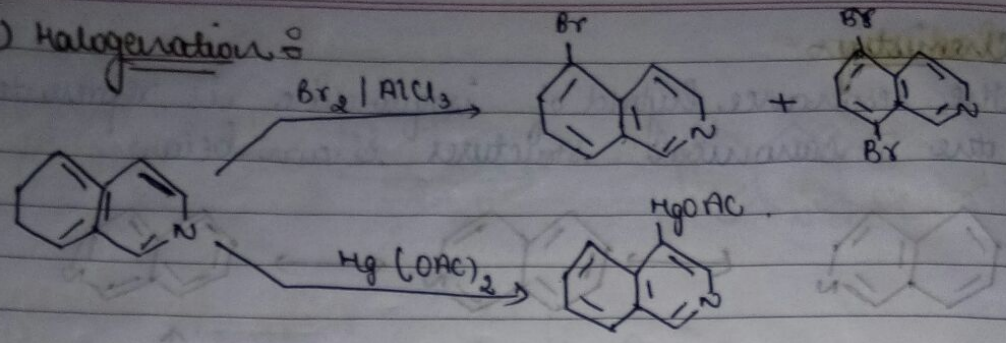
[Chemical]:

(i) Electrophilic substitution -

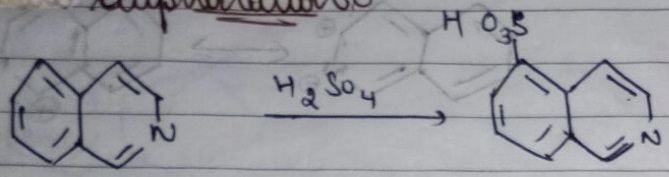
(a) Nitration:



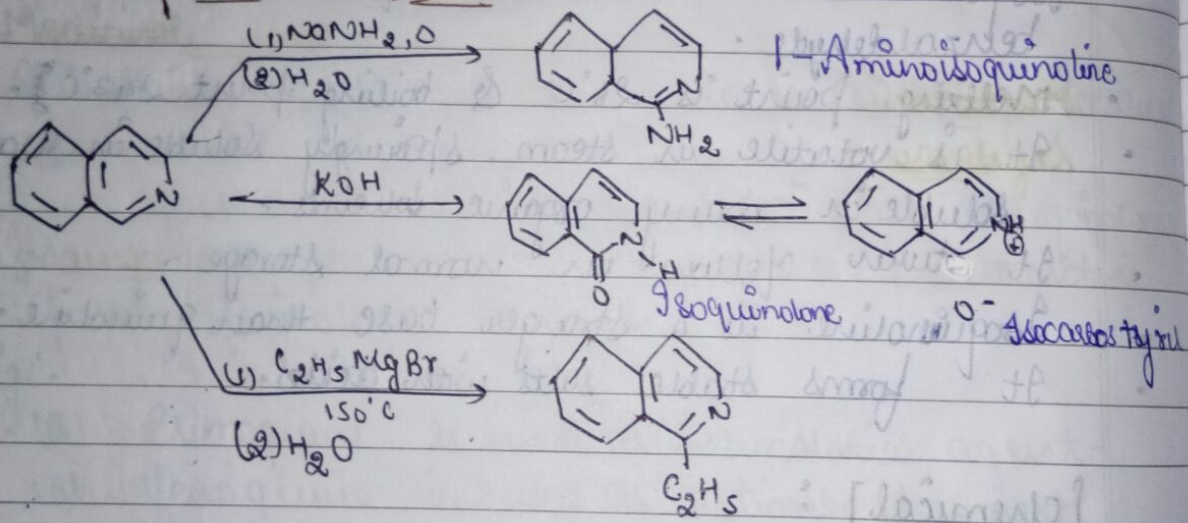
(b) Halogenation :-



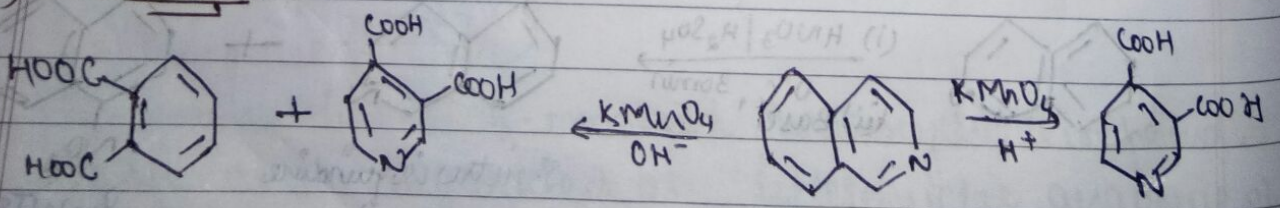
(c) Sulphonation :-



(ii) Nucleophilic Substitution -



(iii) Oxidation -



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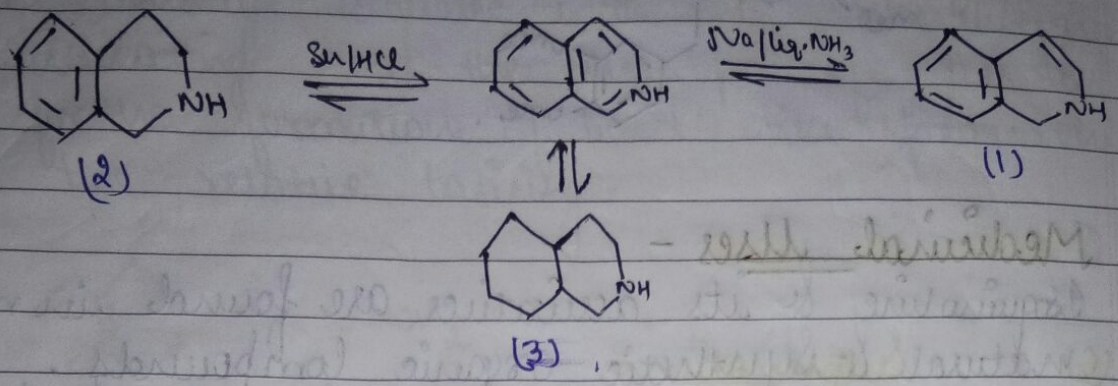
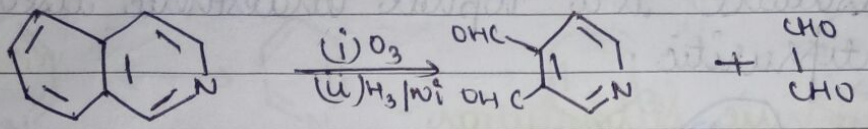
(iv) Reduction -

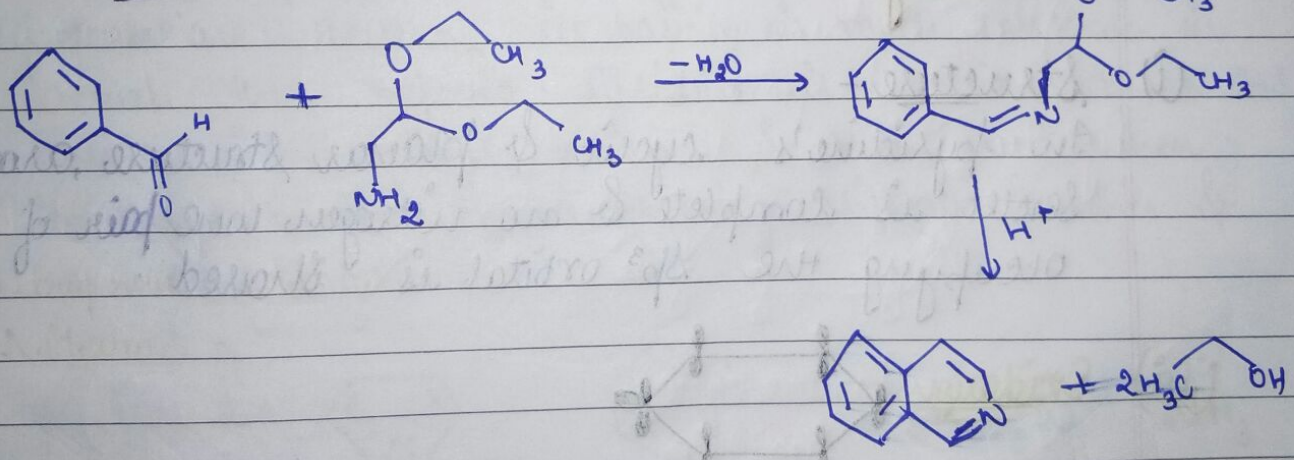


(v) Ozonolysis -

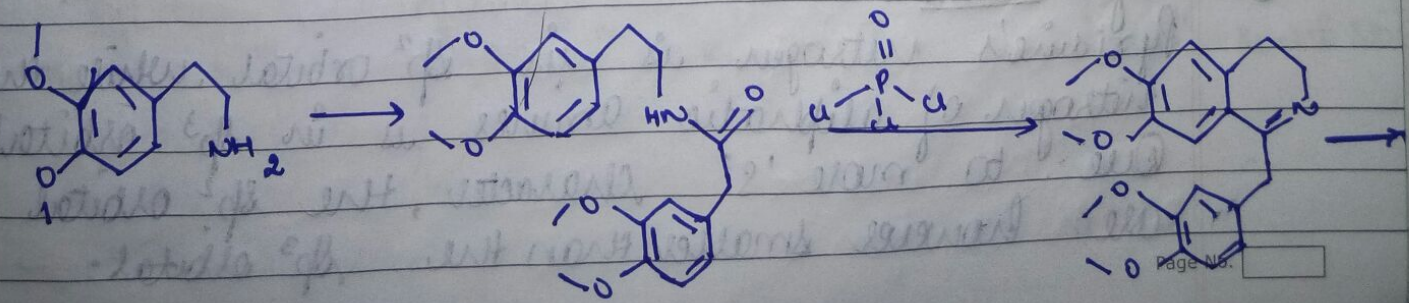


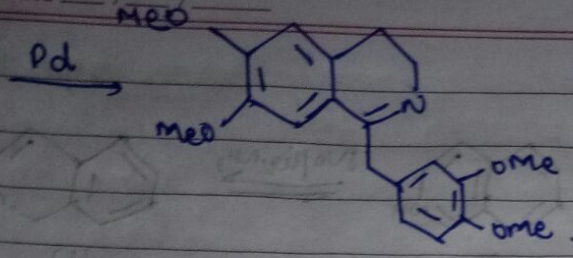
Medicinal Synthesis -

(i) Pomeranz - Fritsch Rx^n -



(ii) Bischler-Napieralski Rx^n -





Medicinal Uses -

- Isoquinoline & its derivatives are found in many natural & synthetic organic compounds.
- Quinapril is used to treat hypertension & heart failure.
- Quinisocaine is a topical anaesthetic used as an antipruritic.

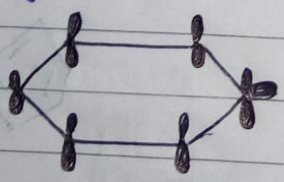
Pyridine : (Imp)

It on a industrial scale is obtained from coal tar (0.1%) or by distillation on bone oil from bones

Chemistry -

(i) Structure -

In pyridine's cyclic & planar structure, aromatic sextet is complete & no nitrogen lone pair of e⁻ occupying the sp^3 orbital is shared.



(iii) Hybridisation -

Pyridine's nitrogen is in sp^2 orbital, while the nitrogen of aliphatic amines is in sp^3 orbital. Due to more 's' character, the sp^2 orbital are however smaller than the sp^3 orbital.

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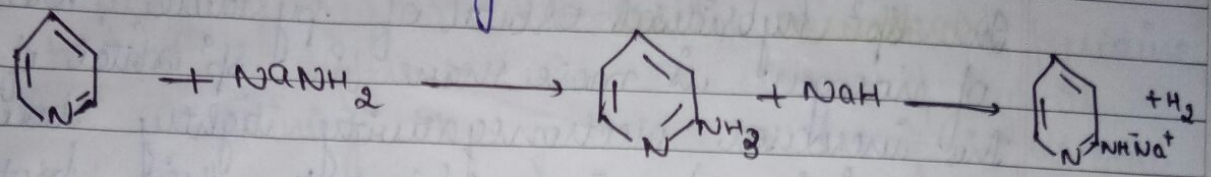
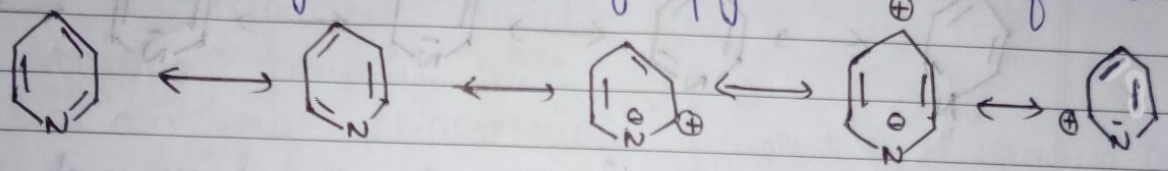
Thus, the lone pair of e^- in the nitrogen of pyridine is closely associated with the nitrogen nucleus, indicating that the lone pair of e^- is less available for the formation of bond with proton. This reduces the relative basicity.

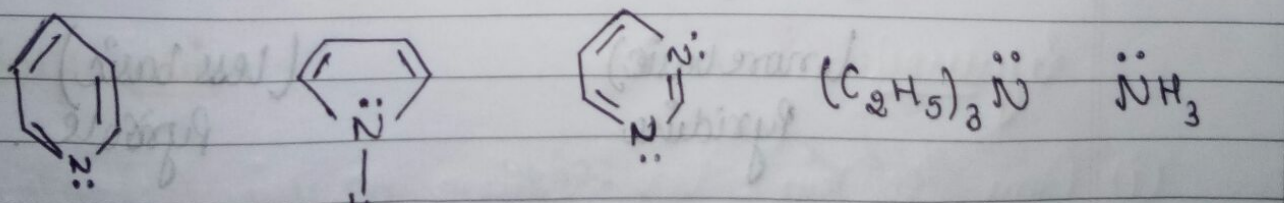


The resonating structures of pyridine are as follows:



(iii) Basicity of Pyridine (imp)

Pyridine is a very strong base due to the presence of a negatively charged Nitrogen atom. The basic nature is also imparted because of the lone pair undergoes rapid protonation. However, its basicity is much less than in actual than expected. Pyridine is a tertiary amine. Its basicity in aqueous solution is lesser ~~than~~ when compared to that of the tertiary aliphatic amines & ammonia.



Pyridine	Pyrrole	Pyrimidine	Triethylamine	Ammonia
$K_b = 1.4 \times 10^{-19}$	$K_b = 2.5 \times 10^{-14}$	$K_b = 5 \times 10^{-12}$	$K_b = 5.6 \times 10^{-4}$	$K_b = 1.8 \times 10^{-5}$

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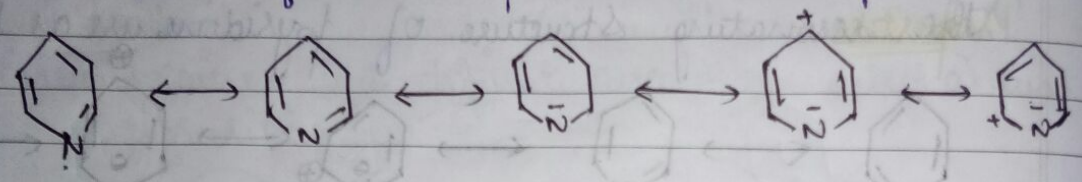
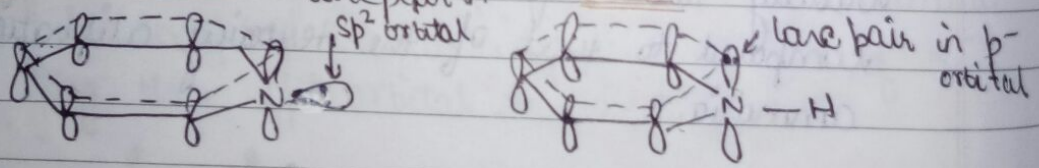
Dipole moment governs that charge separation in pyridine : piperidine (1.17D) & pyrrole (1.81D) have a larger dipole moment than pyridine. Dipole moment in all the cases directs towards the N-atom.

In sp^2 hybridised orbital of pyridine, the electronegativity of nitrogen is more than in sp^3 orbital of triethylamine. This increased electronegativity tightly bounds the lone pair of e^- & prevents their protonation.



Pyridine's basicity is due to the presence of sp^2 hybridised lone pair of e^- in its N-atom. The basic nature of pyridine also indicates that these e^- are not involved in the formation of delocalised π-molecular orbital. The lone pair of e^-, however, readily forms a new N-H bond with proton.

Pyridine is more basic than Pyrrole -



(more basic) Pyridine

(less basic) Pyrrole

The basicity of pyrrole is less than pyridine because the lone pair of e^- on N-atom of pyrrole is in the p-orbital & forms a part of the delocalised π-molecular orbital, also these e^- don't form a new N-H bond with proton.

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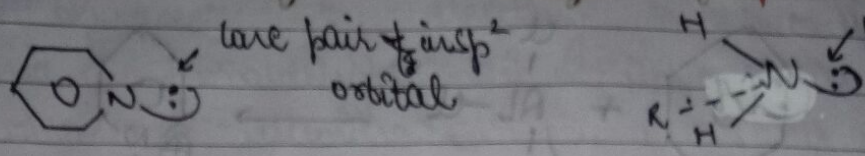
Pyridine is less than Basic than Aliphatic amines -



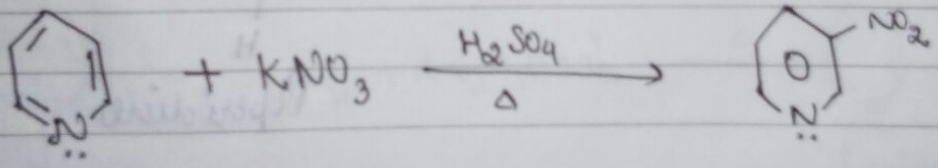
The basicity of aliphatic amine is more than pyridine due to the difference in the nature of hybrid orbitals containing the nitrogen lone pair electrons.

Properties - [Physical]:

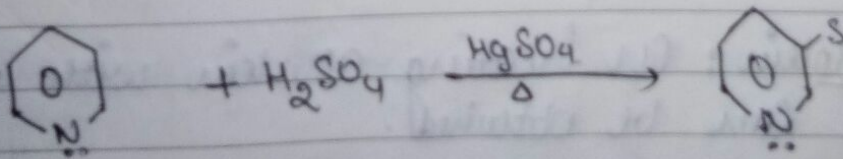
- It is a colourless liquid.
- It boiling point is 115°C.
- It has a very characteristic pungent & disgusting odour
- It is miscible with water & most organic solvent.
- It is very hygroscopic
- It forms an azeotrope with water, which boils at 92-93°C

[Chemical]:

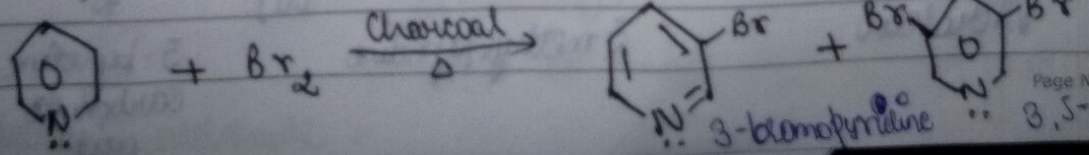
(i) **Nitration -**



(ii) **Sulphonation -**

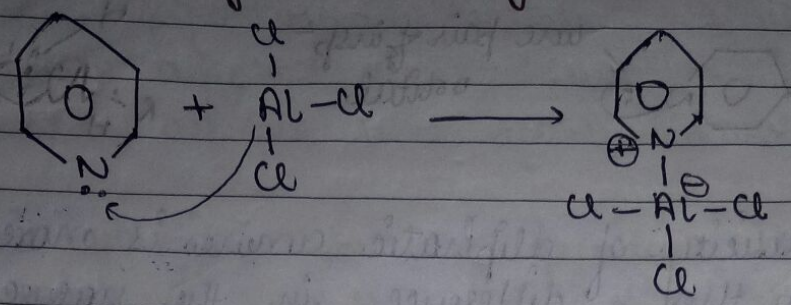


(iii) **Bromination -**



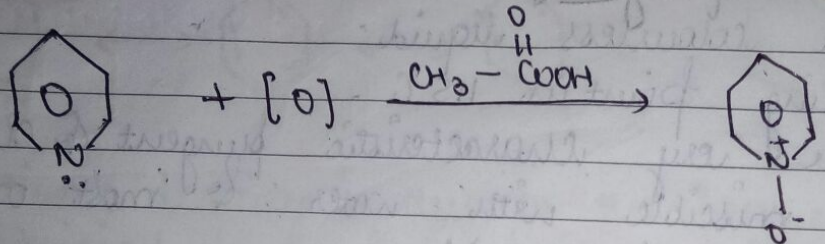
3-bromopyridine 3,5-dibromopyridine

(iv) Friedel Craft Acylation & alkylation -



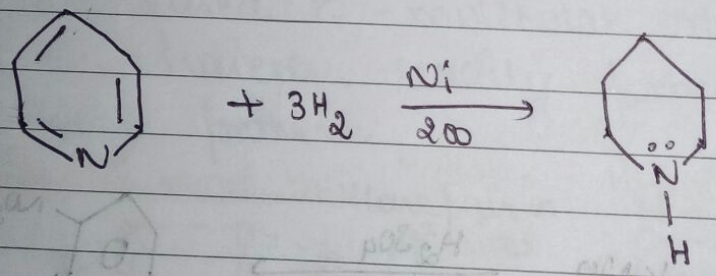
Pyridine-aluminium complex.

(v) Oxidation -



Pyridine-N-oxide

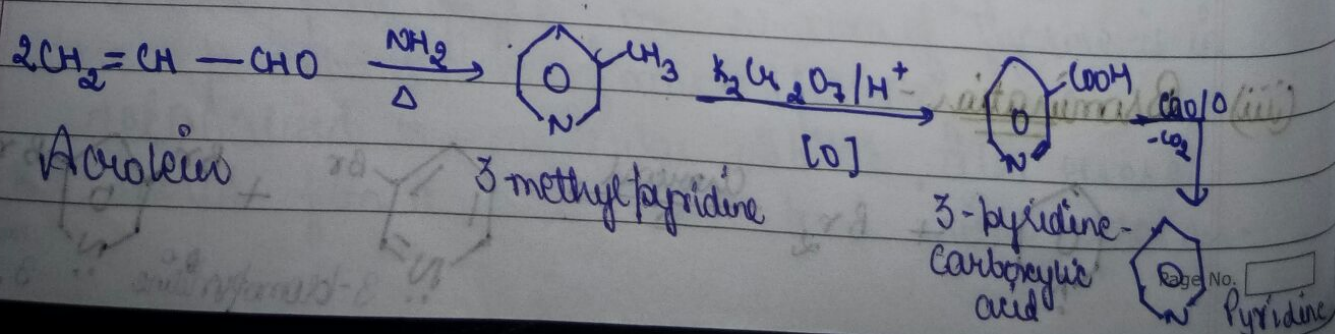
(vi) Reduction -



Piperidine.

Synthesis -

(i) From Acrolein : On treating acrolein with ammonia, pyridine can be obtained.



Acrolein — 3 methyl pyridine — 3-pyridine-carboxylic acid — Pyridine

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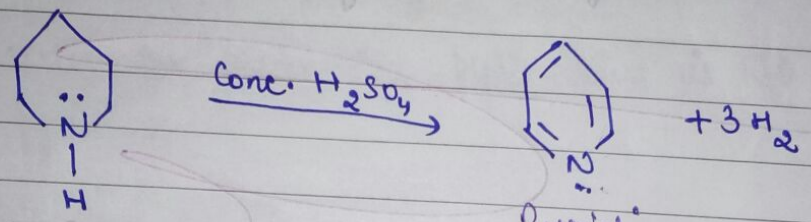
(ii) **Industrial Method** - On an industrial scale, pyridine can be synthesised by heating a mixture of acetylene, ammonia & formaldehyde dimethylacetal at 500°C in the presence of alumina.

$$2HC \equiv CH + NH_3 + CH(OCH_3)_2 \xrightarrow[500^\circ C]{Al_2O_3} \text{Pyridine}$$

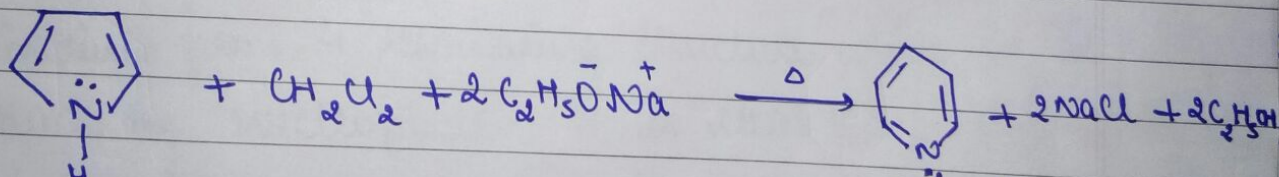
acetylene ammonia formaldehyde dimethylacetal

(iii) By dehydrogenation of piperidine with Conc. H_2SO_4 at 300°C or with nitrobenzene at 250°C.



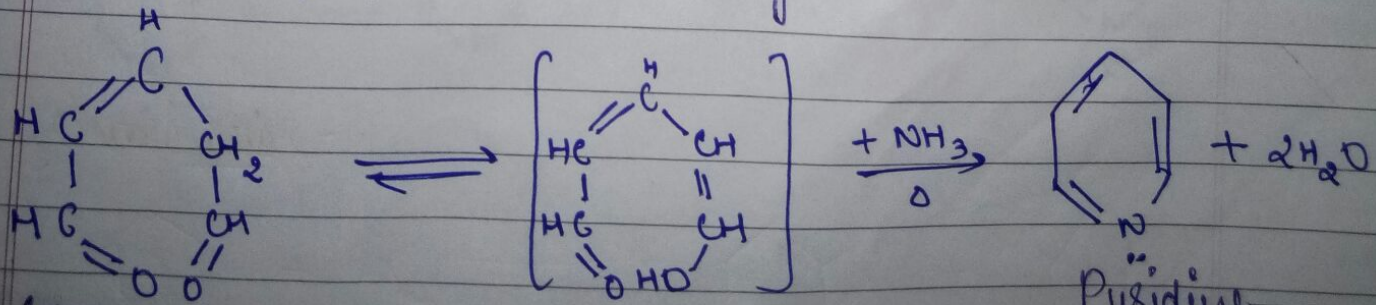
Piperidine Pyridine

(iv) By heating pyrrole with dichloromethane in the presence of Sodium ethoxide.



Pyrrole Pyridine

(v) By heating glutaconic aldehyde with ammonia -



Glutaconic aldehyde Pyridine

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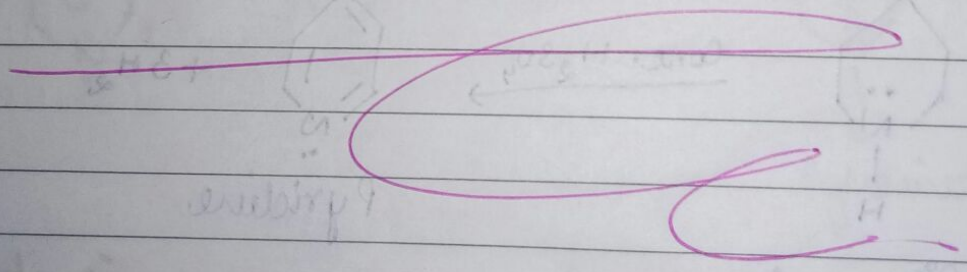
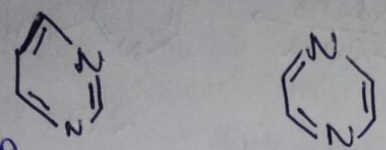
Medicinal Uses -

- It is used as a starting material in the preparation of sulfapyridine, zelatil & niacin.
- It is used as a precursor to agrochemical & pharmaceuticals.
- The pyridine ring occurs in many important compound, including azanes & the vitamins niacin & pyridoxine.
- Isoniazid is an antibiotic used for the treatment of tuberculosis Contains pyridine ring.
- Pyridine is added to ethanol to make it unsuitable for drinking.



(1) Pyrimidine

Pyrimidine is a 6-membered heterocyclic ring having two nitrogen atoms. This ring system is found to be present in many natural products (Eg - nucleic acid) as well as synthetic drugs (eg - barbiturates)



Pyrimidine Pyrazine

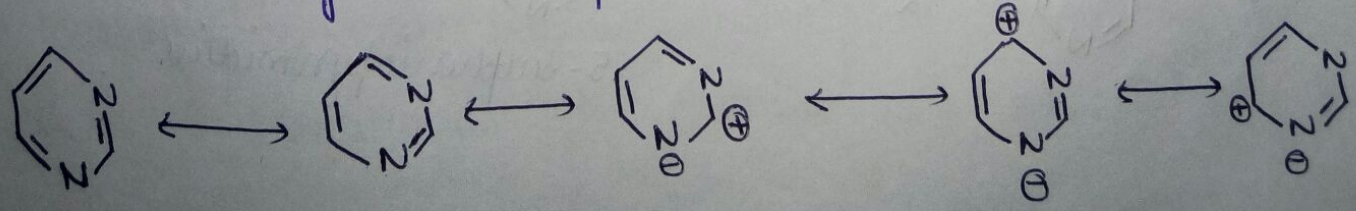
Properties - [Physical] :

- The Boiling point is 124°C & Melting point is 22.5°C of pyrimidine.
- It has a dipole moment of up to 2.42 D.
- The Pka value for protonated pyrimidine is 1.23 in comparison to 5.30 for pyridine.
- It is soluble in water.
- It is a weak base.

[Chemical] :

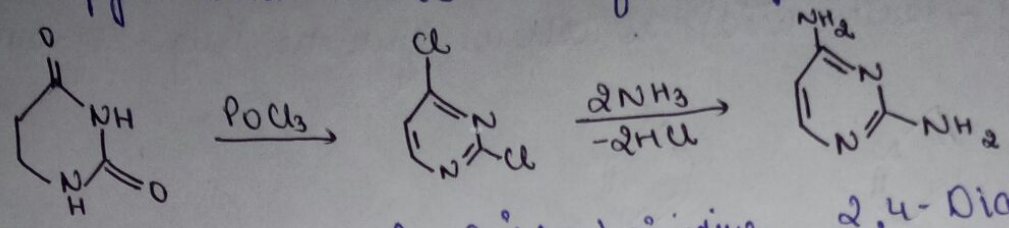
(i) Electrophilic Substitution Reaction -

Pyrimidine forms 4 resonating structure while it is subjected to attack by nucleophile. It is clear that ring is deactivated & position 5 has greatest electron density becoz there is no positive charge at this position.



(ii) Nucleophilic Substitution Reaction –

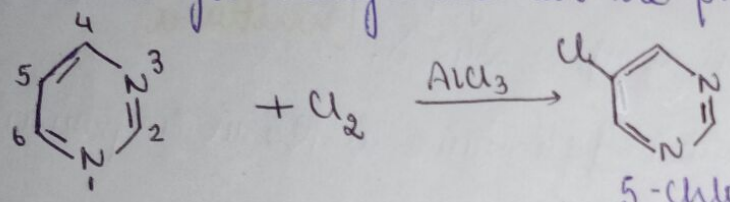
The attack by nucleophilic reagent is facilitated at position 2, 4 & 6 pyrimidine ring. By reaction of phosphorous oxychloride 2,4,6 chloropyrimidines can be made from Pyrimidines.



Pyrimidin-2,4-diane — 2,4-Dichloropyrimidine — 2,4-Diaminopyrimidine

(iii) Halogenation –

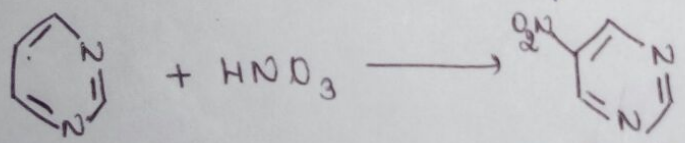
Pyrimidine gets halogenated in the presence of $AlCl_3$



5-Chloropyrimidine

(iv) Nitration –

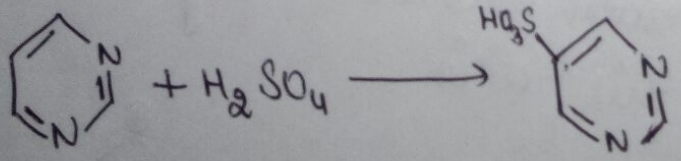
This reaction take place in the presence of nitric acid



5-Nitropyrimidine

(v) Sulphonation –

This reaction occurs in the presence of fuming Sulphuric acid

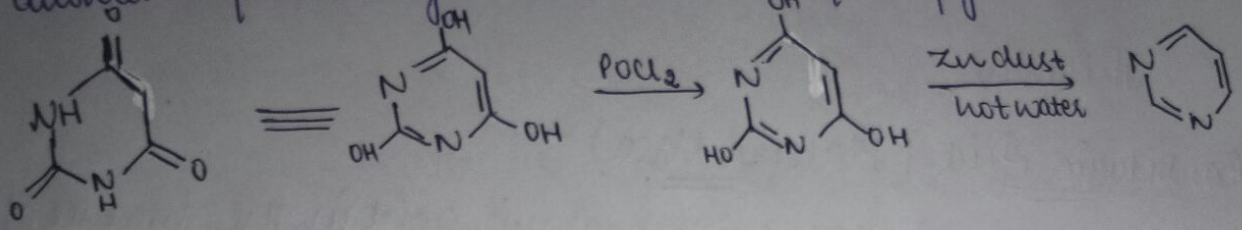


5-Sulphonic pyrimidine

Synthesis -

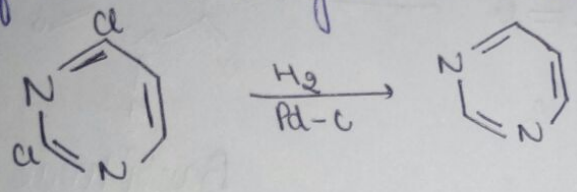
(i) From Barbituric Acid -

Barbituric acid reacts with $POCl_3$ & the resultant mediate further allowed to pass through zinc dust to yield pyrimidine.



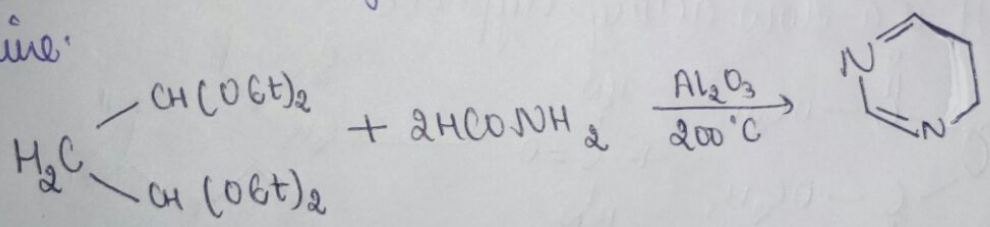
(ii) From 2,4-Dichloropyrimidine -

On heating 2,4-dichloropyrimidine with Hydrogen under pressure of Pd-C & magnesium oxide (Whittaker)



(iii) From formamide -

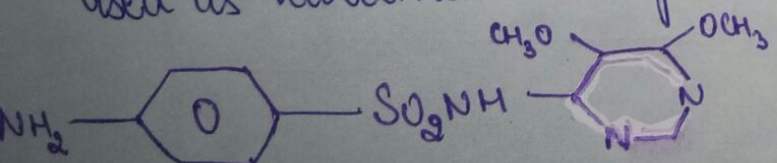
Formamide on reacting with 1,1,3,3-tetraethoxypropane yield Pyrimidine.



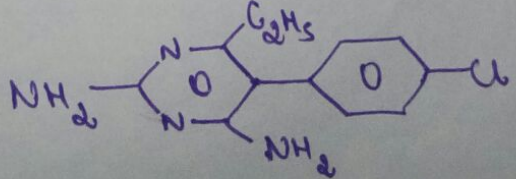
Medicinal Uses -

(i) Synthesis of Antimalarial agent -

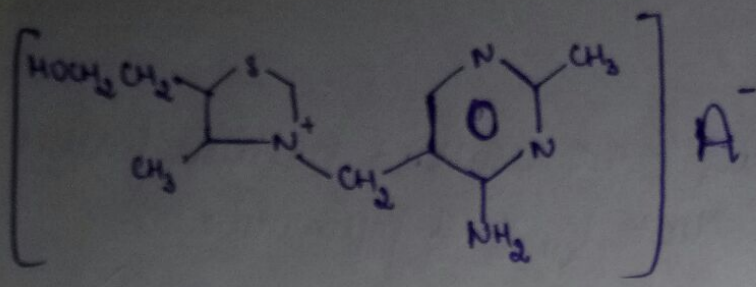
Sulfadoxine & pyrimethamine derived from pyrimidine are used as antimalarial agents. Thiamine is used for treating beri-beri



Sulphadoxine



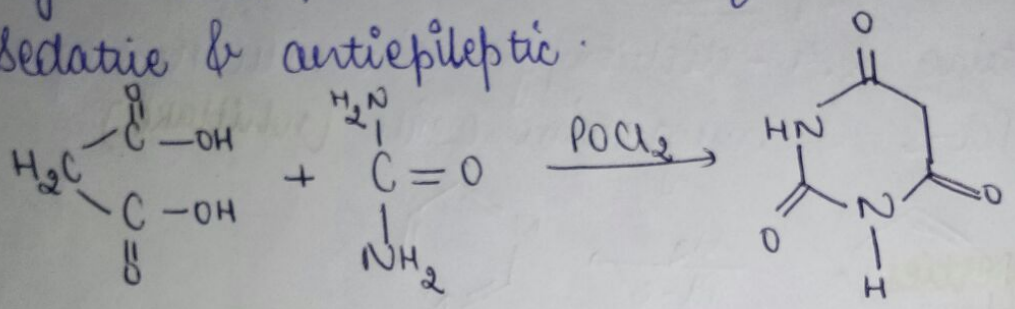
Pyrimethamine



Thiamine

(ii) Barbituric Acid (Malonyl Urea) -

An condensation of urea with malonic acid in the presence of phosphoryl chloride, barbituric acid is formed which is used as sedative & antiepileptic.

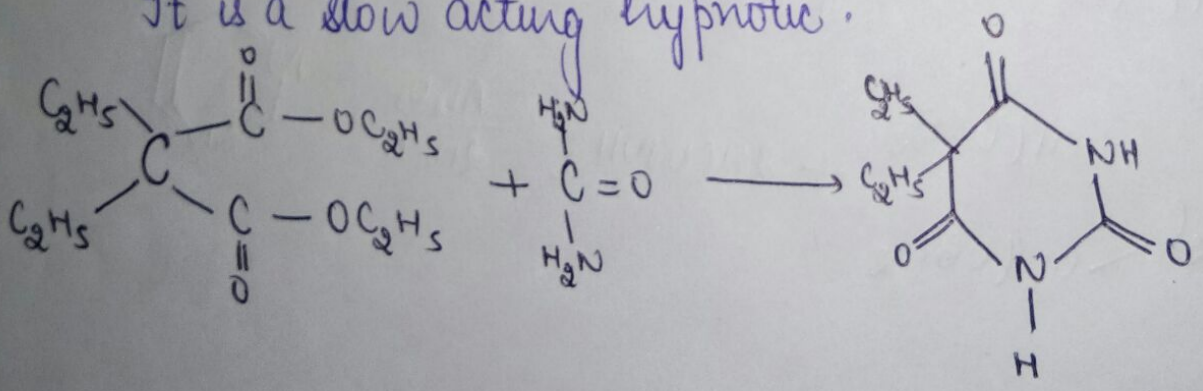


Malonic acid

Barbituric acid

(iii) Synthesis of veronal -

It is a slow acting hypnotic.

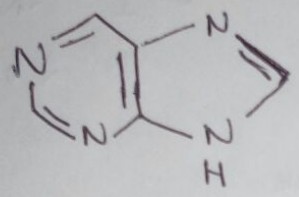


Veronal.

(2) Purine

The word purine was coined by the German chemist Emil Fischer in 1884. He synthesized it for the first time in 1898. The starting material for the reaction sequence was uric acid, which had been isolated from kidney stones by Carl Wilhelm Scheele in 1776.

A purine is a heterocyclic aromatic organic compound that consist of a pyrimidine ring fused to an imidazole ring.



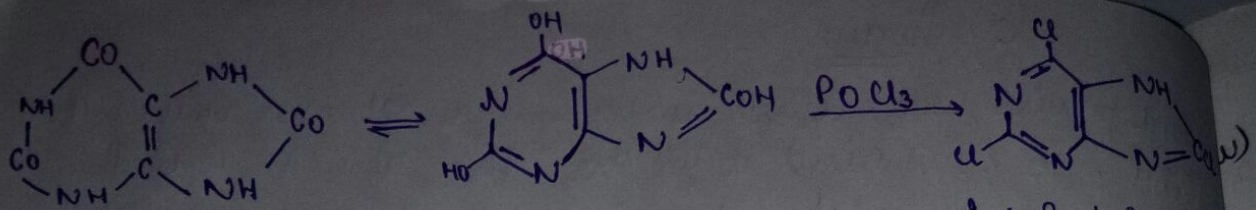
Physical properties -

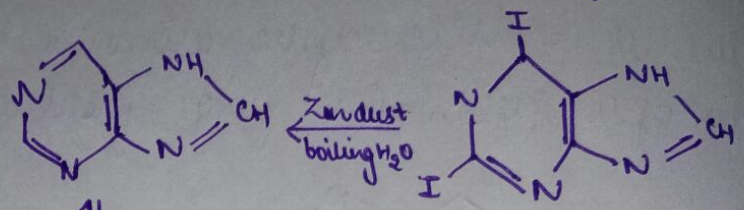
- Purine is both a very weak acid (pK_a 2.39) & even weaker base (pK_a 8.93). If dissolved in pure water, the pH will be half way between these two pK value.
- It is highly soluble in water.
- It have m.p. 217°C.
- It forms salt with acid.

Synthesis -

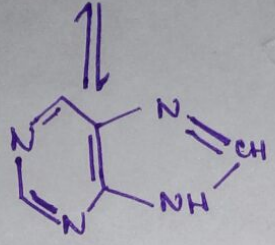
(i) From Uric Acid -

Uric acid was reacted with PCl_5 to give 2,6,8-trichloropurine which was converted with HI & PH_4I to give 2,6-diiodopurine. The product was reduced to purine using Zn dust.



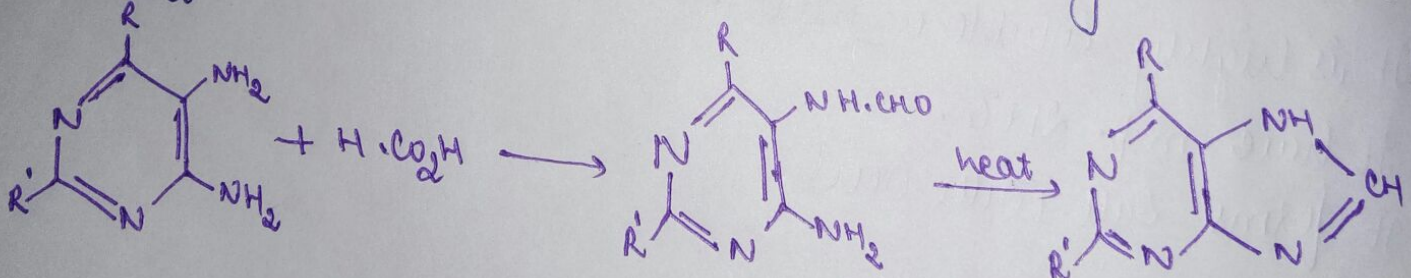


Purine



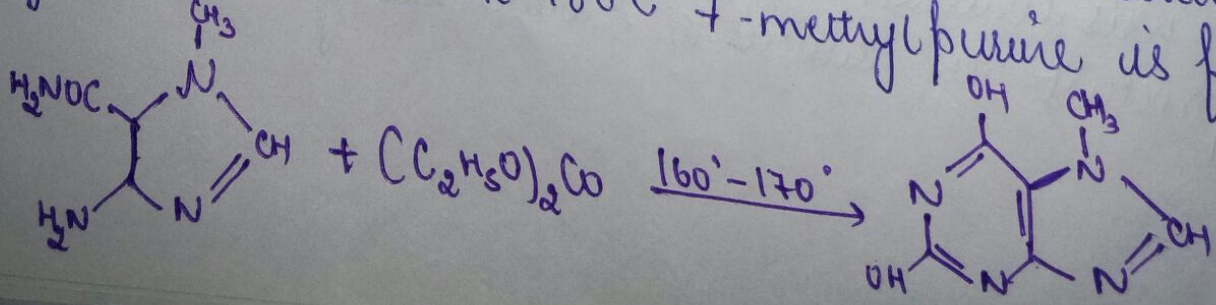
(ii) Traube's Method –

This method consist of reaction b/w 4,5-diaminopyrimidine with formic acid to produced imidazole ring & formyl derivative is ring closed by heating alone or heating with Sodium salt.

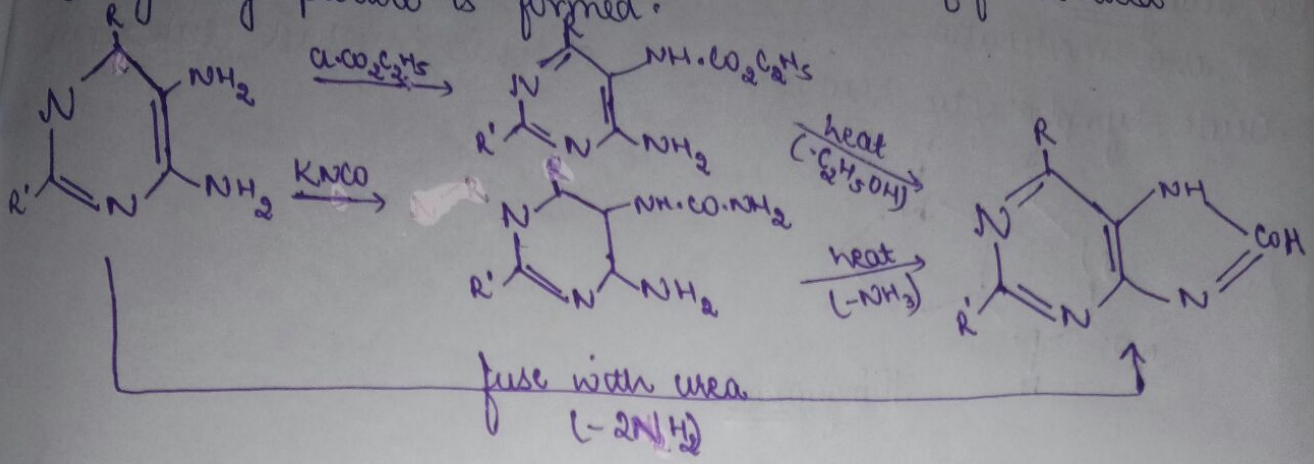


(iii) From imidazole derivative –

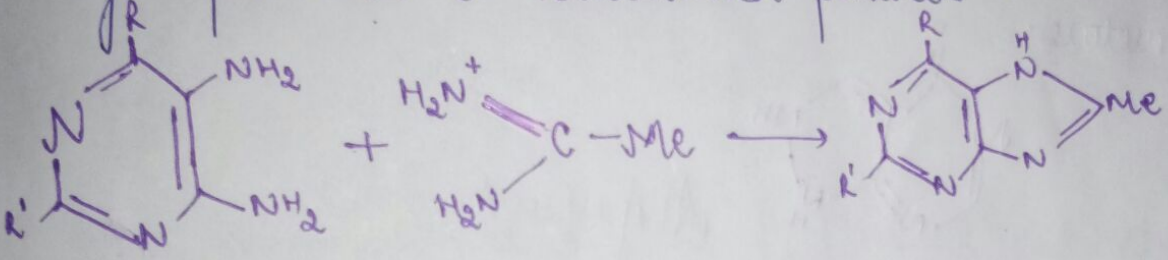
When 4-amino-1-methylimidazole-5-Carbonamide treated with ethylacetoacetate at 170-180°C 7-methylpurine is formed.



(ii) When ethylchloroformate is used instead of formic acid 8-hydroxy purine is formed.



(iii) Condensation b/w 4,5-diamino pyrimidine with amidine may produced 8-substituted purines.

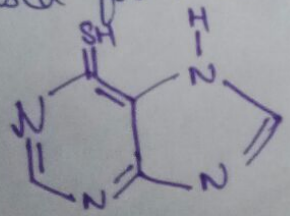


Medicinal Uses -

Purine derivaties are used in pharmaceutical & agricultural industry. Some of the pharmaceutically important purine derivaties are:

(i) Mercaptopurine -

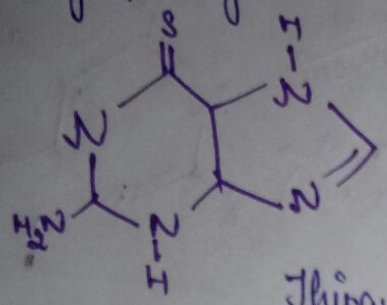
It is used for the treatment of cancer & autoimmune diseases.



Mercaptopurine

(ii) Thioguanine-

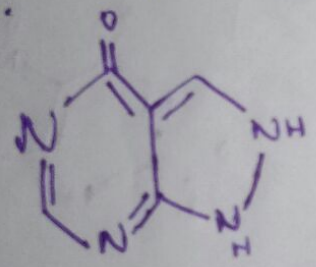
It is a medication for the treatment of acute myeloid leuka Acute lymphocytic leukaemia & chronic myeloid leukaemia.



Thioguanine

(iii) Allopurinol-

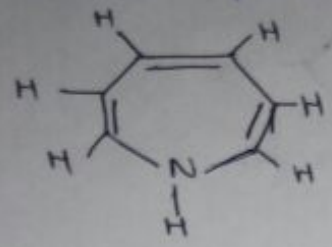
It is a drug used in treatment of gout contains purine Structure.



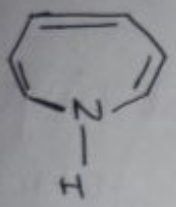
Allopurinol

(3) Azepines

Azepines are the 7-membered heterocyclic rings containing one hetero atom, they are heterocyclic analogues of 1,3,5-cycloheptatriene. These are azepine, oxepin, thiepin.

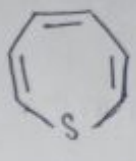


1,3,5-cycloheptatriene



Azepin

Oxepin



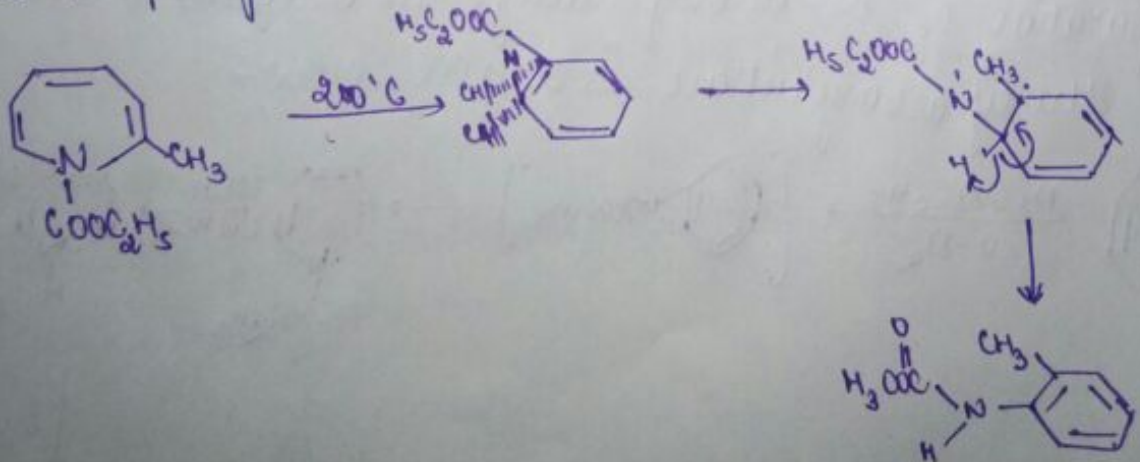
Thiepin

They donot follow Huckel's rule of $(4n+2)\pi$ electron, thus are non-aromatic acid & exhibit a high reactivity.

Chemical Properties –

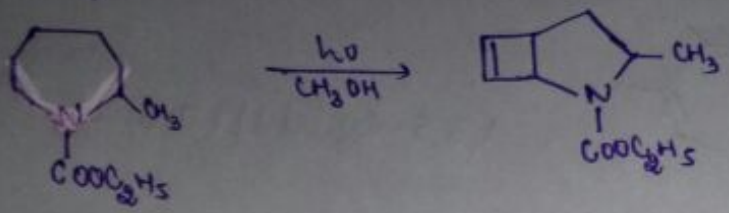
(i) Thermal Reaction –

N-carboethoxy-3H-azepine on heating results in aromatization to give N-phenylcarbamate.



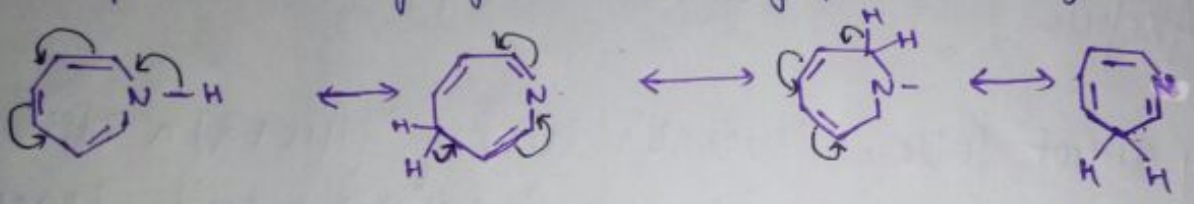
(iii) Ring Contraction-

Azepine undergo photo ring contraction to bicyclic balance tautomers by transformation reaction. The reaction will proceed as follows:



(iii) Hydrogen shift-

Hydrogen shift are common in large unsaturated rings such as azepines. The hydrogen shift may proceed as follows:

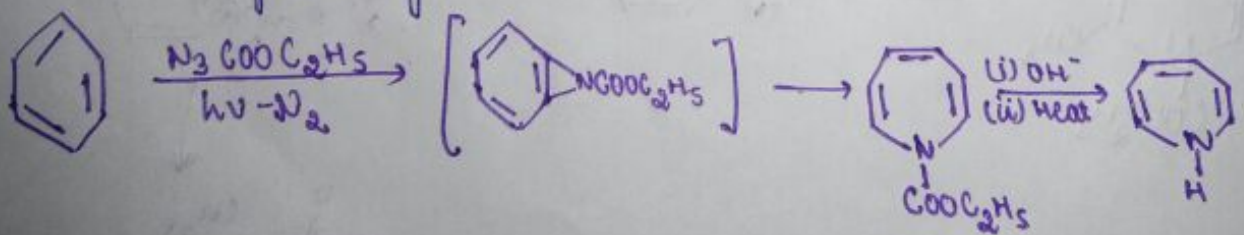


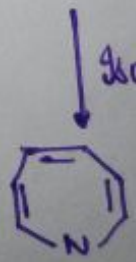
Synthesis -

(i) Valence Bond Isomerization -

This reaction involved reorganization of σ & π electron & does not involve a migration of any atom or group.

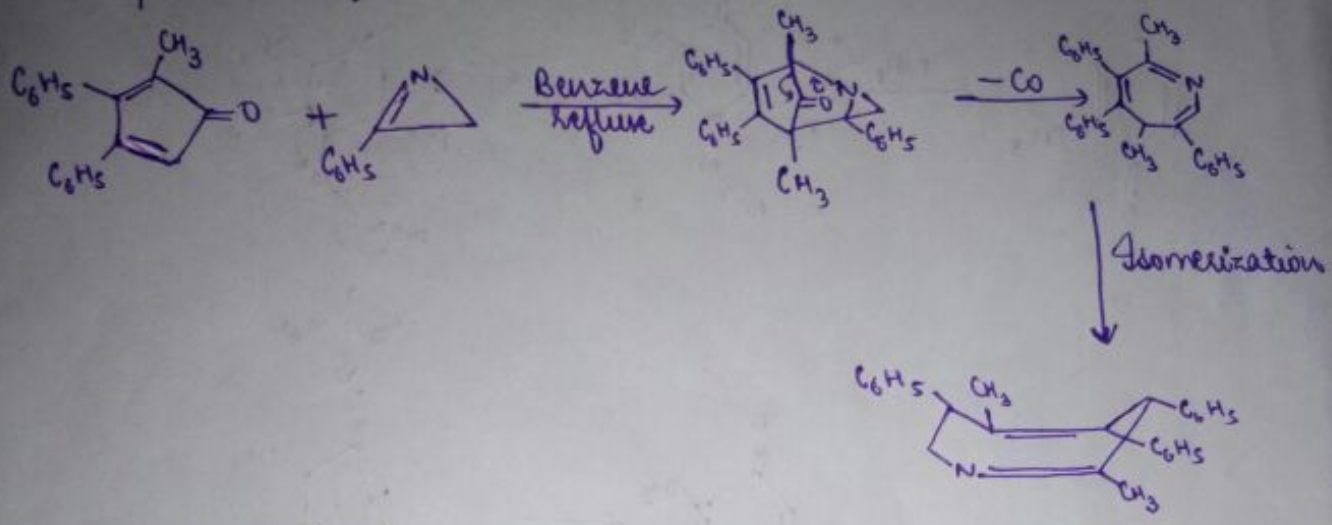
Preparation of N- ethoxycarbonyl -1H azepine from benzene & ethoxycarbonylnitrene is driven below:





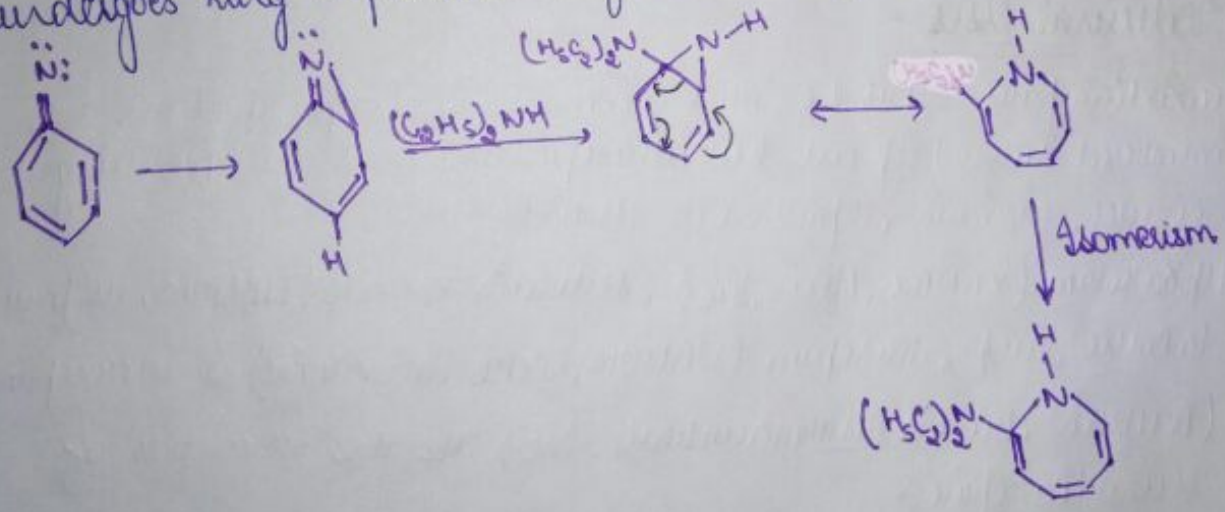
(ii) From Azirines –

Azirines are potential useful precursor for the synthesis of heterocyclic compound. An azirines on addition to cyclopentadienone thermally produces 3H azepine & reaction will proceed as follows:



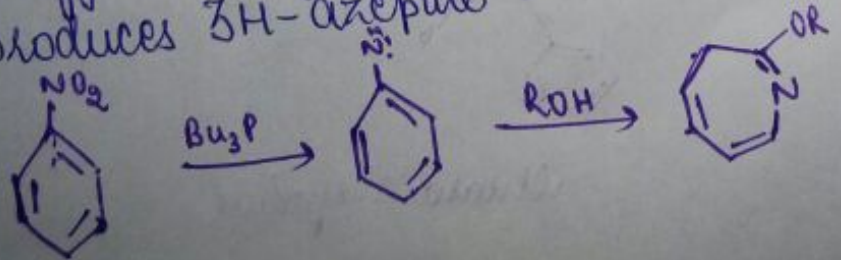
(iii) From Phenylazide –

Phenylazide on decomposition in boiling primary or secondary amine undergoes ring expansion & forms 3H azepine.

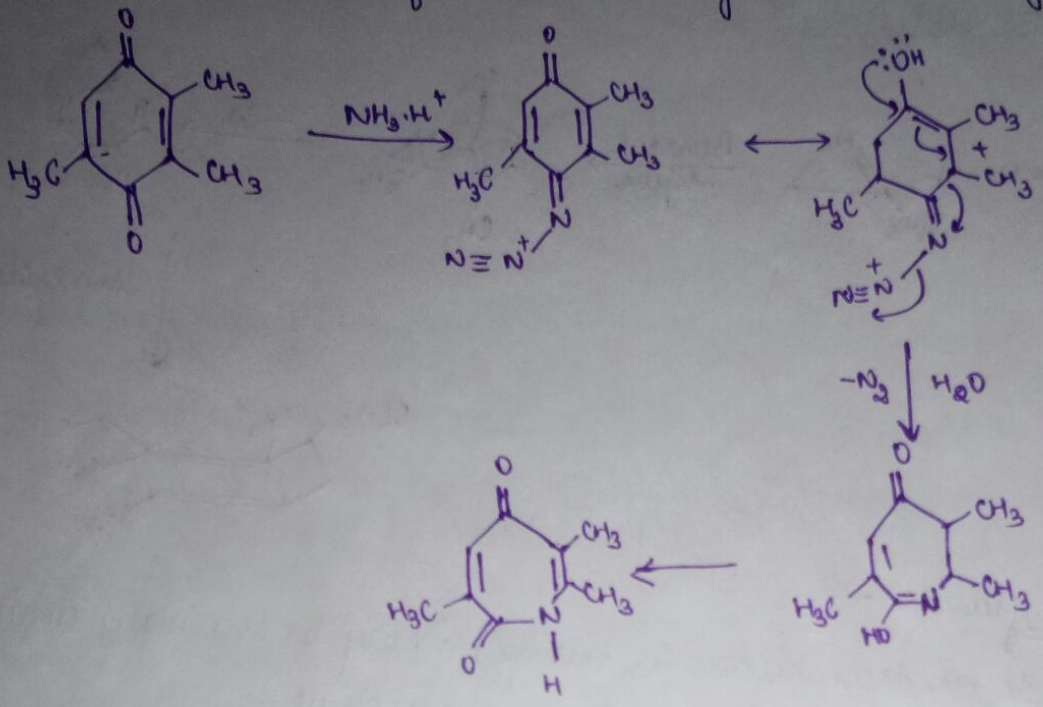


(iv) From Nitrobenzene –

Deoxygenation of nitrobenzene in the presence of tributylphosphine produces 3H-azepine.



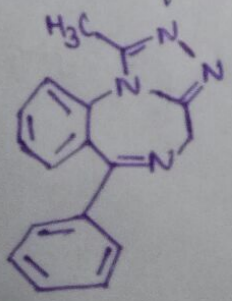
(v) On reacting p-benzoquinone with hydrazoic acid at 0°C and in the presence of sulphuric acid, azepine-2,5-dione is obtained. This synthesis is the Schmidt reaction in which p-quinone is used in place of more commonly used carbonyl compounds.



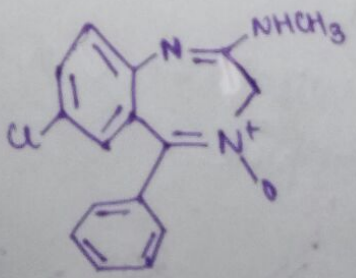
Medicinal Uses -

(i) Benzodiazepines - It is the most common ~~set~~ drugs based on 7-membered rings. Different benzodiazepins are used for treating seizures, insomnia, depression or anxiety.

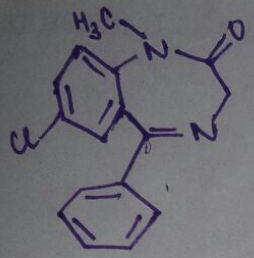
Alprazolam (XANAX, Pfizer, Inc.), chlordiazepoxide (LIBRIUM, Hoffman-laRoche, Inc.), diazepam (VALIUM, ROCHE laboratories) & lorazepam (ATIVAN, Biovail Pharmaceuticals, Inc.) are the examples of benzodiazepines.



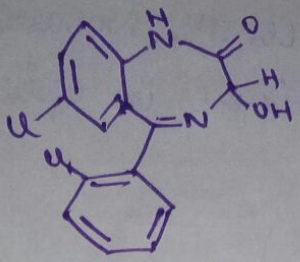
Alprazolam



Chlordiazepoxide

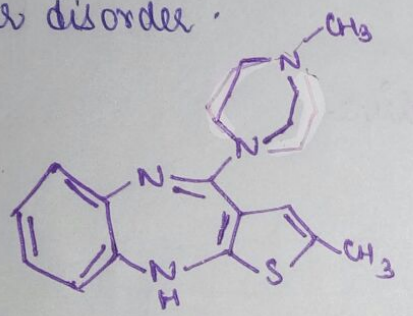


Diazepam



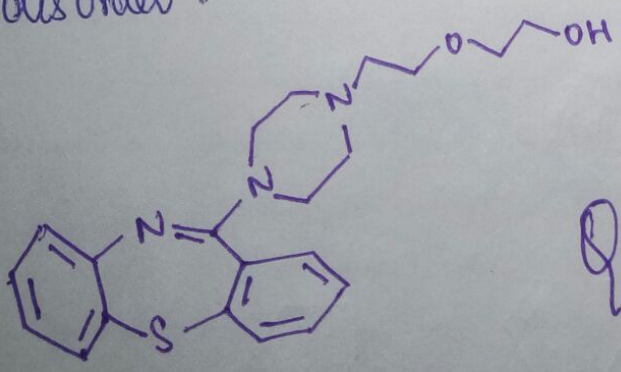
Lorazepam

(ii) Olanzapine – It is a psychotropic agent of the Thienobenzodiazepine class. Olanzapine (ZYPREXA; Eli Lilly & Company) is approved by the USA. FDA to be used for treating the symptoms of schizophrenia & acute mixed, manic episodes or for maintenance treatment of bipolar disorder.



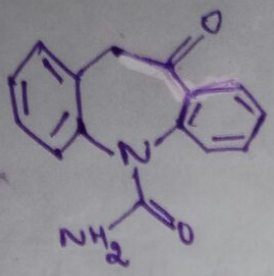
Olanzapine

(iii) Quetiapine – [SEROQUEL, AstraZeneca Pharmaceuticals, LP] is a dibenzothiazepine, & is an FDA approved mood stabilising drug used for treating the high as well as lows of bipolar disorder.



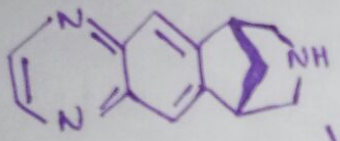
Quetiapine

(iv) Oxcarbazepine - (TRILEPTAL, Novartis Pharmaceutical Corporation) is used in partial seizures in epilepsy patients.



Oxcarbazepine

(v) Varenicline - It is used as (tartaric salt as CHANTIX, Pfizer) (Pfizer) is a smoking cessation drug with a benzazepine ring structure



Varenicline