ORGANIC CHEMISTRY-III

UNIT 4 NOTES

HETEROCYCLIC COMPOUNDS

- PYRAZOLE
- OXAZOLE
- IMIDAZOLE
- THIAZOLE
- PYRIDINE
- QUINOLINE
- ISOQUINOLINE
- ACRIDINE
- INDOLE
- PYRIDINE
- PURINE
- AZEPINES

IMPERFECT PHARMACY

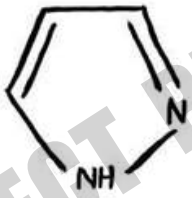
CONNECT WITH US ON :

IMPERFECT PHARMACY APP

@IMPERFECTPHARMACY

PYRAZOLE

- Pyrazole is a five - membered heterocyclic compound that contains 3 carbon atoms & two adjacent nitrogen atoms in the ring.
- Its chemical formula is $C_3H_4N_2$.
- It is a weak base & forms hydrogen bonds, making it soluble in polar solvents.



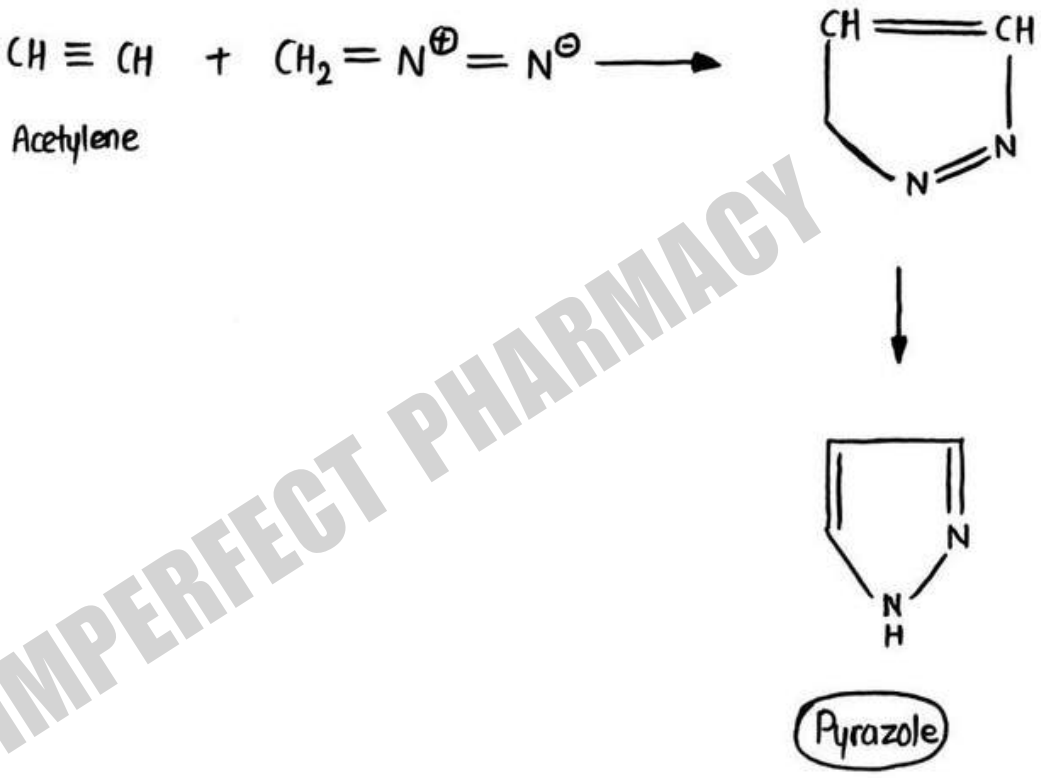
Pyrazole

SYNTHESIS OF PYRAZOLE

- From Acytylene
- From pyrazole Carboxylic acid
- From Acraldehyde

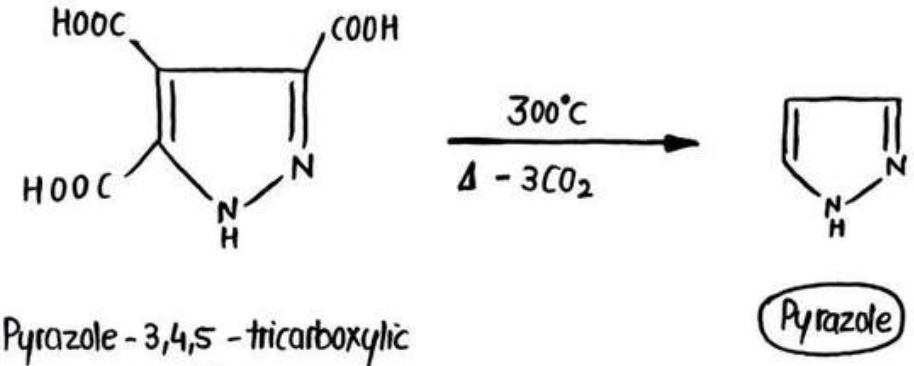
① From Acetylene

Acetylene passed through a cold solution of diazomethane to yeild pyrazole.



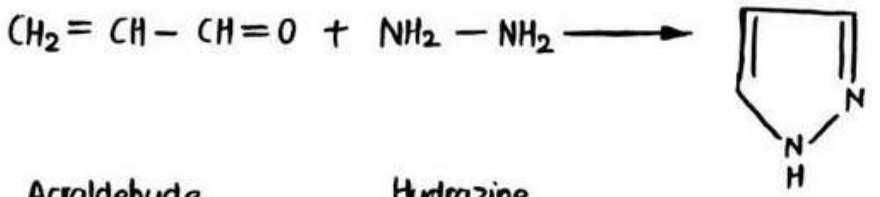
② From Pyrazole carboxylic Acids

Decarboxylation of various carboxylic acids gives pyrazole.



③ From Acraldehyde

Acraldehyde when reacts with hydrazine gives pyrazole.



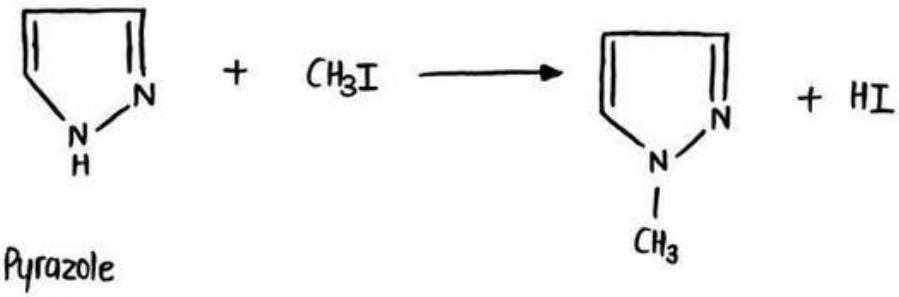
Acraldehyde Hydrazine Pyrazole

CHEMICAL REACTIONS OF PYRAZOLE

- Alkylation
- Electrophillic Substitution Reactions
- Reduction

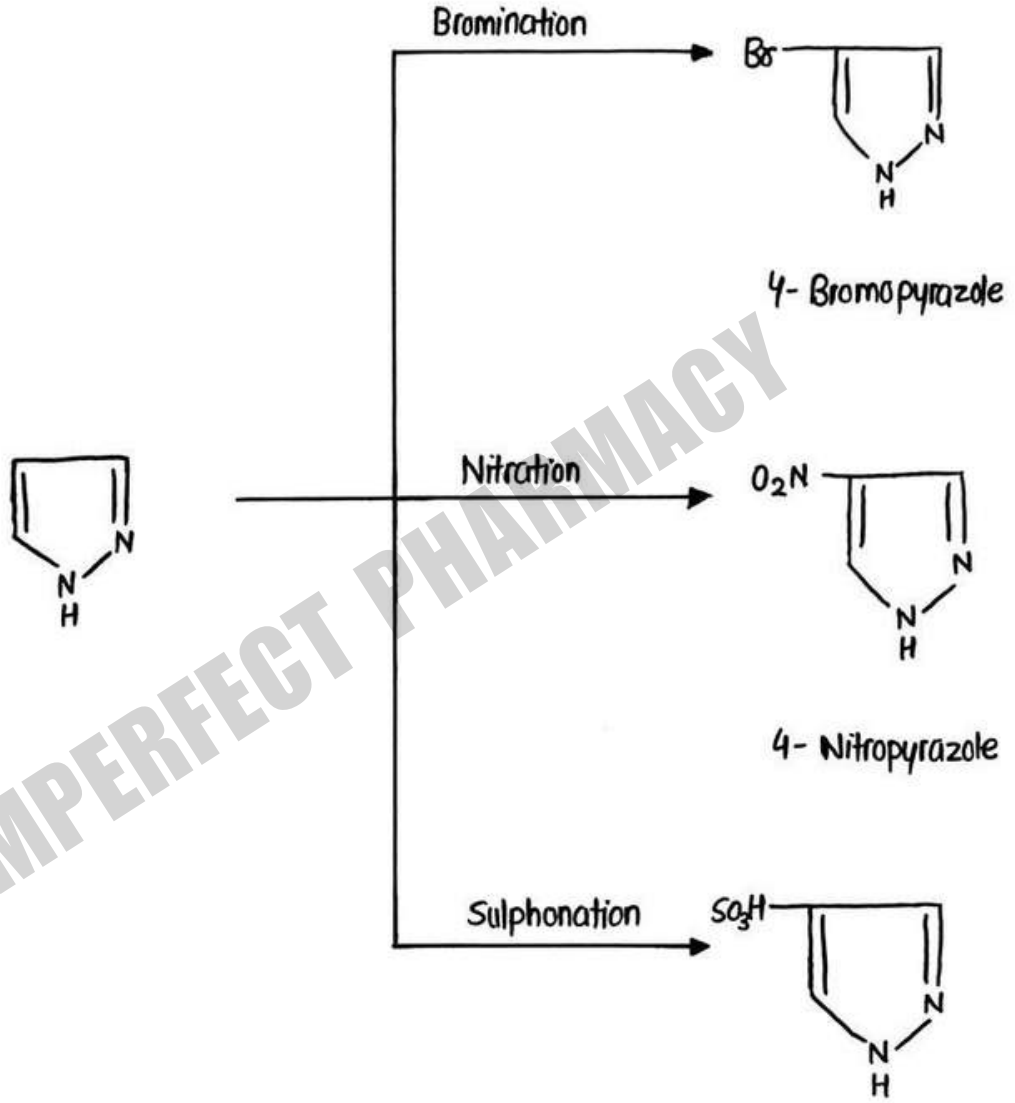
① Alkylation

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



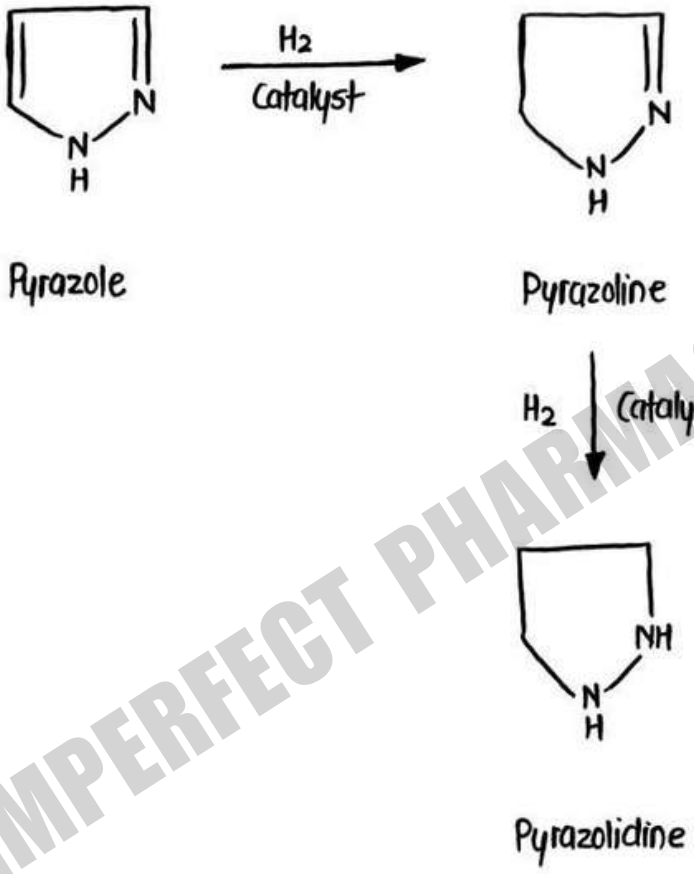
Pyrazole N- methyl pyrazole

② Electrophillic Substitution Reactions

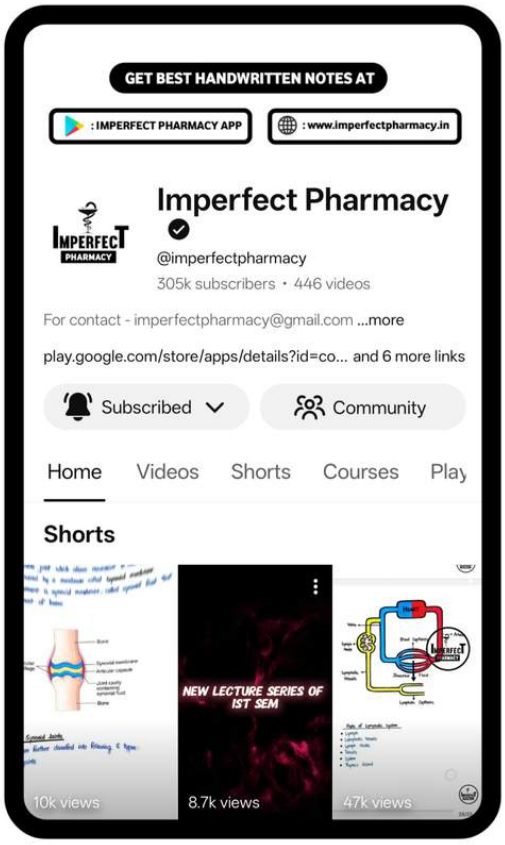


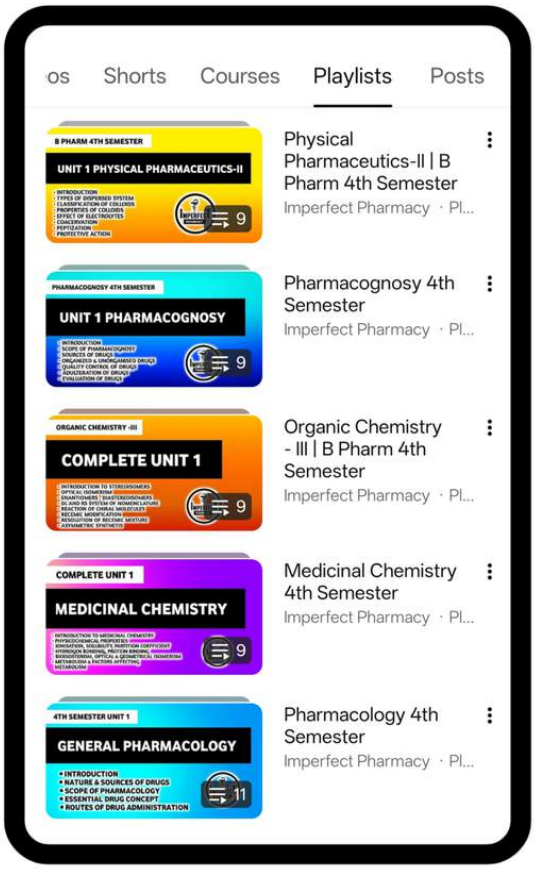
③ **Reduction**

Catalytic reduction of pyrazole yields pyrazolidine and pyrazoline.

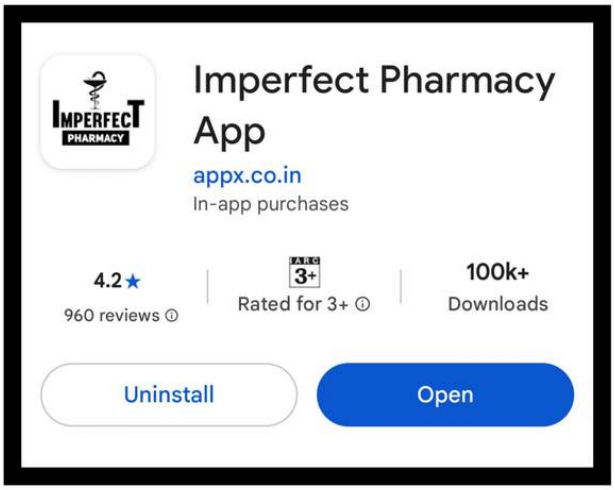


FOR LECTURE VIDEOS VISIT OUR CHANNEL





FOR MORE CONTENT : VISIT OUR APP



Medicinal Uses Of Pyrazole

① Anti-Inflammatory & Analgesic - Used in pain and arthritis (eg., phenylbutazone).

② Antipyretic - Reduces fever.

③ Antigout - Lowers uric acid (eg. Allopurinol - related).

④ Antimicrobial - Some how antibacterial and antifungal action. (Sulphaphenazole)

⑤ CNS Activity - Some derivatives act as sedatives or antidepressants.

IMIDAZOLE

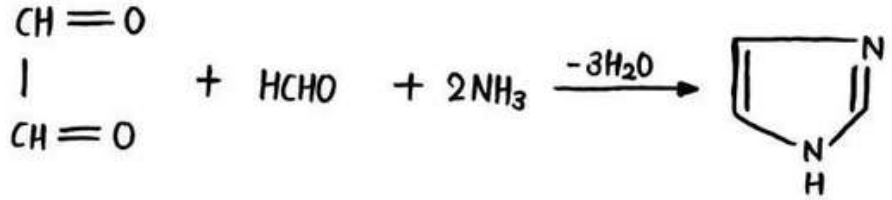
- Imidazole is five membered heterocyclic compound containing two nitrogen atoms at position 1 & 3 of the ring.
- Molecular formula $C_3H_4N_2$
- It is a colourless liquid having boiling point of 256°C.
- The name Imidazole was given by German chemist Arthur Rudolf Hantzch in 1857.

Imidazole

SYNTHESIS

① Debus method

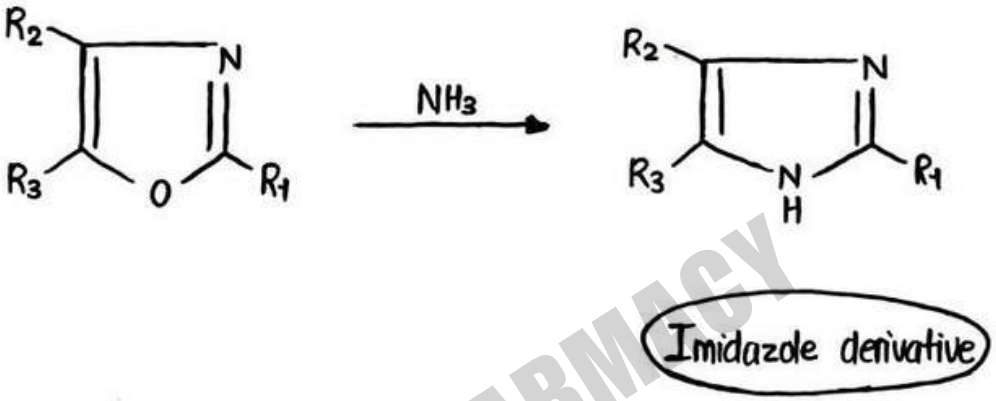
Glyoxal, formaldehyde & Ammonia condensed to form imidazole.



Glyoxal Formaldehyde Ammonia Imidazole

③ from Oxazole

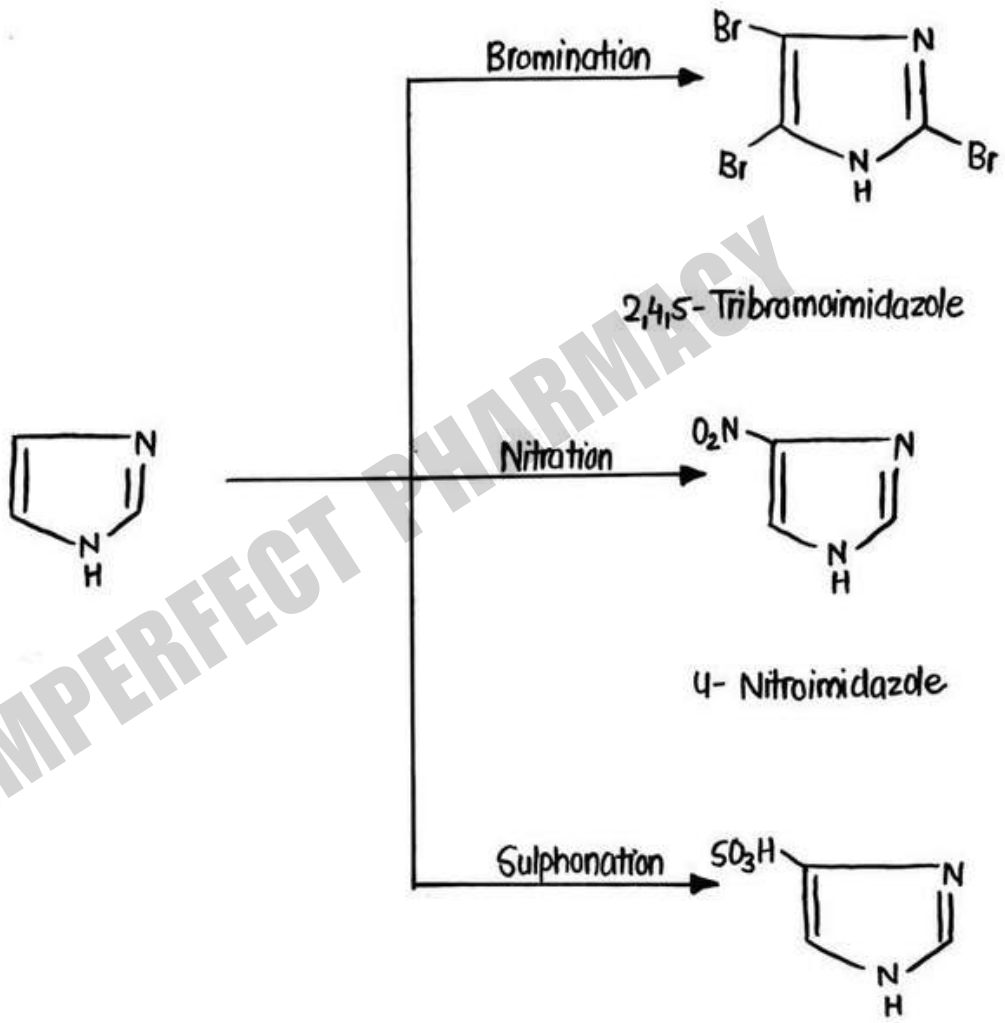
Oxazole when treated with Ammonia in the presence of acids yeilds Imidazole.



Imidazole derivative

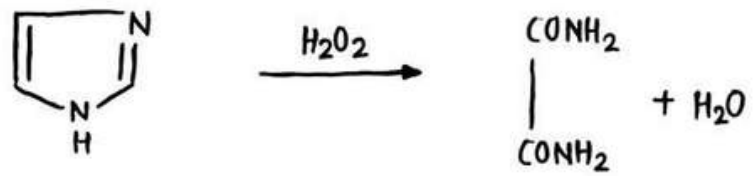
CHEMICAL REACTIONS

① Electrophillic Substitution Reactions



② **Reaction with Hydrogen Peroxide**

Imidazole reacts with Hydrogen peroxide to give Oxamide.



Imidazole — Oxamide

MEDICINAL USES OF IMIDAZOLE

① Antifungal - Used to treat fungal infections (e.g., clotrimazole, ketoconazole).

② Antiprotozoal - Effective against protozoa (e.g., Metronidazole for amoebasis, giardisis).

③ Antibacterial - Active against anaerobic bacteria (e.g., Metronidazole).

④ Antiulcer - Proton pump inhibitors like omeprazole reduce stomach acids.

⑤ Anticancer - Some imidazole derivatives used as kinase inhibitors in cancer therapy.

⑥ Enzyme inhibitors - Inhibit cytochrome P450 enzymes, useful in drug metabolism control.

⑦ CNS activity - Some derivatives acts as sedatives, anxiolytics or anticonvulsants.

OXAZOLE

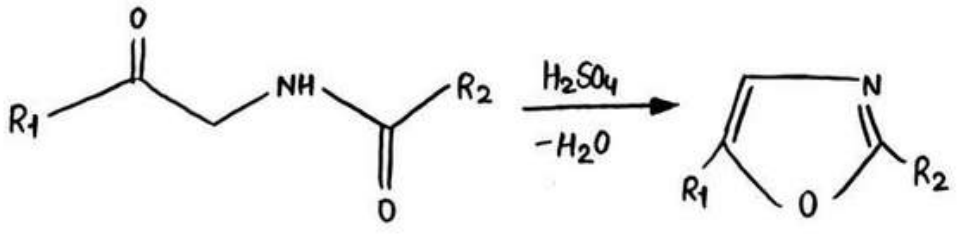
- Oxazole is five membered heterocyclic aromatic compound containing 3 carbon atoms, are nitrogen atom and one oxygen in the ring.
- It was first introduced by Hantzsch in 1857.
- It has boiling point of 69°C.
- It is weakly basic in nature.

Oxazole

SYNTHESIS

① Rabinson - Gabriel Synthesis

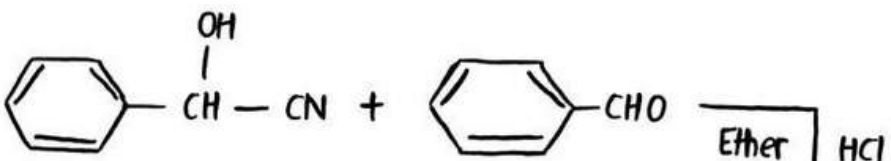
Dehydration of 2- acylamino - ketones yeilds Oxazoles.



Pyrazole derivative

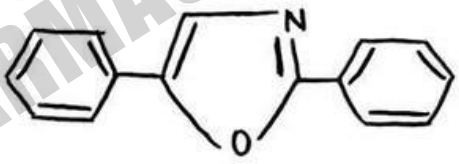
② Fischer Synthesis

- This synthesis was given by Emil fisher in 1896.
- A Cyanohydrin (Mandelic acid nitrile) reacts with an aldehyde in presence of anhydrous HCl to give substituted oxazole.



Mandellic Acid Nitrile

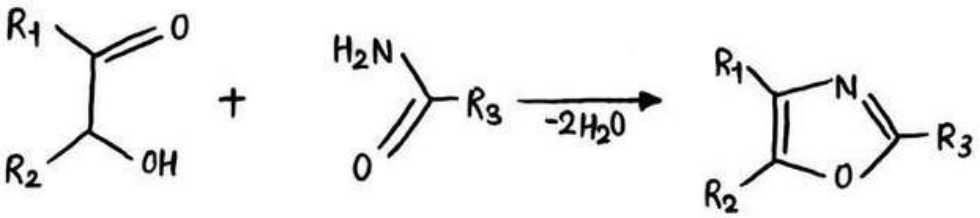
Benzaldehyde



2,5 - Diphenyl Oxazole

③ From α - Hydroxy - Carbonyl Component

α- Hydroxy - ketones when reacts with amide yields substituted oxazole.



α- hydroxy ketones

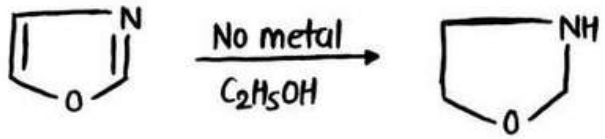
amide

Substituted oxazole

CHEMICAL REACTIONS

① Reduction

Oxazole reduced to give oxazolidine.



Oxazole — Oxazolidine

② Nucleophillic Substitution Reaction

Oxazole when reacts with a Nucleophillic (such as methylamine) under Nucleophillic substitution.

4-chloro-oxazole + Methylamine → 4-(methylamine) Oxazole

Medicinal Uses Of Oxazole

① Antibacterial - Active against Gram - positive bacteria. (e.g., Linezolid).

② Antifungal - Some oxazole derivatives show antifungal activity. (e.g., Oxiconazole).

③ Anti - inflammatory - Oxazole derivatives show anti - inflammatory properties. (e.g. Meloxicam).

④ CNS Activity - Some oxazoles act as anticonvulsants or anxiolytics. (e.g. Zonisamide).

THIAZOLE

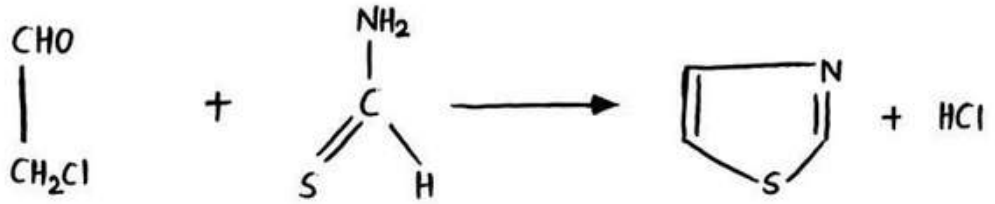
- Thiazole is a heterocyclic compound that contains both sulfur and nitrogen atoms in a 5-membered aromatic ring.
- Chemical formula C_3H_5NS
- It is a pale yellow liquid having a boiling point of 116°-118°C.
- It was first described by Hantzsh & Weber in 1887.

Thiazole

SYNTHESIS

① From chloroacetaldehyde

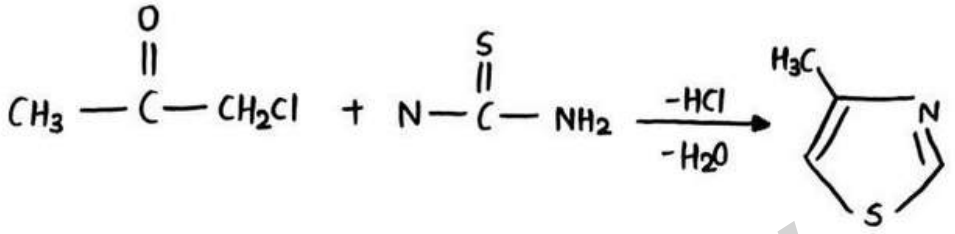
Reaction of chloroacetaldehyde with thioformamide yields Thiazole.



Chloroacetaldehyde Thioformamide Thiazole

② Hantzsch Synthesis

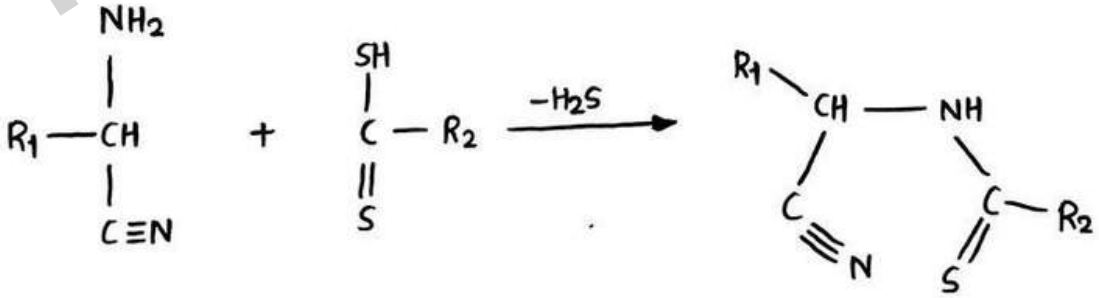
α- chloro acetone when treated with Thioamide gives Thiazole derivative.



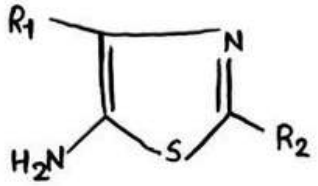
α- chloro acetone Thioamide 4- methyl Thiazole

③ Cook - Heilborn Synthesis

Reaction of α- amino nitrile with Dithio acid under mild conditions yeilds 5 - aminothiazoles.



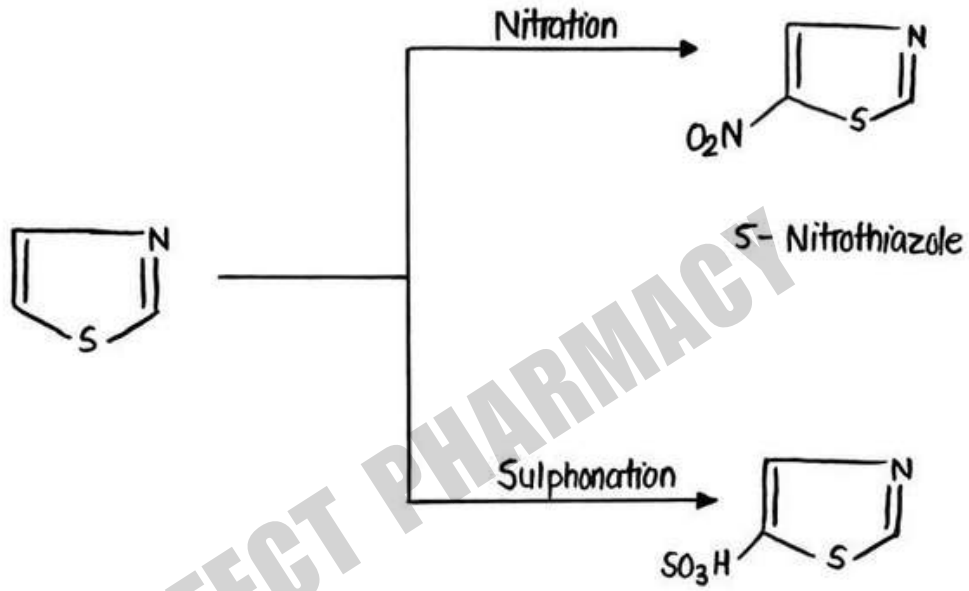
α- amino nitrile Dithio Acid



5- Aminothiazoles

CHEMICAL REACTIONS

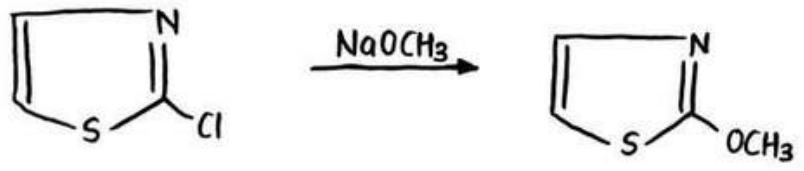
① Electrophillic Substitution Reaction



Thiazole - 5- Sulphonic Acid

② Nucleophillic Substitution Reaction

Thiazole undergoes nucleophillic substitution reaction at position 2.

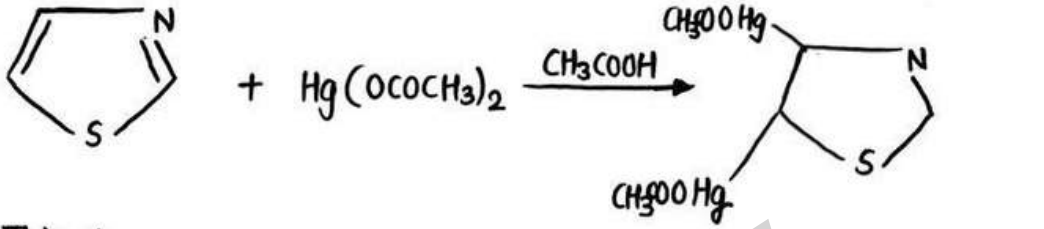


2- Chlorothiazole

2- methoxythiazole

③ **Mercuration**

On treatment with mercury acetate, thiazole is mercurated at preference order of $C_5 > C_4 > C_2$



Thiazole — Mercury acetate — 4-5-Bis(acetoximercuri) thiazole

MEDICINAL USES OF THIAZOLE

① Antibacterial - Present in Sulfonamide antibiotics like sulfathiazole.

② Antifungal - Thiazole rings are part of some azole antifungals.

③ Antiviral - Some thiazole derivatives show activity against HIV and hepatitis viruses.

④ Anti-inflammatory - Thiazole compounds act as COX inhibitors.

⑤ Anti-cancer - Used in designing tyrosine kinase inhibitors and other cancer drugs.

⑥ Anticonvulsant - Thiazole derivatives helps in epilepsy treatment.

PYRIDINE

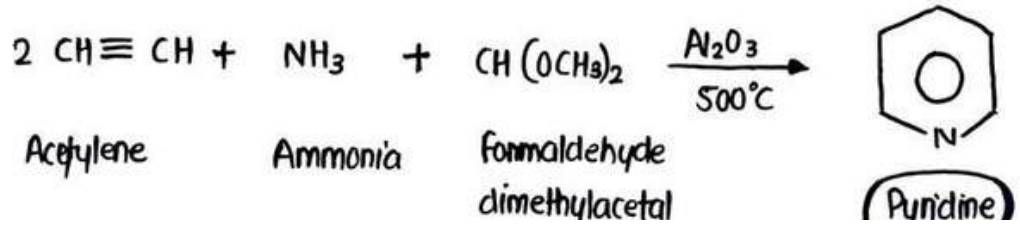
- Pyridine is a basic heterocyclic aromatic compound with molecular Formula C_5H_5N.
- It consist of a six-membered ring with 5 carbon atoms & one nitrogen atom, resembling the structure of benzene where one CH group is replaced by a nitrogen atom.
- It is a colourless liquid with a boiling point of 115°C.

Pyridine

SYNTHESIS

① Industrial Method

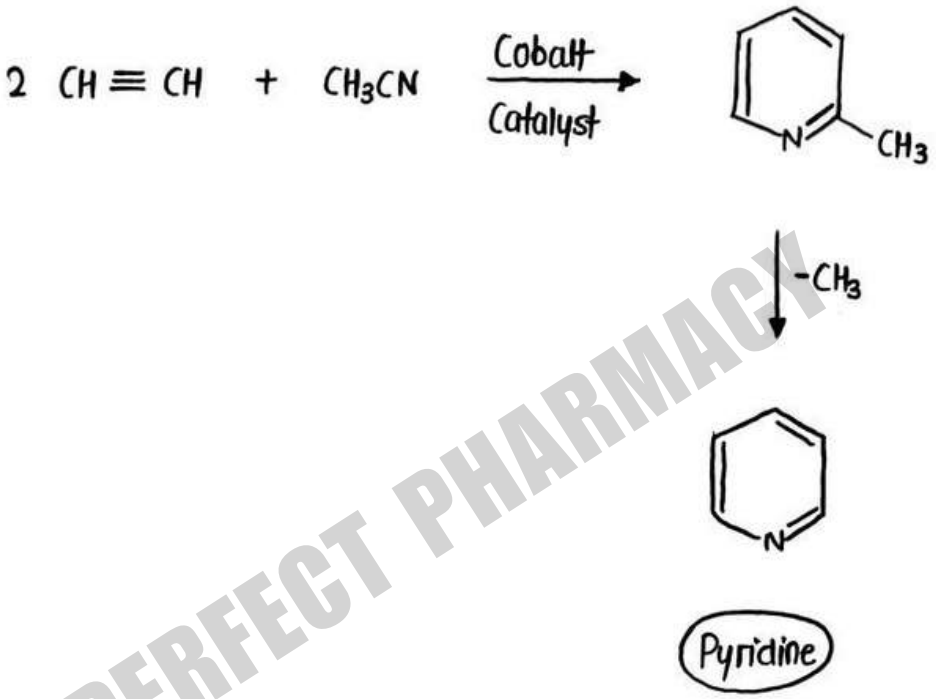
On Industrial scale, pyridine can be synthesized by heating a mixture of acetylene, amonia & formaldehyde at 500°C in presence of alumina.



Acetylene — Ammonia — Formaldehyde dimethylacetal — Puridine

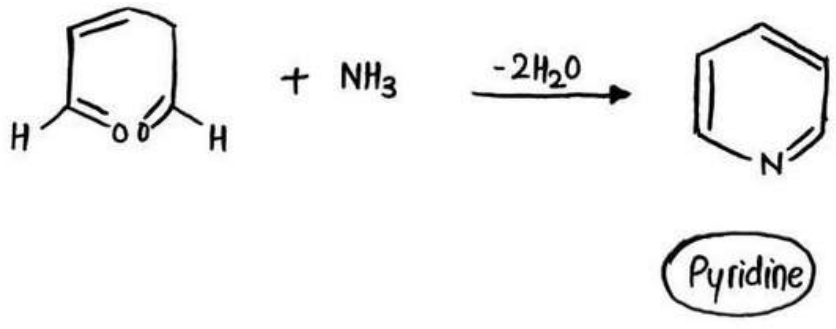
② **Bonnemann Cyclization**

It involves trimerization of one part of a nitrile molecule & two parts of acetylene either by heat or light.



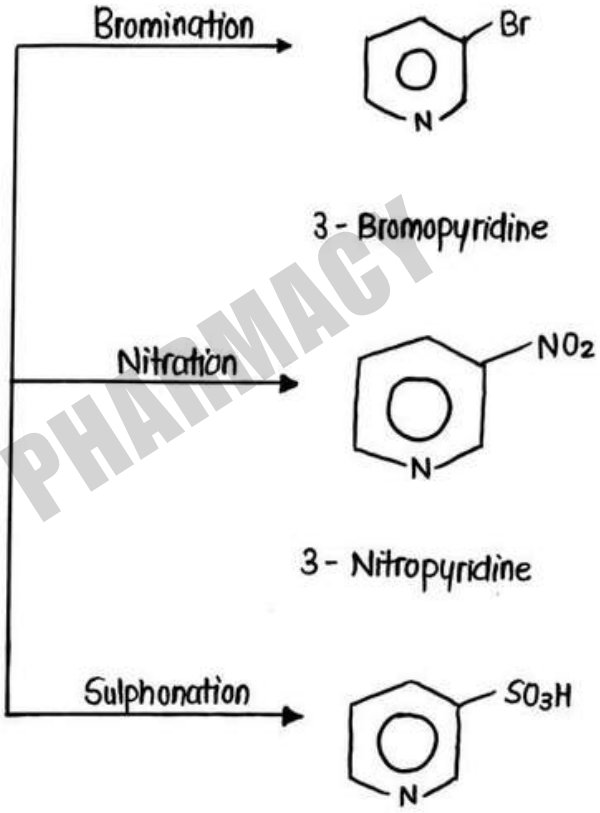
③ **From 1,5 Dicarbonyl Compound**

Reaction of 1,5 dicarbonyl compound with Ammonia yeilds Pyridine.



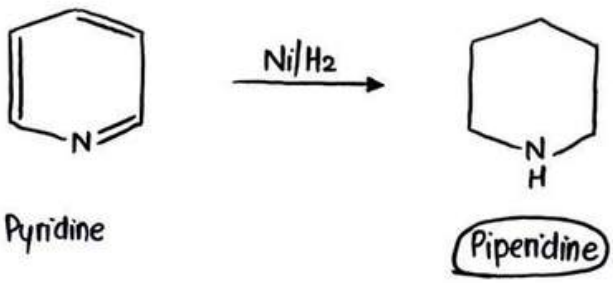
Chemical Reactions

① Electrophillic Substitution Reaction



② Reduction

Pyridine undergoes reduction in the presence of a catalyst (Ni/H_2) to yield piperidine.



Medicinal Uses Of Pyridine

1. Antitubercular - Found in Isoniazid and pyrazinamide for treating tuberculosis.

2. Antihypertensive - Used in drugs like Nifedipine (a calcium channel blocker).

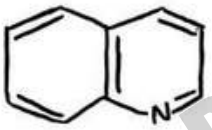
3. Anti-Inflammatory - Present in certain NSAIDs like Phenylbutazone.

4. Anticancer - Pyridine rings are part of kinase inhibitors used in cancer therapy.

5. CNS Agents - Included in antidepressants and antipsychotic drugs.

QUINOLINE

- Quinolines are heterocyclic compound consisting of a benzene ring fused to a pyridine ring.
- Chemical formula : C_9H_7N
- It was first isolated form coal tar by Friedlieb Ferdin & Runge.
- It is weakly basic in nature.

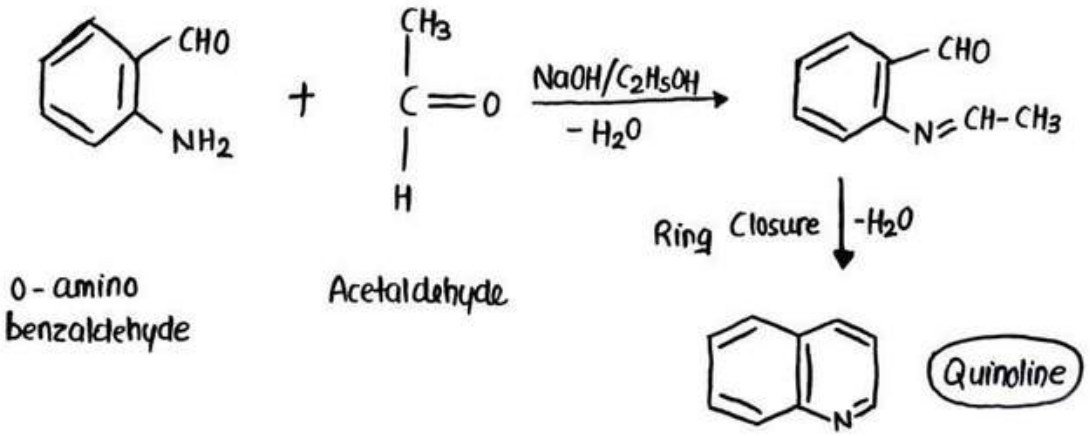


Quinoline

SYNTHESIS

① Friedlander Synthesis

When o-aminobenzaldehyde condensed with an aldehyde or ketone group in alcoholic sodium hydroxide solution, it yeilds quinoline.

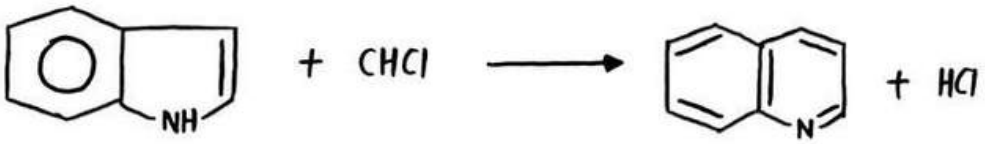


o-amino benzaldehyde

Acetaldehyde

② From Indole & Chloromethylene

Indole when treated with Chloromethylene yeilds quinoline.

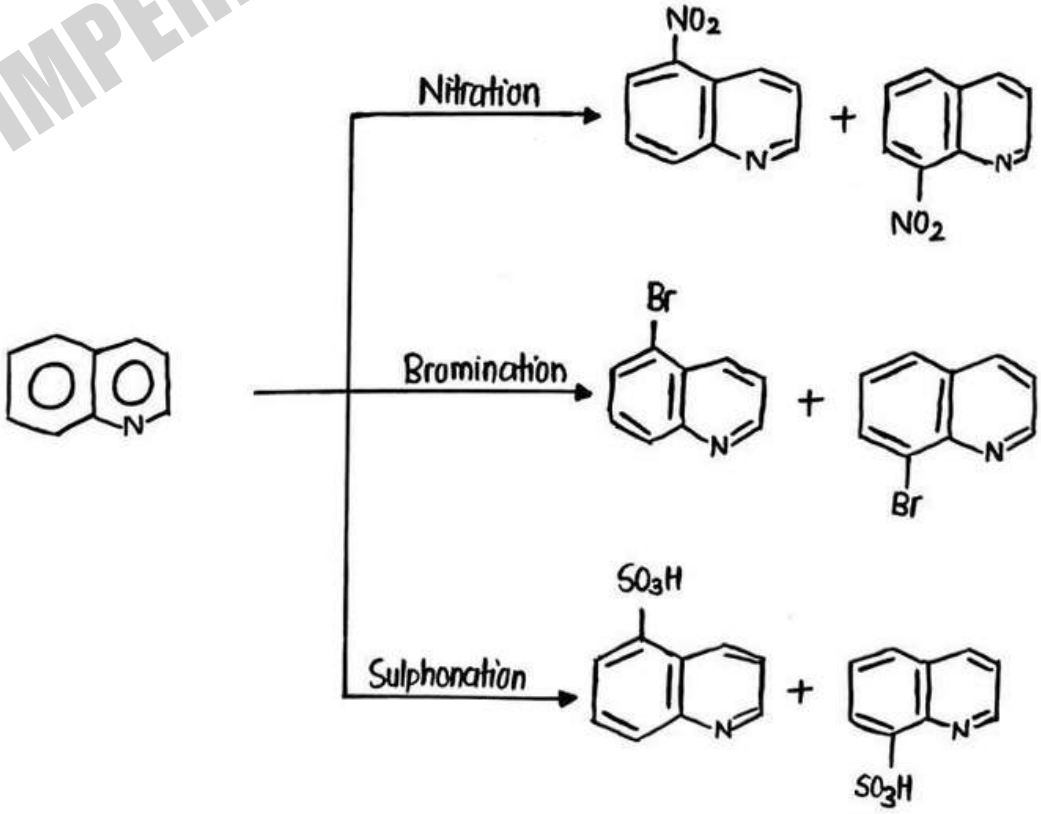


Indole Chloromethylene Quinoline

CHEMICAL REACTIONS

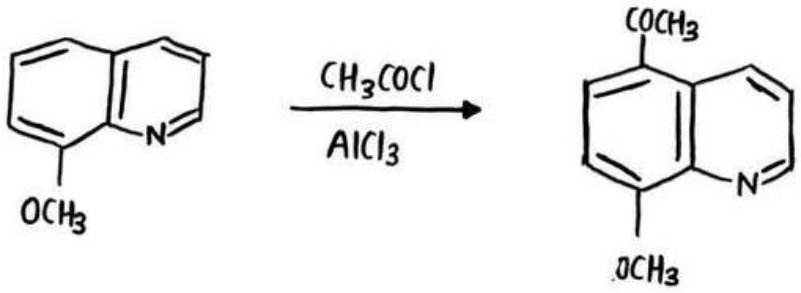
① Electrophillic Substitution Reaction

Quinoline gives Electrophillic Substitution Reactions at 5 & 8 positions.



② Acylation & Alkylation

Quinoline undergoes acylation / alkylation in the presence $AlCl_3$.

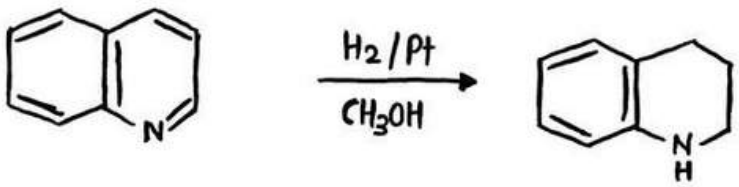


8-methoxyquinoline

5-Acetoxy-8-methoxy quinoline

③ Reduction

Using catalytic hydrogenation in methanol, quinoline is converted to 1,2,3 & 4-tetrahydroquinoline.



Quinoline

1,2,3,4-tetrahydroquinoline

Medicinal Uses Of Quinolines

① Antimalarial - • Most important use (e.g. Chloroquine)
• Effective against Plasmodium species.

② Antibacterial - Some derivatives (e.g. ciprofloxacin - a fluoroquinoline) are potent against Gram-positive and Gram-negative bacteria.

③ Antitubercular - Quinolines like Clofazimine show activity against Mycobacterium Tuberculosis.

④ Anti-inflammatory - Used in diseases like rheumatoid arthritis (e.g. Hydroxychloroquine).

ISOQUINOLINE

- Isoquinoline is a heterocyclic aromatic compound made up of a benzene ring fused to a pyridine ring, but unlike quinoline the nitrogen atom is at position 2.
- Molecular formula : C_9H_7N
- Like quinoline it is also a weak base.
- It is a colourless hygroscopic liquid having an unpleasant odour.

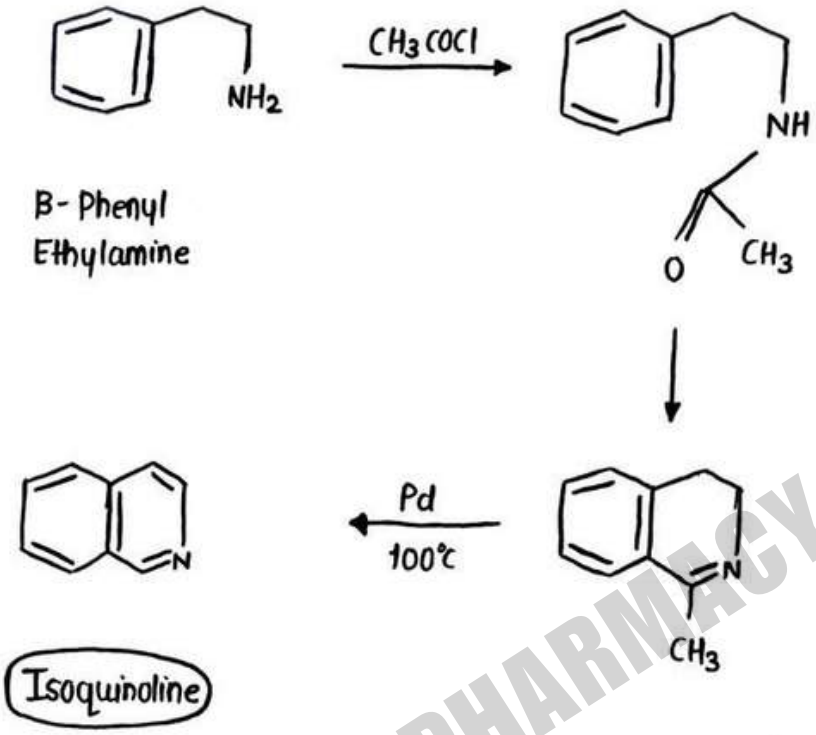
Isoquinoline

SYNTHESIS

① Bischler - Napieralski Synthesis

It involves following steps :

- First a β-phenyl ethylamine is acylated using acetyl chloride to form an amide.
- This amide can be cyclised with a loss of water using a lewis acid to give 1-substituted-3,4 dihydro isoquinoline.
- Now this intermediate readily dehydrogenated to isoquinoline using palladium as catalyst.

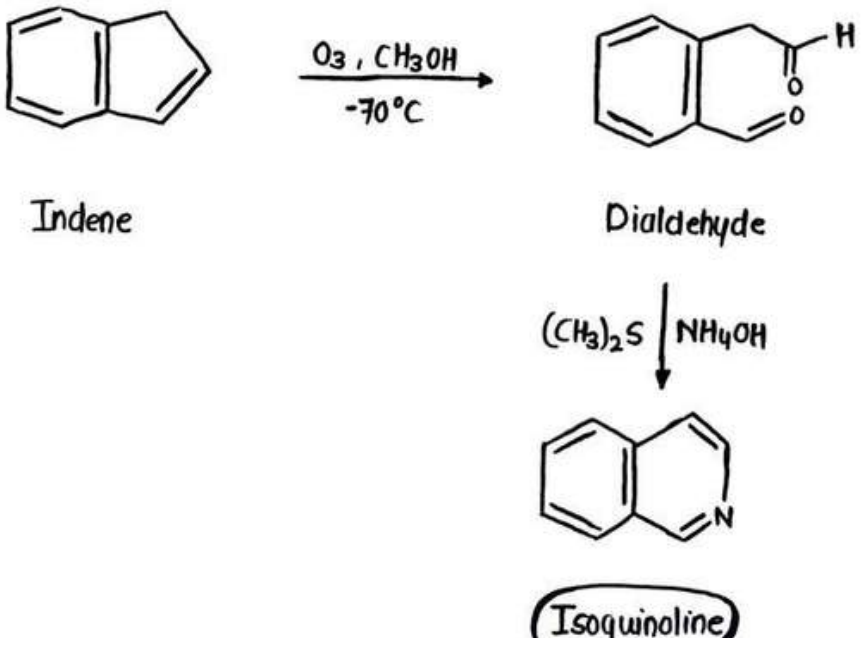


B- Phenyl Ethylamine

Isoquinoline

② Ozonolysis of Indene

Indene when treated with ozone at -70°C, give dialdehyde which or reduction followed by cyclization with dimethyl sulfide in the presence of NH_4OH yields isoquinoline.



Indene

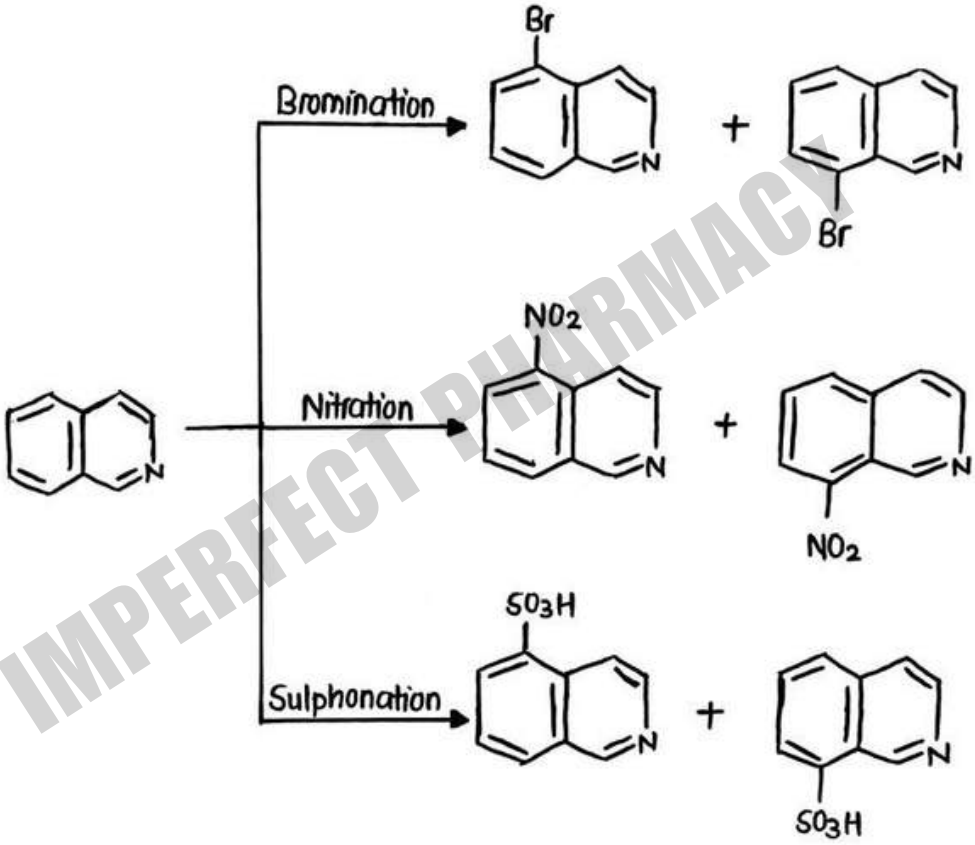
Dialdehyde

Isoquinoline

Chemical Reactions

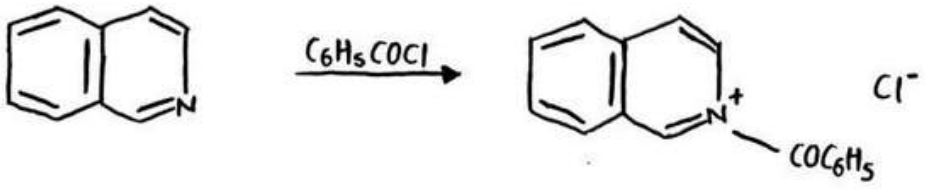
① Electrophillic Substitution Reactions

Like Quinoline, Isoquinoline also gives Electrophillic Substitution Reaction at position 5 & 8.



② Reaction with Benzoyl Chloride

Isoquinoline reacts with benzoyl chloride & gives quaternery salts.



Isoquinoline

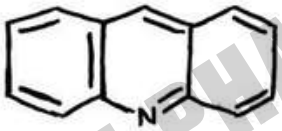
2- Benzoyl Isoquinolinium Chloride

Medicinal Uses Of Isoquinoline

- Antispasmodic - e.g, papaverine.
- Antihypertensive - e.g. Drotavenine
- Antimalarial - e.g., Berberine
- Antimicrobial - antibacterial & antifungal activity.
- Anti-inflammatory - Reduce inflammation.

ACRIDINE

- Acridine is a tricyclic aromatic compound consisting of two benzene ring fused on either side of a central pyridine ring.
- Chemical formula : $C_{13}H_9N$
- It resembles Anthrancene , but with a nitrogen atom replacing one of the central carbon atoms.

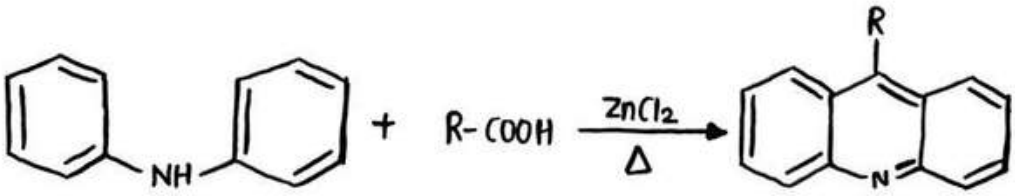


Acridine

SYNTHESIS

① Bernthsen Acridine Synthesis

When diphenyl amine is condensed with carboxylic acids in presence of zinc chloride, it provides acridines.

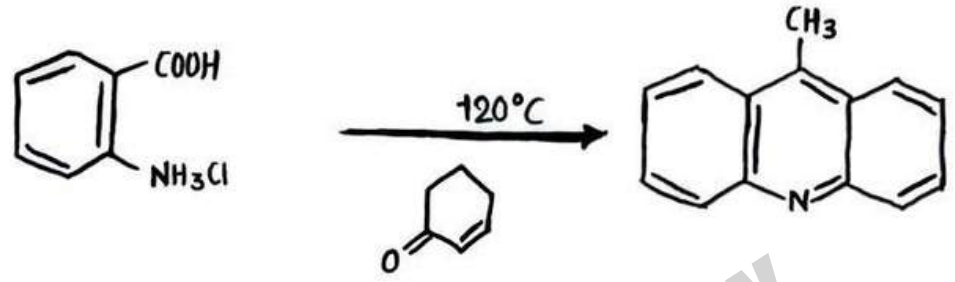


Diphenylamine

9- Substituted acridines

② Friedlander Synthesis

The salf of an anthranilic acid is treated with cylonex - 2 - enone at 120°C to give 9- methyl acridine.



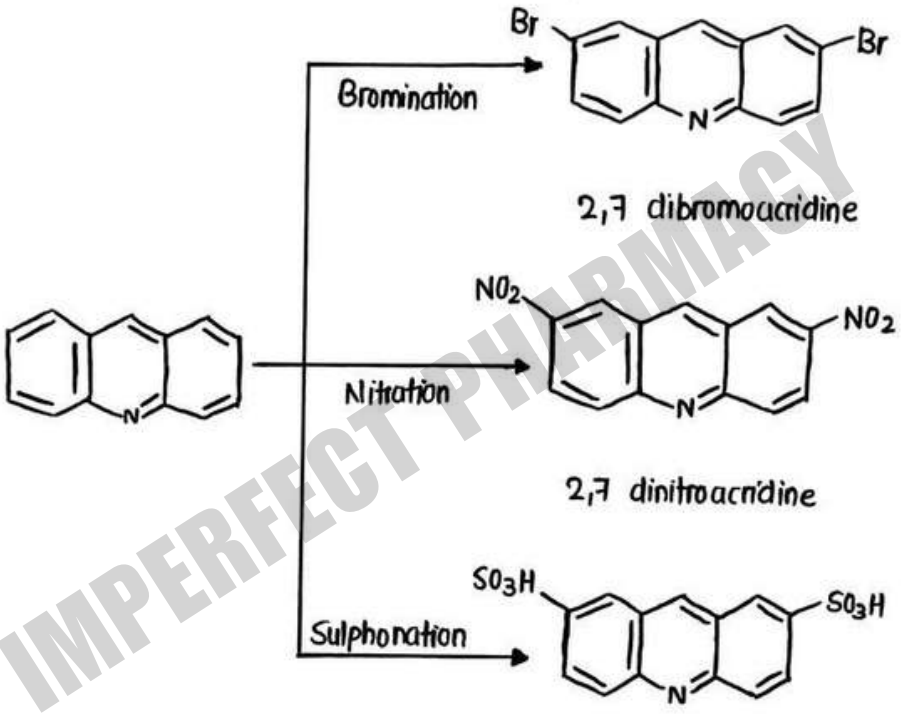
Anthranilic acid salt

9- Methyl Acridine

CHEMICAL REACTIONS

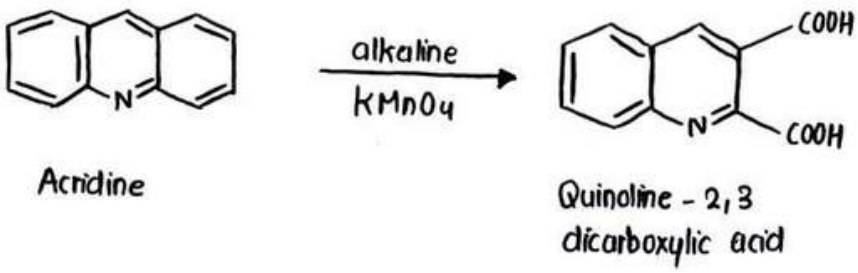
① Electrophillic Substitution Reactions

Acridine gives electrophillic substitution preferably at 2 & 7 positions resulting in di - substitution.



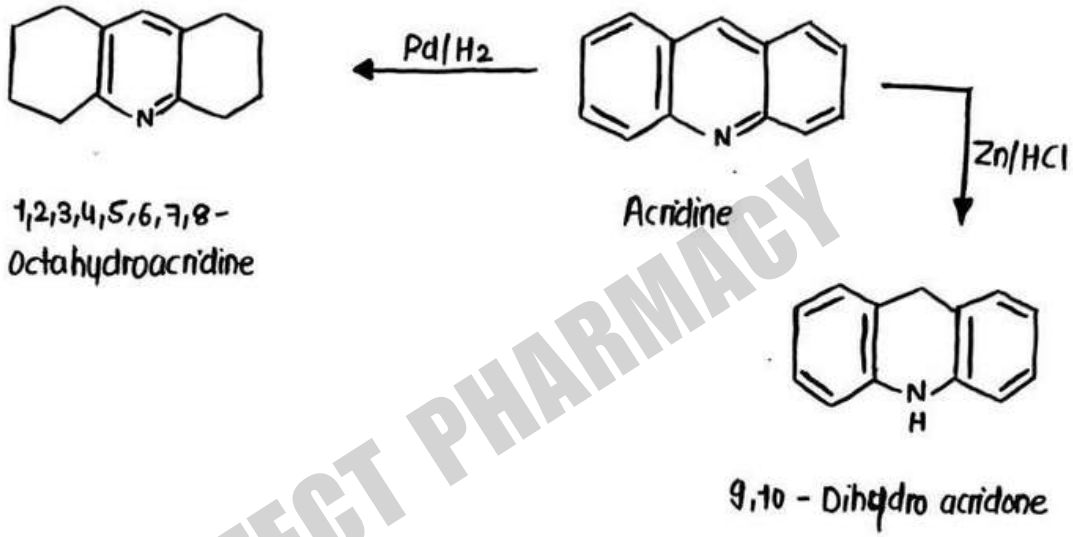
② Oxidation

Acridine in the presence of alkaline $KMnO_4$ reduced into Quinoline-2,3 - dicarboxylic acid.



③ **Reduction**

The benzene ring of acridine can be selectively reduced by catalytic hydrogenation while pyridine ring can be selectively reduced by Zn/HCl to give 9, 10 - dihydroacridine.



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

Acridine

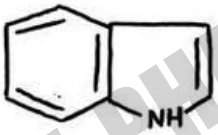
9,10 - Dihydro acridone

MEDICINAL USES OF ACRIDINE

- Antibacterial - Acriflavine
- Antiprotozoal - Quinacrine (for malaria, giardiasis)
- Antiseptic - Proflavine (Wound dressing)
- Anticancer - Amsacrine (Leukemia treatment)

INDOLE

- Indole is an aromatic heterocyclic compound consisting of a benzene ring fused to a five - membered nitrogen containing pyrrole ring.
- Molecular formula : C_8H_7N
- It is a white solid having melting point 52°– 54°C.

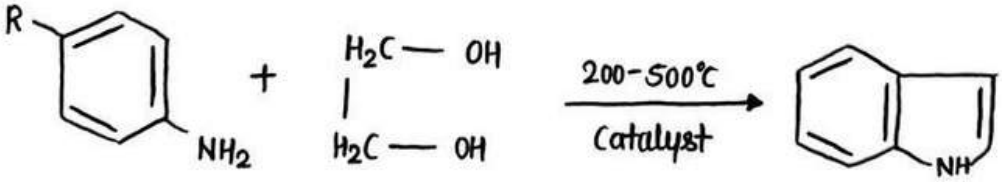


Indole

SYNTHESIS

① From Aniline

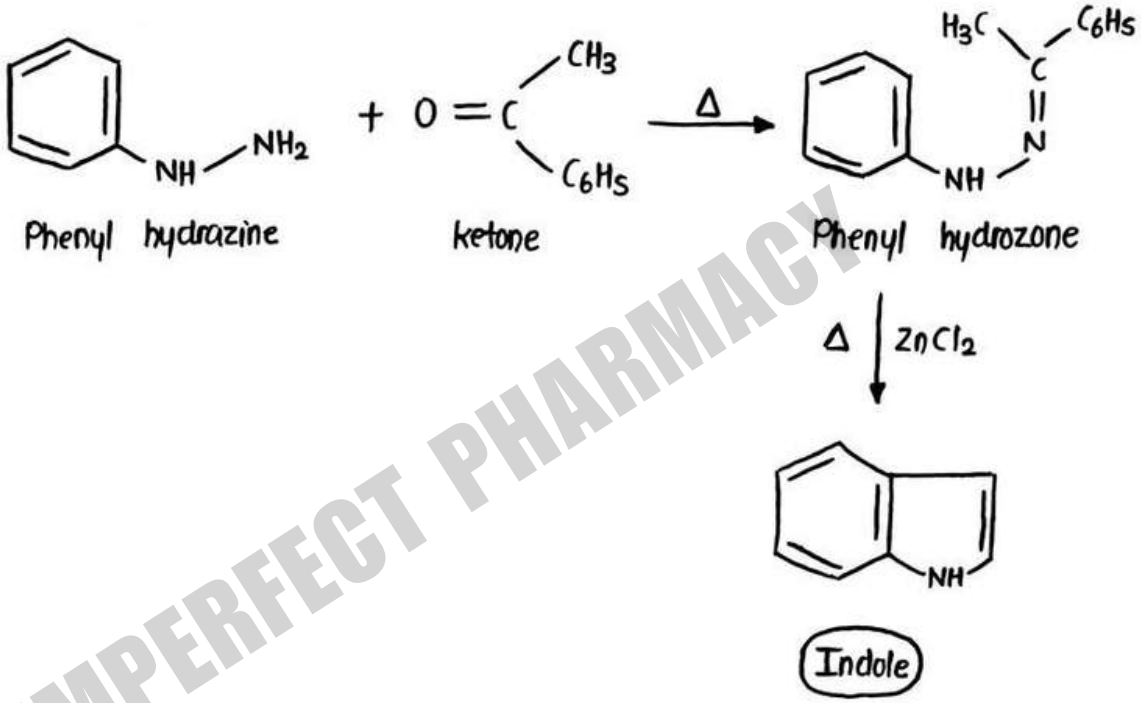
Aniline when treated with Ethylene Glycol in the presence of catalyst gives Indoles.



Aniline Ethylene Glycol Indole

② Fischer - Indole Synthesis

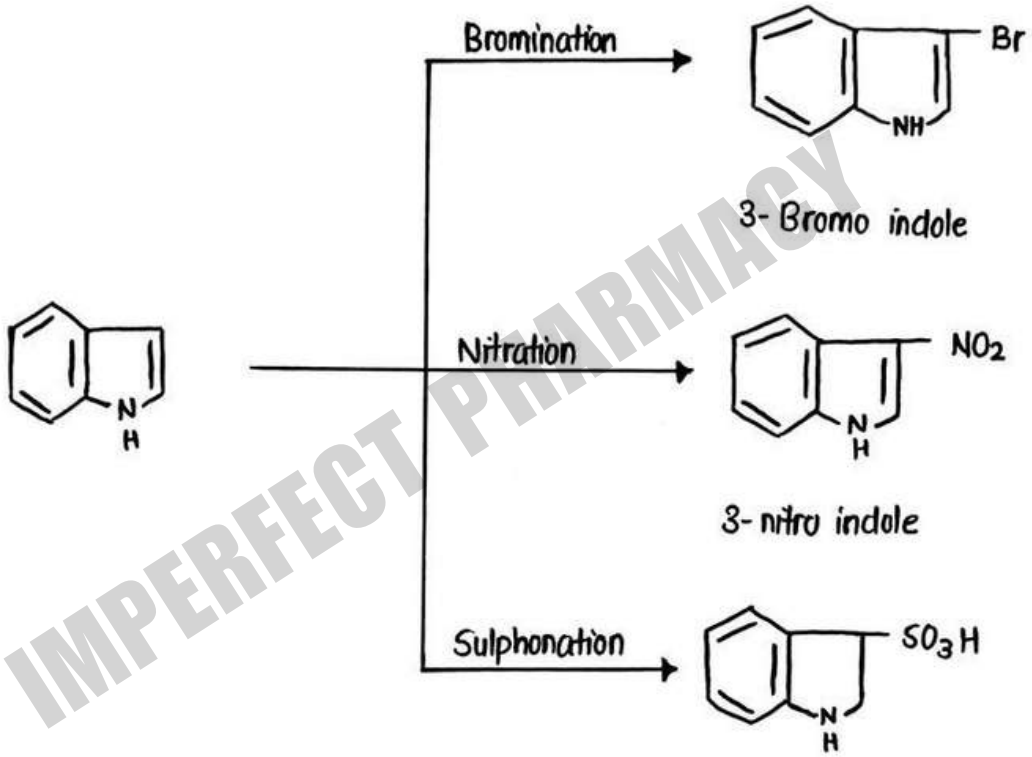
It involves heating an arylhydrazine with an aldehyde or ketone, followed by acid catalyzed rearrangement of resulting arylhydrazone with a loss of ammonia gives an indole.



Chemical Reactions

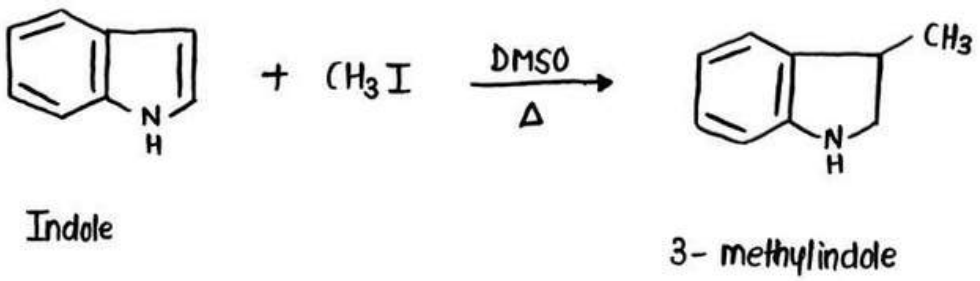
① Electrophillic Substitution Reactions

Indole gives electrophillic substitution at 3rd position.



② Alkylation

Indole undergoes alkylation reaction in the presence of dimethyl sulphoxide (DMSO) with methyl iodide at 80°C to produce 3 methyl indole.

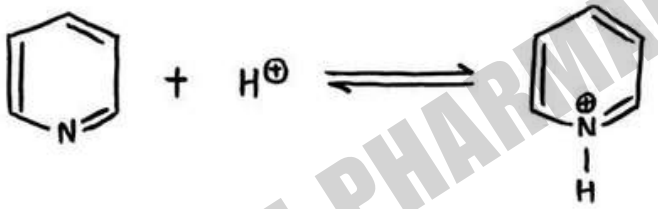


Medicinal Uses Of Indole

- Antidepressant - Serotonin
- Antimigraine - Sumatriptan
- Anticancer - Vincristine, Vinblastine
- Antihypertensive - Reserpine
- Anti-inflammatory - Indomethacin

Basicity Of Pyridine

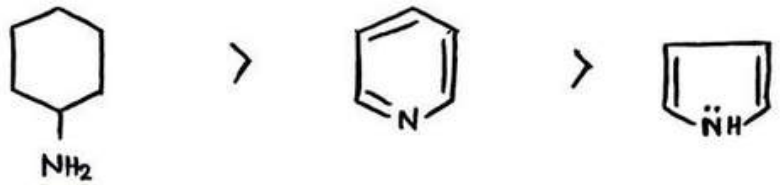
- Pyridine is a weak base due to presence of a lone pair of electrons on the nitrogen atom, which is available for protonation.
- Basicity of pyridine refers to it ability to accept a proton (H^+) at the nitrogen atom.



Pyridine Pyridinium salt

Comparison Of Basicity

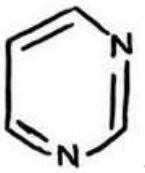
- Pyridine is less basic than aliphatic amines because nitrogen atom of pyridine is Sp^2 hybridized & sp^2 orbitals hold electrons more tightly compare to sp^2 hybridized nitrogen of aliphatic amines.
- However pyridine is more basic than pyrrole, where the nitrogen lone pair is delocalized in the aromatic ring & available for protonation.



Aliphatic amine Pyridine Pyrrole

PYRIMIDINE

- Pyrimide is a six - membred aromatic heterocyclic compound containing two nitrogen atoms at position 1 & 3 in the ring.
- Molecular foomula : $C_4H_4N_2$
- It is basic in nature due to nitrogen lone pairs.

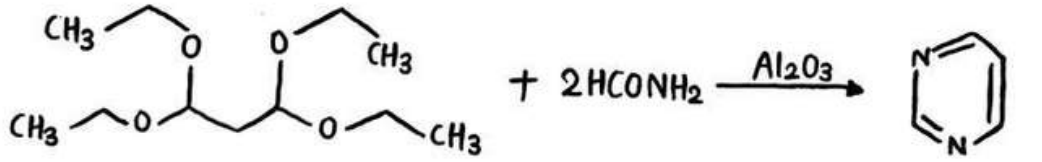


Pyrimidine

SYNTHESIS

① From Formamide

Formamides on reacting with 1,1,3,3 - tetraethydroxypropane yeilds pyrimidine.

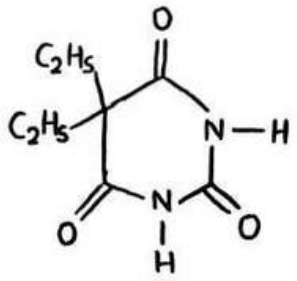


1,1,3,3- Tetraethydroxypropane

Pyrimidine

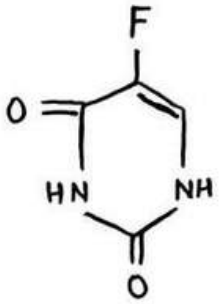
Medicinal Uses Of Pyrimidine

① Phenobarbitone It is used as sedative and hypnotic.

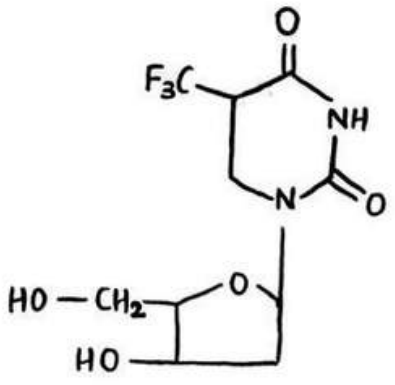


② Barbital It is used as sedative and hypnotic.

③ 5-Flurouracil It is used as an anti-cancer agent.

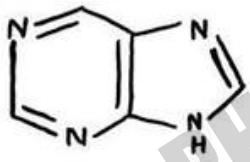


④ Trifluridine It is used as an anti-viral agent.



PURINE

- Purine is a heterocyclic aromatic compound made up of a fused ring system consisting of:
  - A six membered pyrimidine ring
  - A five membered imidazole ring
- Molecular formula: $C_5H_4N_4$

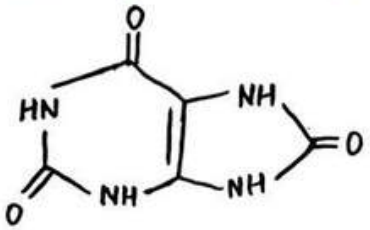


Purine

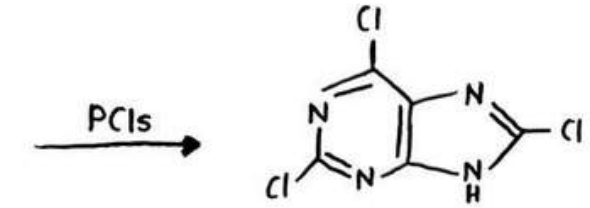
SYNTHESIS

① From Uric Acid

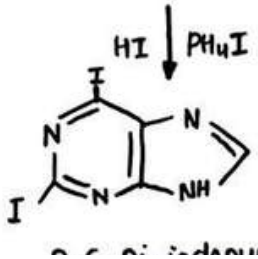
Purine can be synthesized by reduction of uric acid through a multi step chemical process.

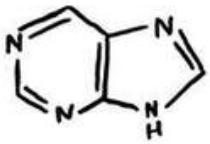


Uric Acid



2,6,8 – Trichloropurine

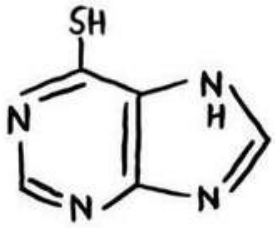




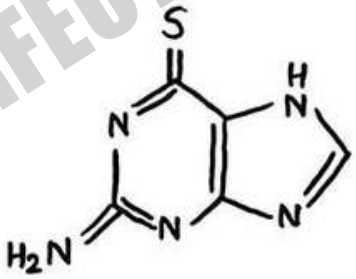
Purine

Medicinal Uses Of Purine

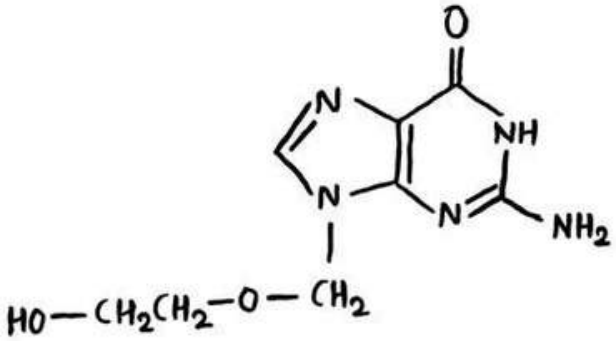
① 6- Mercaptopurine — It is used an anti-cancer treatment.



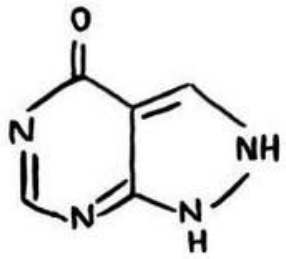
② 6- Thioguanine — It is used as an anti-cancer agent.



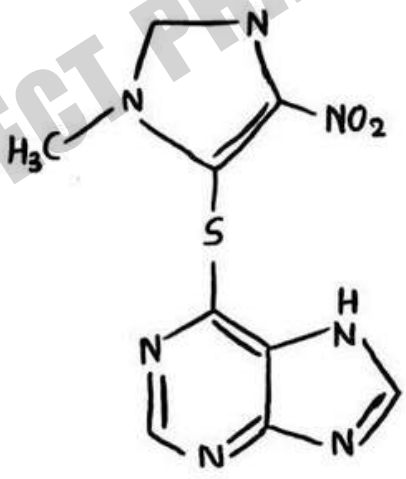
③ Acyclovir — It is used as an anti-viral agent.



④ Allopurinol It is used as NSAIDs.

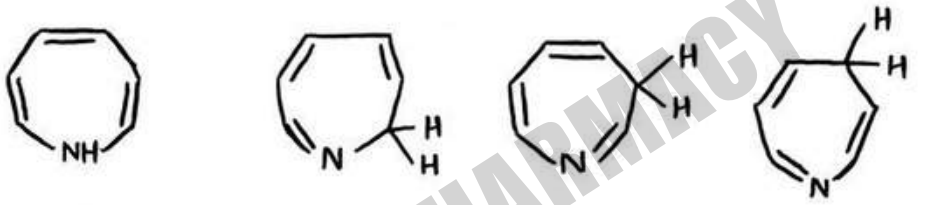


⑤ Azathiopurine It is used as sedative and hypnotic.



AZEPINES

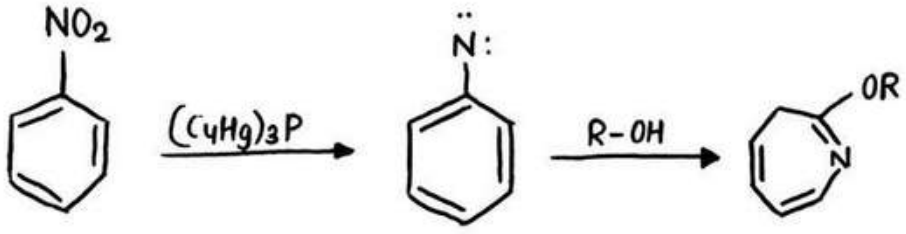
- Azepines are seven- membered heterocyclic compounds that contain one nitrogen atom in the ring structure.
- General formula : C_6H_7N
- They are non - aromatic heterocyclic compounds.



1H - Azepine 2H - Azepine 3H - Azepine 4H - Azepine

SYNTHESIS

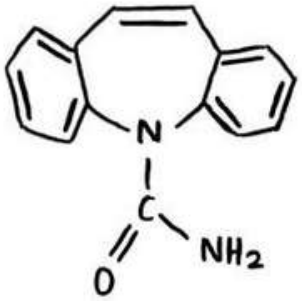
- The nitrobenzene is deoxygenated using Tributylphosphine.
- The resulting arylnitrene undergoes ring expansion through intramolecule rearrangement in the presence of primary / secondary alcohol to give 2- alkoxy -3H- azepines.



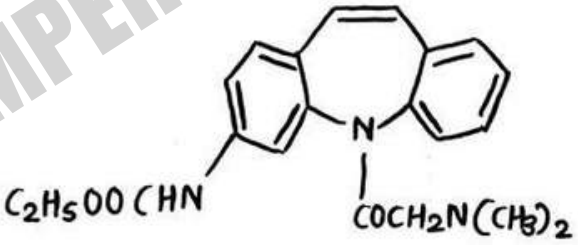
Nitrobenzene Arylnitrene 2- Alkoxy - 3H Azepine

MEDICINAL USES

① Carbamazepine It is used as an anticonvulsant.



② Tiracizine It is used as an anti-arrythmic agents.



THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

IMPERFECT PHARMACY

JOIN US ON :


IMPERFECT PHARMACY


IMPERFECT PHARMACY


@IMPERFECTPHARMA


IMPERFECT PHARMACY


@IMPERFECTPHARMACY


IMPERFECT PHARMACY


IMPERFECTPHARMACY@GMAIL.COM