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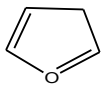
B.Pharmacy-IIIrd Semester
Sub-Pharmaceutical Chemistry-III (Heterocyclic Chemistry)
Model Answer

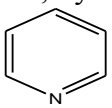
Section A

1. **A)** What do you mean by heterocyclic compounds?

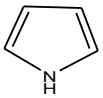
Ans: A cyclic organic compound containing all carbon atoms in ring formation is known as a *carbocyclic* compound. If at least one atom other than carbon (like nitrogen, oxygen, sulphur etc.) forms a part of the ring system then it is designated as a heterocyclic compounds.
Or
Heterocyclic compounds are the cyclic organic compounds which composed of common hetero atoms like nitrogen, oxygen and sulphur and along with carbon.
Example: Furan, Pyrrole, pyridine.



Furan



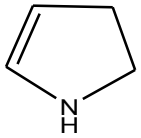
Pyridine



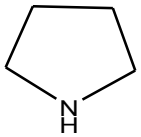
Pyrrole

B. Partially saturated (dihydropyrrole) known as……. and fully saturated (tetrahydro) Pyrrole known as …….. and give their structures.

Ans: Dihydropyrrole known as 2, 3-pyrroline and tetradydro-pyrrole known as 2, 3, 4, 5 perhydro Pyrrole or pyrrolidine

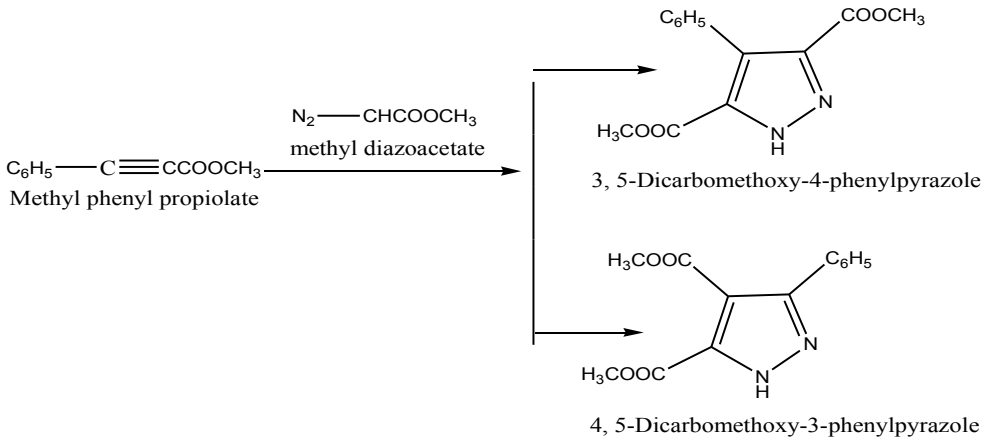


2, 3-pyrroline or



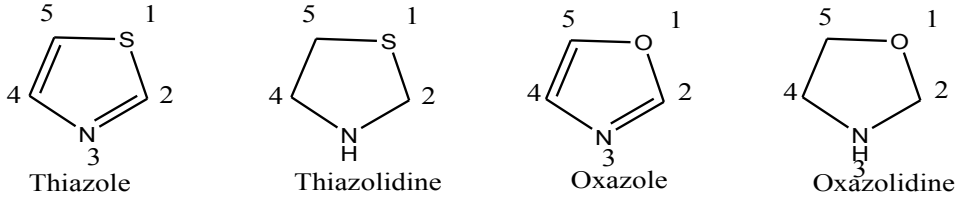
2, 3, 4, 5-Perhydro pyrroleor Pyrrolidine

C) Explain 1, 3 dipolar addition reaction with example.
Ans: A diazo compounds adds to an acetylenic derivative which has it activated by an eleetron-withdrawing substituent and this reaction is usually carried out in suitable solvent at room tem known as *1, 3 dipolar* addition reaction.
Example: Diazomethene or methyl or ethyl-diazoacetate is commonly empolyed.
Thus methyl diazoacetate and methyl phenyl propiolate give isomeric pyrazoles.



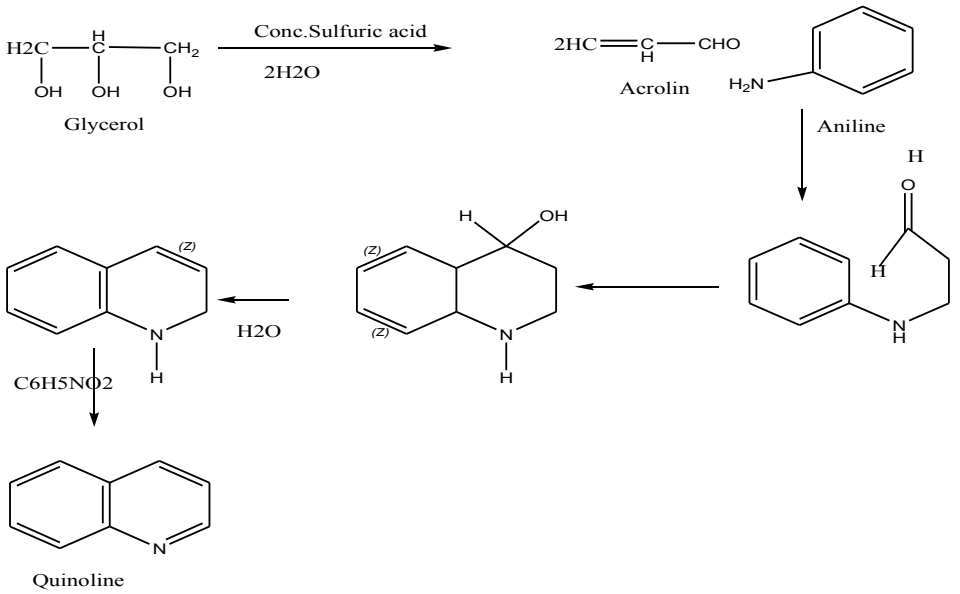
B) Draw the structures of Thiazole, Thiazolidine, Oxazole and Oxazolidine.

Ans:

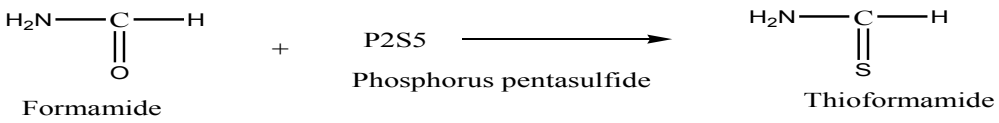


C) Skraup synthesis for Quinoline.

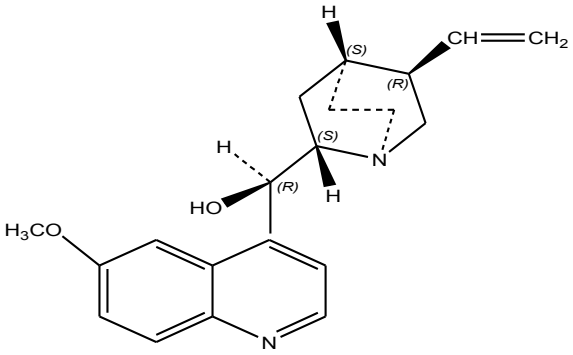
Ans: Skraup synthesis for Quinoline is the most important synthesis in this method an aniline or its derivatives having a vacant *ortho* position is heated with glycerol, conc. Sulfuric acid and oxidizing agent. In the simple case when the amine is aniline and oxidizing agent is nitrobenzene, the overall the reaction of refluxing in sulfuric acid is shown below:



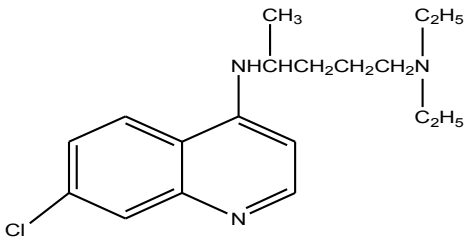
D) Write dawn the synthetic route of the Thioformamide.
Ans: Thioformamide obtained by reacting phosphorus pentasulfide and formamide at room temperature.



E) Write down the name and structure of the antimalarial compounds having quinoline scaffold.



Quinine

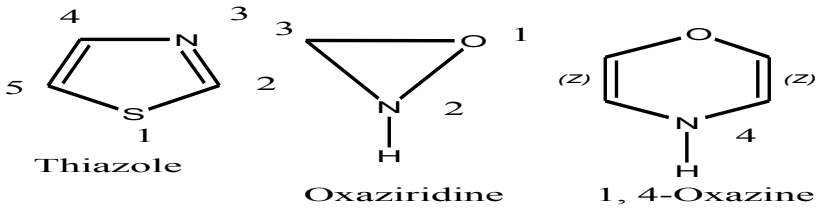


Chloroquine

Ans : the two antimalarial compound having quinoline scaffold are quinine and chloroquine.

F) The numbering of heterocyclic compounds starts with hetero atom. If there is more than one hetero atom present then the numbering will start from which atom. Explain with example.

Ans: If two or more different hetero atoms present in the ring then it name by combining the prefixes and the numbering runs in such a direction that as many heteroatoms as possible lowest numbers. Example: sulfur is given a lower number than nitrogen and oxygen lower than either.

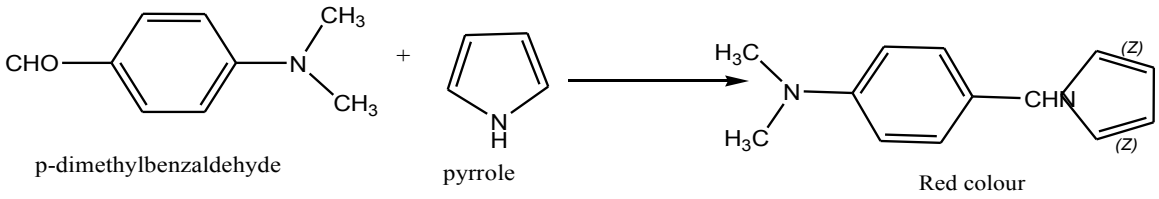


Thiazole

Oxaziridine

1, 4-Oxazine

G) Explain *Ehrlich test* for Pyrrole.



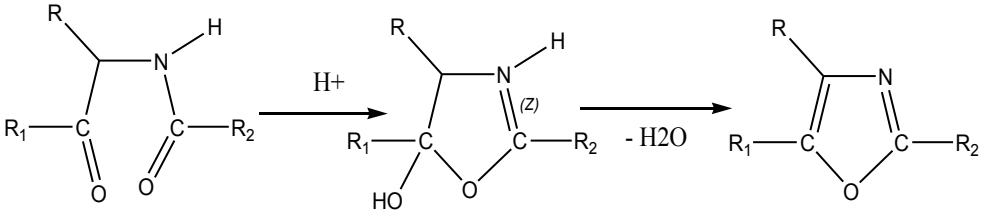
Ans: Pyrrole reacts with *p*-dimethylaminobenzaldehyde it gives intense *red* colour this test known as *Ehrlich test.*

H) Define azoles.

Ans; In the five member ring system or five member carbocyclic compounds contain two hetero atoms and among which one of them must be nitrogen they are called Azoles. or

An Azole is a class of five member nitrogen heterocyclic ring compounds contain at least one other non-carbon atoms of nitrogen, sulfur or oxygen. (Example, pyrazole, Imidazole, Oxazole)

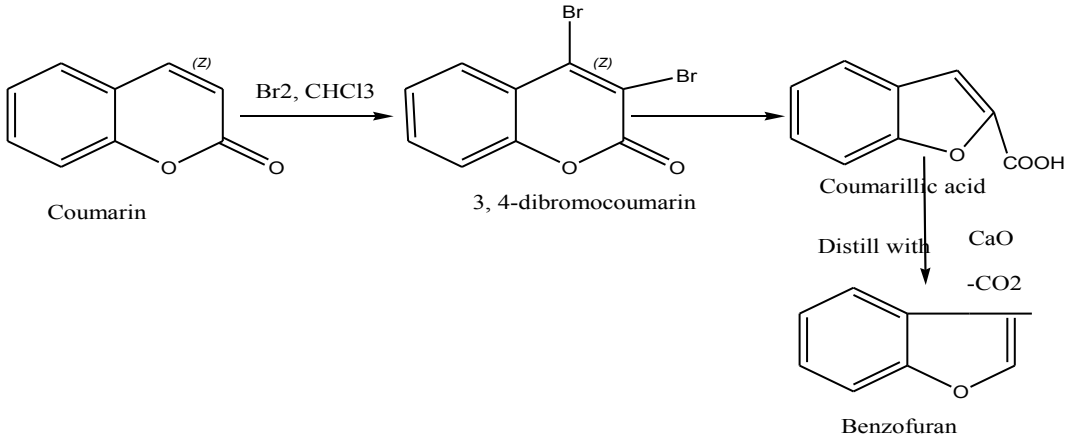
I) Rabinson-Gabriel synthesis for Oxazole.



Ans: In this method an α-Acylamino ketone which undergoes cyclization and dehydration in the presence of phosphorus pentoxide or a strong mineral acid. This is especially applicable for the formation of 2, 5-diaryloxazole. The mechanism outline is below;

J) Synthesis of benzofuran from coumarin.

Ans: this method involved the bromination of coumarin to 1, 4-dibromocoumarine followed by treatment with alkali to coumarillic acid then acid decarboxylates to Benzofuran.



SECTION- B **14X4= 56**

Q2 to Q.7 (Descriptive type, may contain subquestions)

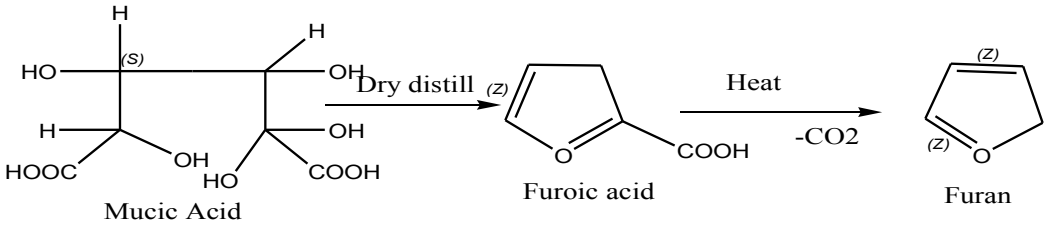
2. Discuss the methods of preparation, chemical reactions of furan along with its medicinal importance.

Ans: the furan aromatic ring system though not found in animal metabolism but occurs in secondary plant metabolite in Terpinoids.in case of furan 2, 3 dihydrofuran and 3, 4-dihydrofuran are possible and the fully saturated compound is known as tetrahydrofuran.

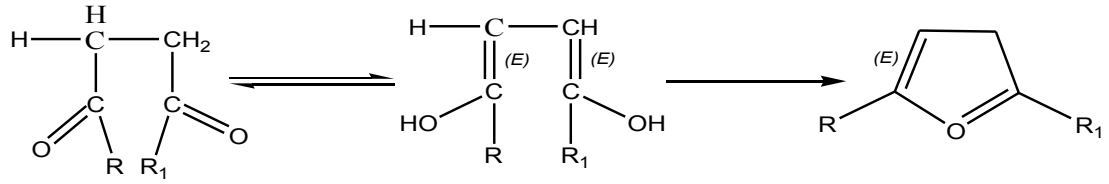
Properties; colourless, liquid, bp-31.5^{o}C. it possesses a chloroform like odor and is soluble in most organic solvent but slightly miscible with water.

Preparation:

i) Furan prepare from mucic acid which gives furoic acid on dry distillation, the latter acid is then decarboxylate at its b. p at to furan.



ii)

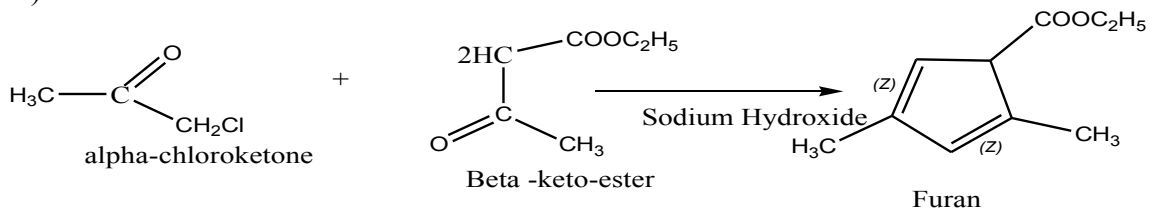


1, 4-dicarbonyl compound

Pall-

Knorr synthesis of pyrroles: 1, 4-dicarbonyl compounds on treatment with dehydrating agents, such as H_2SO_4, $Zncl_2$, P_2O_5 etc, are converted into furan.

iii)



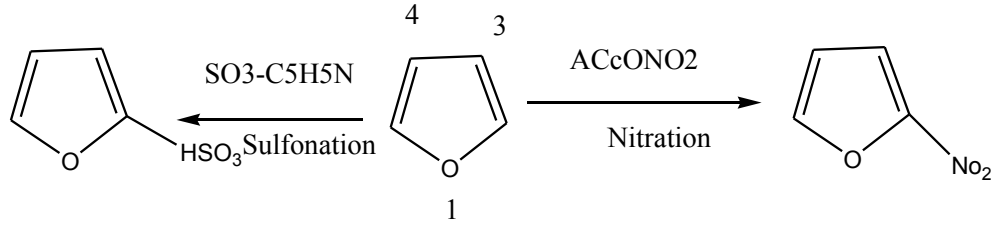
Th

e Fiest –Benary synthesis: I n this synthesis an α-chloroketone is condense with β-keto ester in sodium hydroxide.

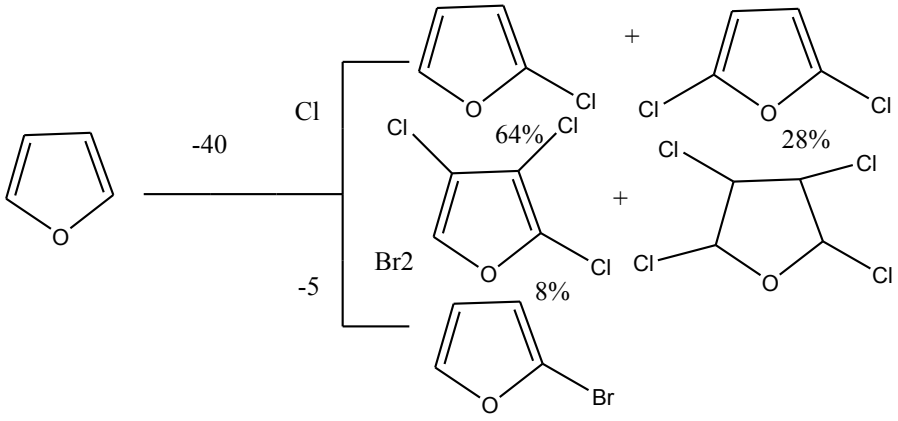
Chemical reaction of furan:

Electrophillic reaction: in case of furan the π excessive heterocyclic compound have higher electron density on the ring carbon atoms than the benzene. And electrophilic substitution occurs at position 2 or 5 than the 3position.

Nitration and sulfonation:

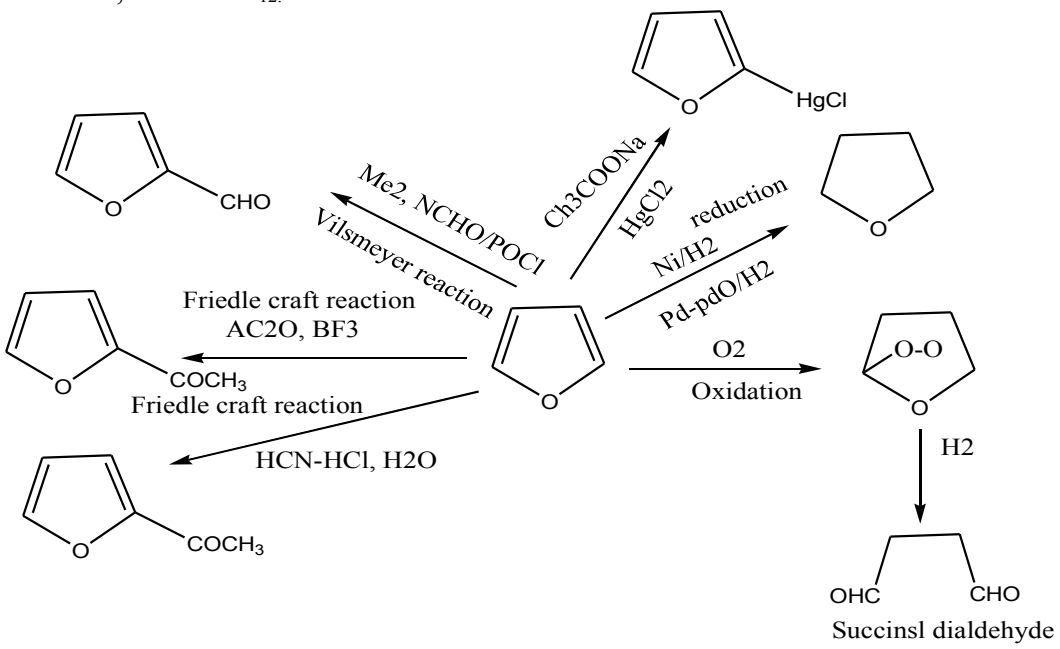


Halogenation; furan under goes chlorination at -40 then yield 2 chloro, 2,5-dichloro and 2, 3, 5-trichlorofuran (8%) if increase the amount of chlorine yield tetrachlorofuran.
In case bromination at -5^{0}C gives 2-bromofuran.



The friedle –Craft reaction, gatterman-koch reaction, oxidation reduction, Mercuration should explain with reaction.

Pyrrole is the most important among all the membered heterocyclic compounds because its nucleus occurs in the various important natural products, eg; chlorophyll, haemin, bilirubin alkaloids, vitamin B_{12}.

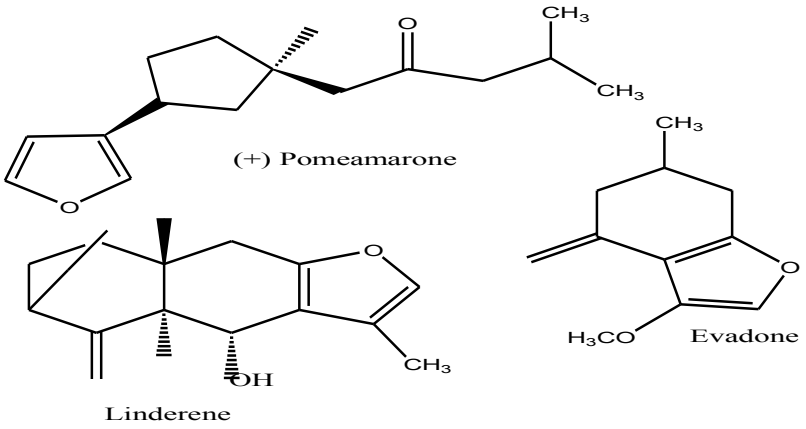


Medicinal Important of Furan:

Simple monocyclic furan derivatives are found in natural product although as a group such substance are not of wide spread occurrence.

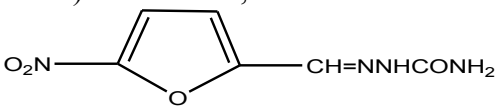
i) 2-methylfuran for intense, finds its origin in oil of turpentine. Furfural, furfural alcohol and 5-methylfurfural occure in iodium fragile and roasted coffee and 4, 5-dimethylfuran-3-carbadehyde occurs in oil of cloves.

ii) The (+) 1-pomeamarone, Iinderene, evadone ete, occure naturally.



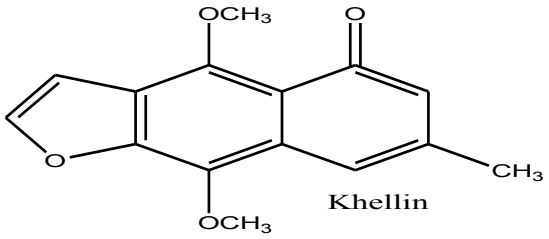
Linderene

iii) Furacin,or 5-nitrofurfural semicarbazide is a useful as antibacterial agents.



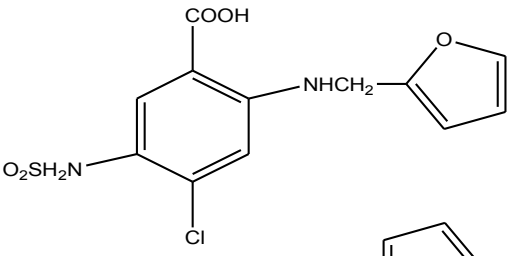
Furacin

iv) **Khellin** a medicinal agent has been used for a variety of pharmacological indicators including hypertension, renal and biliary colic and stomach disorder.

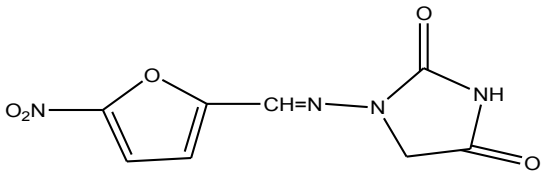


Khellin

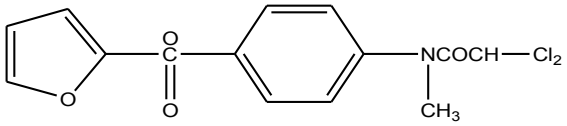
v) Some synthetic product:



Frusemide Used as Diuretic

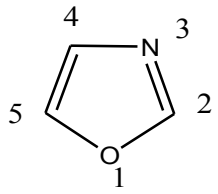


Nitrofurantoin used as bactericidalin vitro



Diloxanide Furate used as Antiamoebic drugs

3. i) Oxazole is a 1, 3-azole having an oxygen atom and a pyridine type nitrogen atom at the 3position in five membered ring. Oxazole does not occure in nature and thus does not play any part in fundamental metabolism as do Imidazole and Thiazole.



Partially reduce Oxazole are called oxazoline nd three type are possible depending on the position of the double bond. These are 2-oxazoline, 3-oxazoline, 4-oxazoline, and fully saturated system called oxazolidine.
Properties: Oxazole is a liquid, b. p-69^{0}C and has an odor resemble like pyridine. It is miscible with water and many organic solvents. It weakly basic

Following point should be include
(Should be include at leat three synthesis)

i) From Ethyl-α-Hydroxy keto succinate, Robinson-Gabriel synthesis, From isocyanides, From α-Aminocarbonyl Compounds.from pomeranz-Fritsch synthesis.
ii) Chemical reaction include. Electrophillic reaction, Nucleophillic reaction, oxidation and reduction reaction, photochemical reaction.
iii) Discuss naturally obtain active compounds and synthetic compounds.(medicinal Important in brief)

ii) Pyrazole was first describe by Buchner in 1889.pyrazole have interesting application in drugs, dyes and as anaesthetics. Pyrazole have also been used as antioxidants in fuels but their major applications have been in medicinal and agricultural field.the dihydropyrazole are called pyrazoline.

Properties: pyrazole is a colourless solid m. p 70^{0}C and is soluble in water and oder like amine.

In synthetic part include: from dicarbonyl compounds, from α, β-Ethylenecarbonyl compounds, from 1, 3-Dipolar addition, from other ring system.

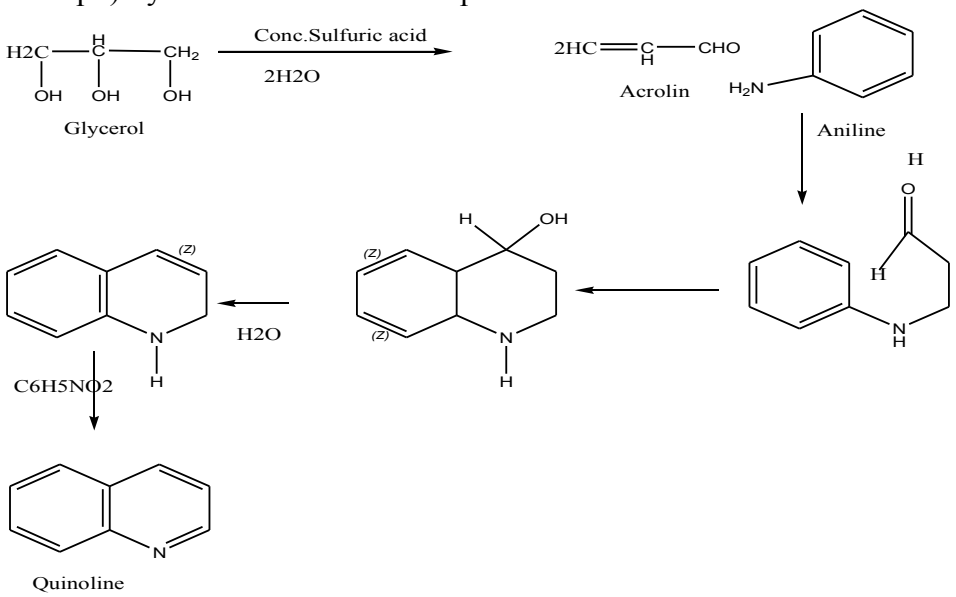
Its chemical reaction: Electrophillic substitution, oxidizing an reducing reaction.
Medicinal important include naturally active and biologically active compound and synthetic compounds with their chemical structure.

ii) Thiazole same as Oxazole

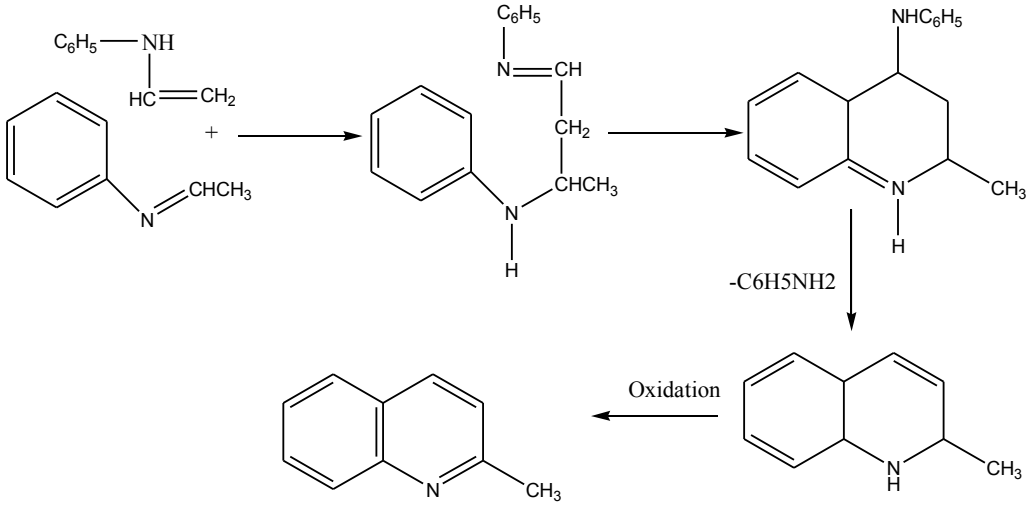
4. discuss in detail synthetic route of following compounds.

Quiniline:

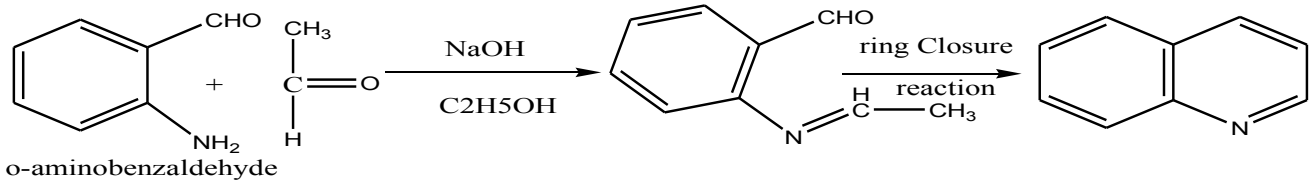
Skraup i) Synthesis: it Should be explain



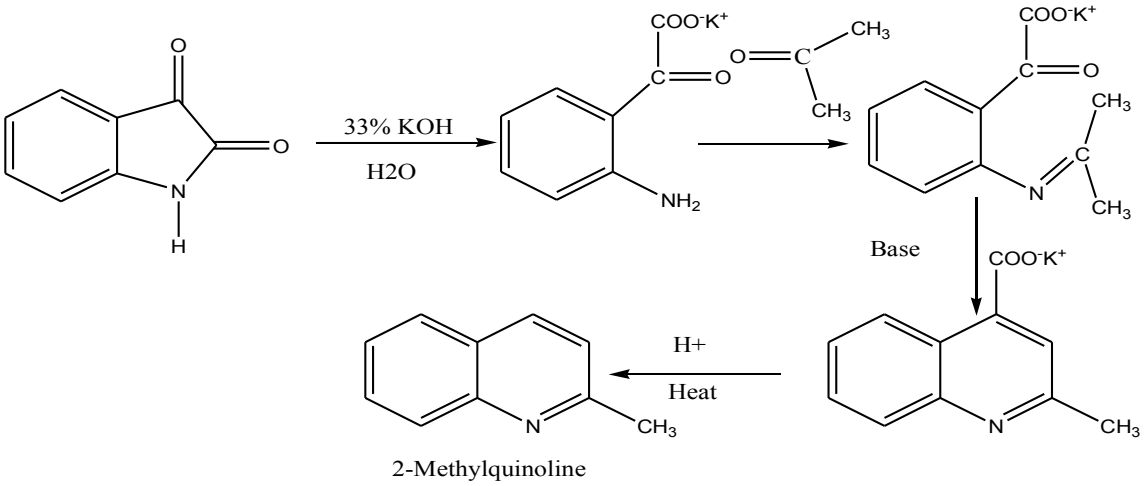
ii)The Doebner-Miller Synthesis: it Should be explain with name.



iii) The Friedlander Synthesis:

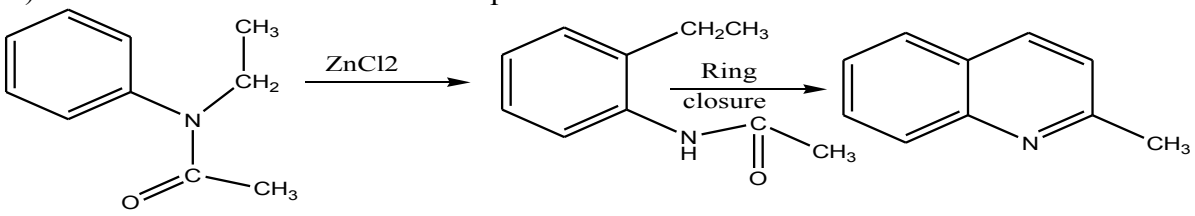


o-aminobenzaldehyde



iii) The Pfitzinger synthesis:

iv) The Pictet Method: it should be Explain with the Name.



ii. Indole (Synthesis include) i) The Fischer-Indole Synthesis ii) The Madelung synthesis iii) The Bischler Sythesis iv) The Reissert Synthesis.

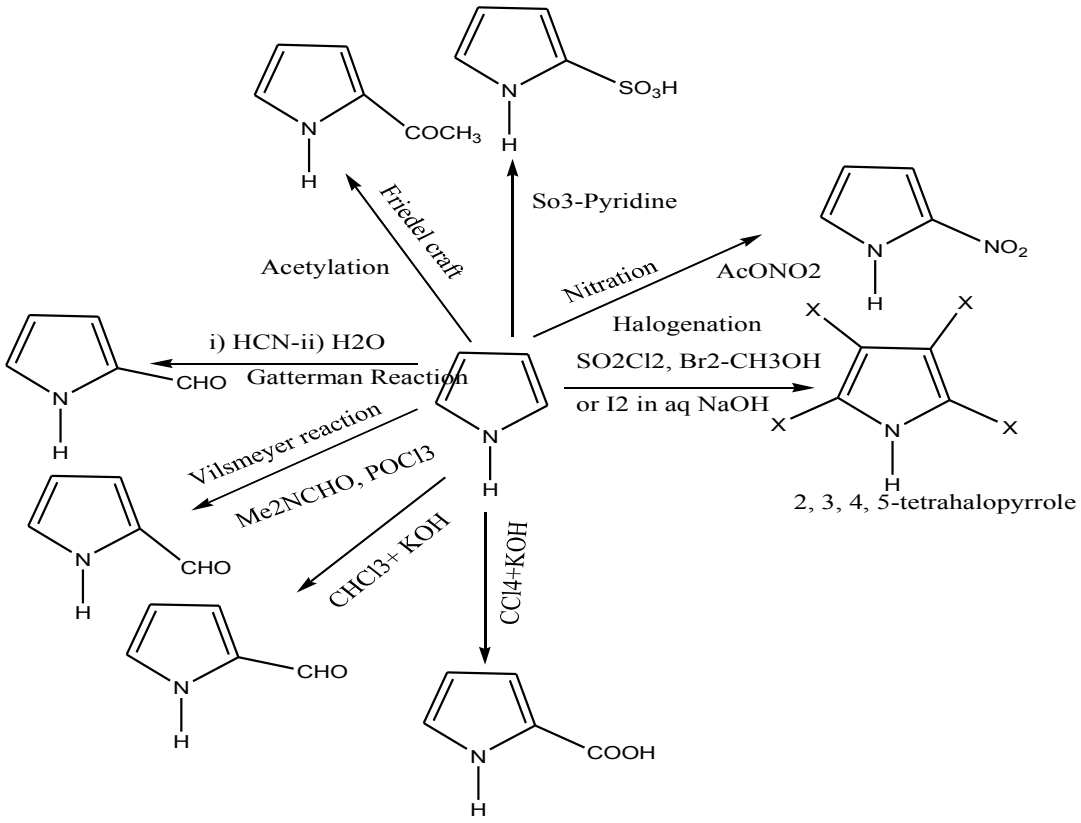
ii**Isoquinoline (Synthesis include) i) The Bischler-Napieralski synthesis ii) the Picte-Gams Synthesis iii) The Pomeranz-Fritsch Synthesis iv) From Indene.**

iv) Write dawn the chemical reaction of the following moiety

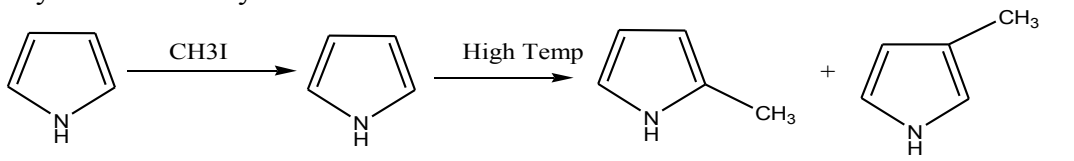
i) In case of , **Pyridine** and **pyridazine** following point should be include: reaction with acids, Electrophilic substitution, Halogenation, Sulfonation, the friedel crafts reaction, mercuration , Quaterinization, reaction with reducing agents, reaction with oxidizing agents and Nucleophillic substitution, reaction, Photo chemical reaction.

ii) In case of , **Pyrimidine** following point should be include: reaction with acids, Electrophilic substitution, Halogenation, Sulfonation, the friedel crafts reaction, mercuration , Quaterinization, reaction with reducing agents, reaction with oxidizing agents and Nucleophillic substitution, reaction, the claisen rearrangement, Photo chemical reaction.

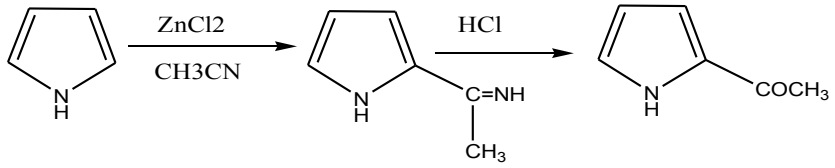
6. Pyrrole: Pyrrole is the most important among the all the five membered heterocyclic compounds because is nucleus in the various important natural producteg, chrophylln, haemin, bilirubin, alkaloids, vitamin $B_{12.}$ Pyrrole is colorless liuid, b. p, 130^0C, it has odour resembleing that of chloroform.
   Chemical reaction of Pyrrole:


SO3H
COCH3
Friedel craft
Acetylation
So3-Pyridine
Nitration
AcONO2
NO2
Halogenation
SO2Cl2, Br2-CH3OH
or I2 in aq NaOH
2, 3, 4, 5-tetrahalopyrrole
i) HCN-ii) H2O
Gatterman Reaction
CHO
Vilsmeyer reaction
Me2NCHO, POCl3
CHCl3+ KOH
CCl4+KOH
COOH

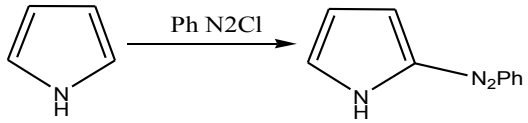
Alkylation and acetylation:



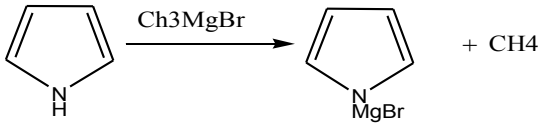
Houben-Hoesh reaction:



Coupling reaction:



Reaction with Grignard reagent:



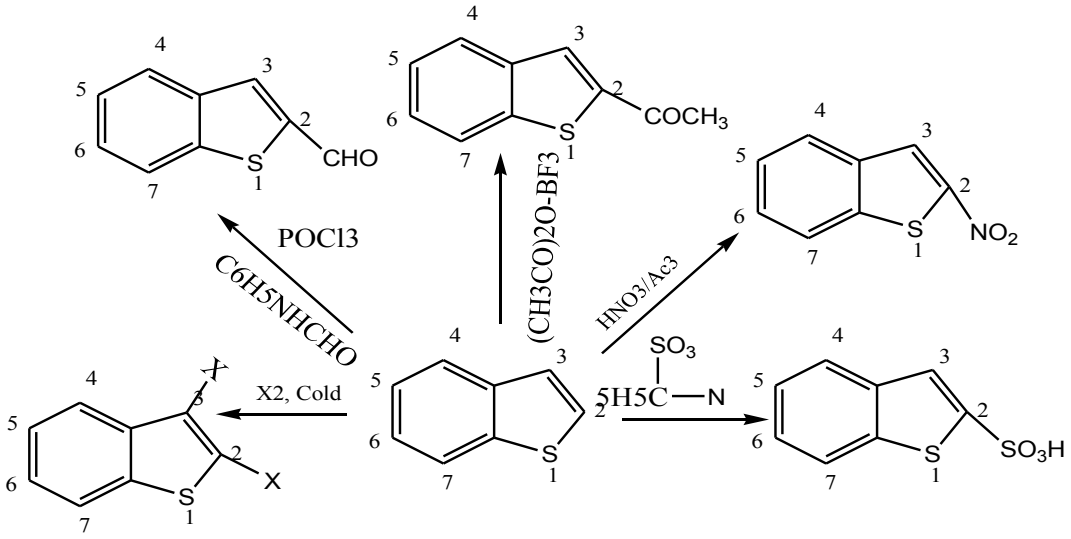
Also include; Reduction and oxidation, mannich reaction, Hofman's exhaustive methylation, condensation with aldehyde,

Medicinal important include: Naturally active compounds as well synthetic compounds like… proline, Porphyrins, Etioporphyrins, Hemin, Chlorophylls, Vitamine $B_{12,}$ bile pigments discuss in details.

7. Write short notes on: (Any two)

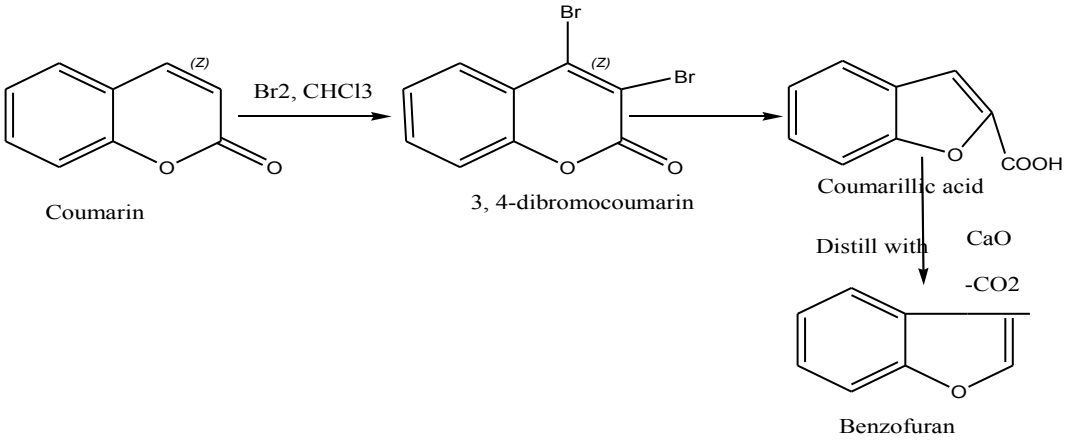
   i) Chemical properties of Benzothiophene: Benzothiophene is a colouless l solid b. pt. 32^0C. it is much stable to chemical attach than furan electrophilic substitution occurs in mild condition and attack place in 2 and position 3.

   As well as discuss the reduction and oxidation of Benzothiophene.

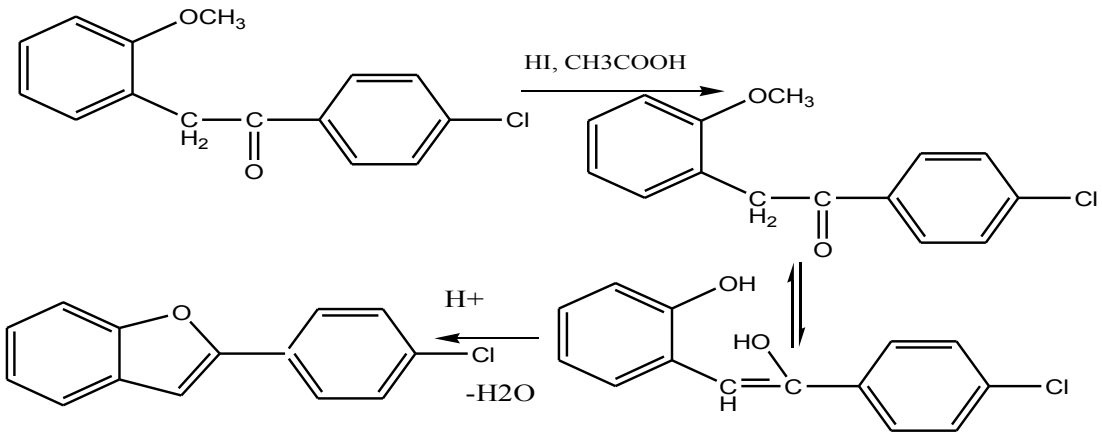


ii) Synthetic route of Benzo(b)Furan

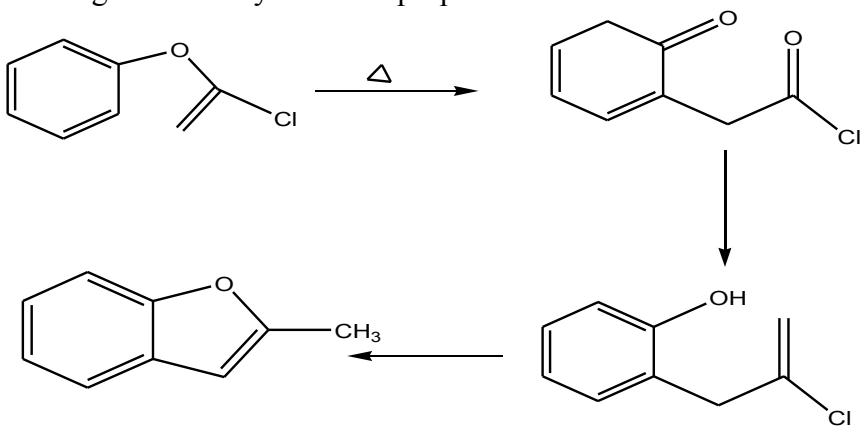
Benzo(b)furan from coumarin: in this method involved the bromination of coumarin to 1, 4-dibromocoumarine followed by treatment with alkali to coumarillic acid then acid decarboxylates to Benzofuran.



2. In another method 2-methoxy -2methylphenylmethyl 4-chlorophenyl ketone is firet with HI (47%) CH3COOH to bring an either cleavage and subdesuent cyclization of the intermediaste leads to benzofuran.

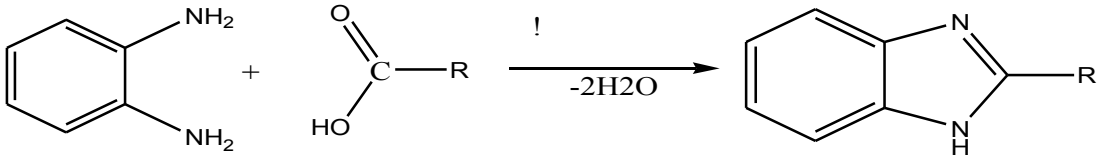


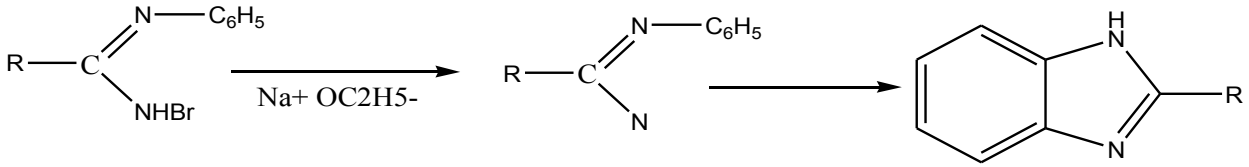
4. **Claisen Rearrangement:** 2-Methylbezofuran may be prepared by a Clainsen rearrangement of aryl-2-chloroprop-2en ether.



iii) Synthetic route of Benzimidazole:

a. Benzimidazole prepared from 1, 2-diaminobenzene condenses with a carboxylic acid in an acidic medium to give Benzimidazole.





b.The Cyclization of N-Haloamidines with sodium ethoxide form Benzimidazole v*ia a* nitrene intermediate.