

MEDICINAL CHEMISTRY-I

UNIT 3 NOTES

DRUGS ACTING ON ANS

- CHOLINERGIC NEUROTRANSMITTERS
- PARASYMPATHOLYTIC AGENTS
- CHOLINERGIC BLOCKING AGENTS



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HETEROCYCLIC COMPOUNDS

- Heterocyclic compounds are organic compounds that contain a ring structure composed of at least one atom other than carbon within the ring.
- These non-carbon atoms are called Heteroatoms and commonly include Nitrogen, Oxygen or Sulfur.



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CLASSIFICATION OF HETEROCYCLIC COMPOUNDS

They can be classified on various basis as follows :

- ① Based on Ring size
- ② Based on Aromaticity
- ③ Based on Number of rings
- ④ Based on type of Heteroatom

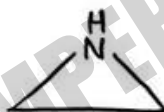
① BASED ON RING SIZE

- Three membered Heterocyclic Compounds
- Four membered Heterocyclic Compounds
- Five membered Heterocyclic Compounds
- Six membered Heterocyclic Compounds
- Seven membered Heterocyclic Compounds

(a) THREE MEMBERED HETEROCYCLIC COMPOUNDS

These are three membered ring compounds with one or two hetero atoms.

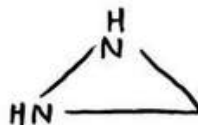
- 1) With 1 Heteroatoms : Aziridine, Oxirane, Azirine
- 2) With 2 Heteroatoms : Diaziridine, Diaxirane



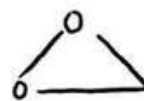
Aziridine



Oxirane



Diaziridine



Diaxirane

(b) FOUR MEMBERED HETEROCYCLIC COMPOUNDS

These are four membered ring compounds with 1 or more hetero atoms.

- 1) With 1 Heteroatoms : Azetidine, Oxetane
- 2) With more than 1 Heteroatoms : Diazetidine, Oxazetidine



Azetidine



Oxetane



Diazetidine

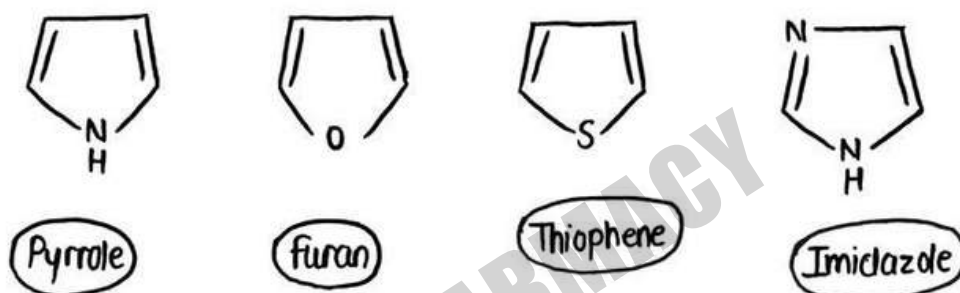


Oxazetidine

c) 5 MEMBERED HETEROCYCLIC COMPOUNDS

These are 5 membered rings with 1 or more than 1 heteroatoms.

- With 1 Heteroatoms : Furan, Pyrrole, Thiophene
- With more than 1 Heteroatoms : Imidazole, Oxazole, Thiazole



d) 6 MEMBERED HETEROCYCLIC COMPOUNDS

These are 6 membered rings with 1 or more than 1 heteroatoms.

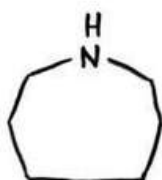
- With 1 Heteroatoms : Pyridine, Puran, thiopyran
- With more than 1 Heteroatoms : Pyridazine, Pyrimidine



② 7 MEMBERED HETEROCYCLIC COMPOUNDS

These are 7 membered rings with 1 or more than 1 heteroatoms.

- With 1 Heteroatoms : Azepane , Oxepane, Thiapene
- With more than 1 heteroatoms : Diazepene, Thiazepene



Azepane



Thiazepene

② BASED ON AROMATICITY

- Aromatic Heterocyclic Compounds
- Non - Aromatic Heterocyclic Compounds

④ AROMATIC HETEROCYCLIC COMPOUNDS

- Follow Huckel's Rule
- Example: Pyridine, Pyrrole, furan, Thiophene



Furan



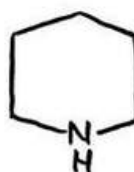
Thiophene

⑥ NON - AROMATIC HETEROCYCLIC COMPOUNDS

- Do not Follow Huckel's rule
- Example: Tetrahydrofuran, Piperidine etc.



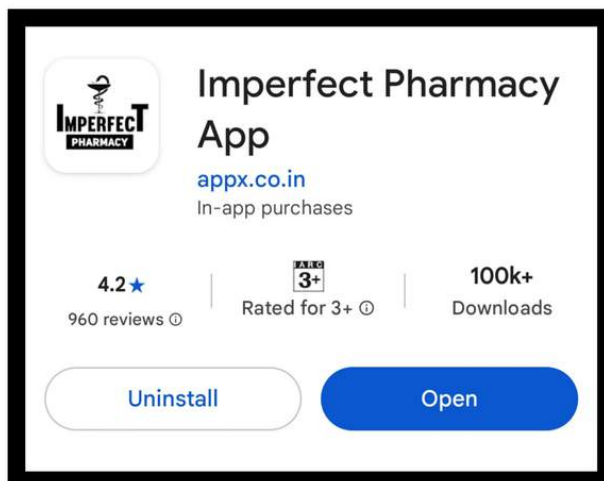
Tetrahydrofuran



Piperidine



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③ BASED ON NUMBER OF RINGS

- Monocyclic
- Bicyclic or Polycyclic

④ MONOCYCLIC

- One or more heteroatoms in a single ring.
- Example: Pyridine, Furan



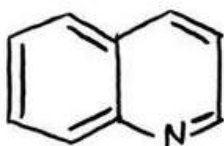
Furan



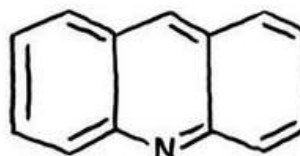
Pyridine

⑤ BICYCLIC OR POLYCYCLIC

- Two or more fused rings
- Example: Quinoline, Acridine



Quinoline



Acridine

④ BASED ON TYPE OF HETEROATOM

- OXYGEN CONTAINING : Furan , Oxazole etc
- NITROGEN CONTAINING : Pyridine , Imidazole etc
- SULFUR CONTAINING : Thiophene , Thiazole etc
- MIXED HETEROATOMS : Oxazole , Thiazole etc.



Furan



Pyridine



Thiophene



Oxazole

NOMENCLATURE OF HETEROCYCLIC COMPOUNDS

There are various methods for nomenclature of Heterocyclic compounds in which Hantzsch - Widman system is widely used & accepted.

HANTZSCH - WIDMAN NOMENCLATURE

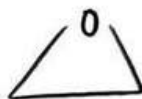
- The hantzsch - widman Nomenclature is a systematic method for naming heterocyclic compounds based on:
 - Ring size
 - Saturation/ Unsaturation
- This system is widely used in IUPAC Nomenclature for naming simple & complex monocyclic heterocycles.

Prefix + Stem + Suffix

NOMENCLATURE OF HETEROATOMS

Type of Heteroatom	No. of Atoms	Saturation	Unsaturation	Saturation with 'N'
Oxygen = Oxa	3 = ir	irane	irene	iridine
Sulphur = Thia	4 = et	etane	ete	etidine
Nitrogen = Aza	5 = ol	olane	ole	olidine
Phosphorus = Phospha	6 = in	inane	ine	
Arsenic = Arsa	7 = ep	epane	epine	
Silicon = Silia	8 = oc	ocane	ocene	
Tin = Stanna	9 = on	onane	onine	
Lead = Plumba	10 = ec	ecane	ecine	

Example : ① Oxirane



Here in Oxirane

- Since it has oxygen = Oxa
- Have 3 atoms in ring = ir
- Saturated ring = ane

Hence → Oxirane

② Aziridine



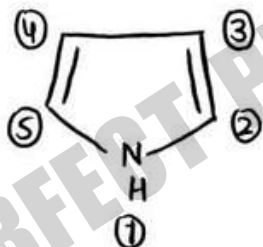
Here,

- Nitrogen = Aza
- 3 atoms = ir
- Saturation with "N" = idine

Hence → Aziridine

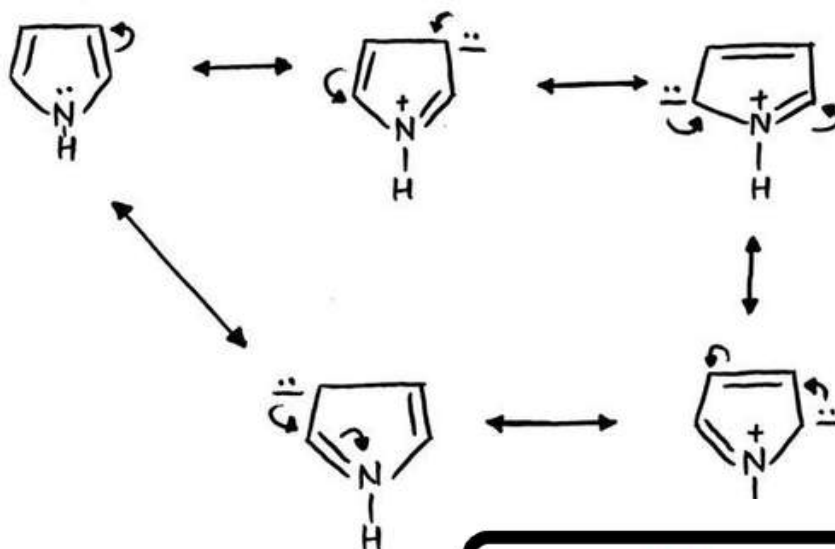
PYRROLE

- Pyrrole is a five membered aromatic heterocyclic compound with molecular formula C_4H_5N .
- It is a colorless volatile liquid that darkens readily upon exposure to air.
- It is considered to be one of the most essential five membered heterocyclic rings, as it is present in various natural products such as Haemoglobin, Chlorophyll, Alkaloids etc.



RESONANCE IN PYRROLE

Resonance in pyrrole refers to the delocalization of π -electrons (including lone pair on nitrogen) across entire 5-membered aromatic ring which gives pyrrole its aromatic character.



SYNTHESIS OF PYRROLE

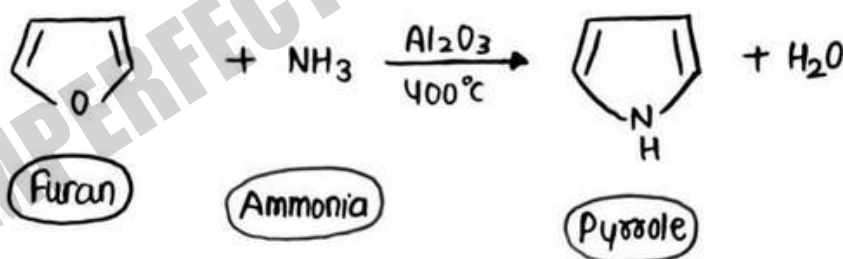
Also known as Method of preparation.

It involves:

- Industrial Method
- From Acetylene
- Paal Knorr Synthesis
- Hantzsch - Pyrrole Synthesis
- From succinimides

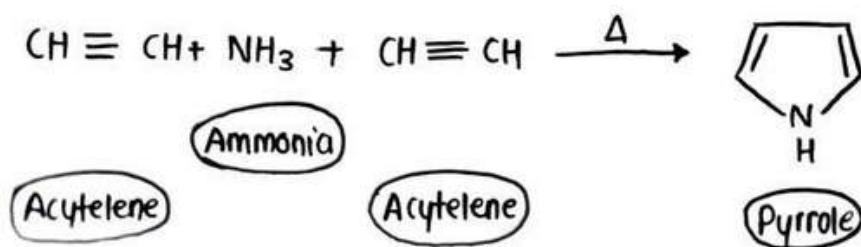
① INDUSTRIAL METHOD

Furan when treated with Ammonia under high temperature & pressure yields pyrrole.



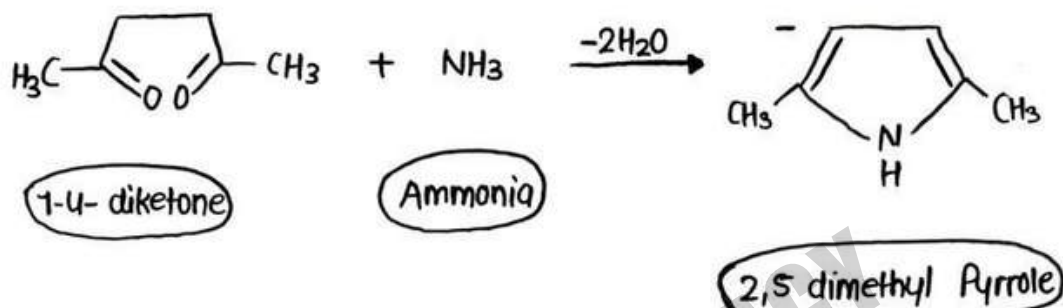
② FROM ACETYLENE

Pyrrole is obtained by passing acetylene and ammonia through a red hot tube.



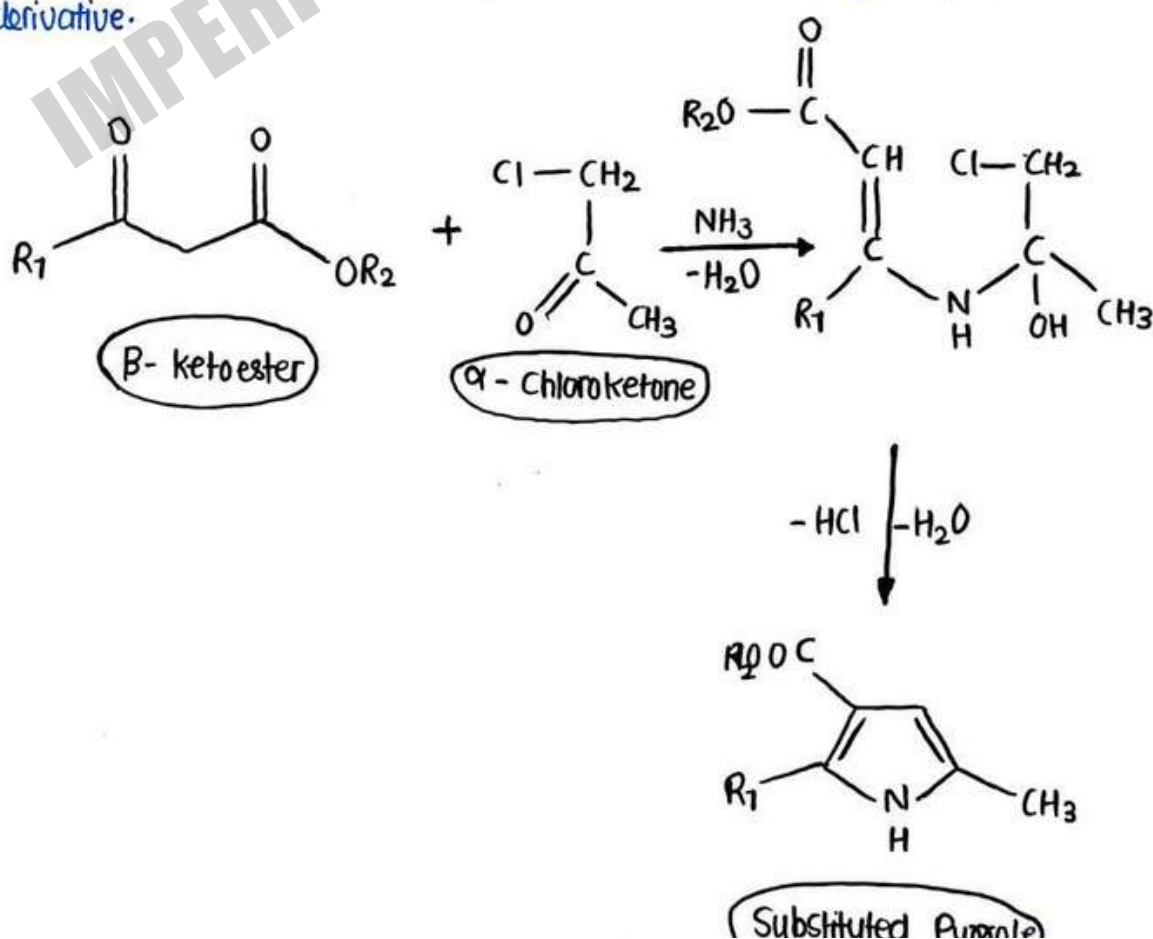
③ PAAL - KNORR SYNTHESIS

In this 1,4-diketone is treated with primary amine (often ammonia or alkyl amines) to yield pyrrole derivatives.



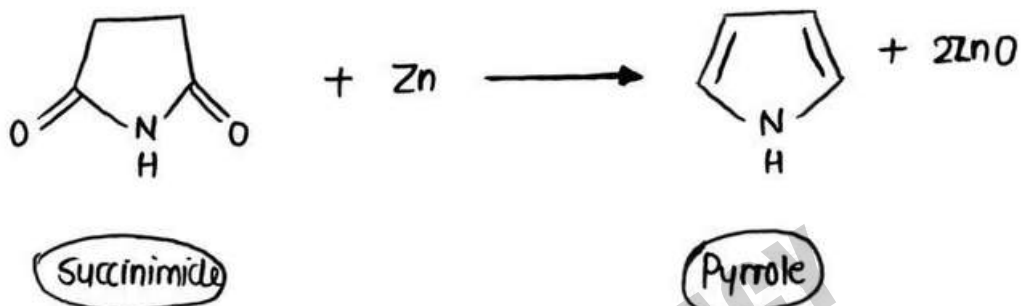
④ HANTZSCH PYRROLE SYNTHESIS

In this β -ketoester (Ethyl acetoacetate) reacts with α -chloroacetate (α -haloketone) in the presence of Ammonia to give pyrrole derivative.



⑤ FROM DISTILLATION OF SUCCINIMIDE

Pyrrole is obtained by the distillation of succinimide with zinc dust.



CHEMICAL REACTIONS OF PYRROLE

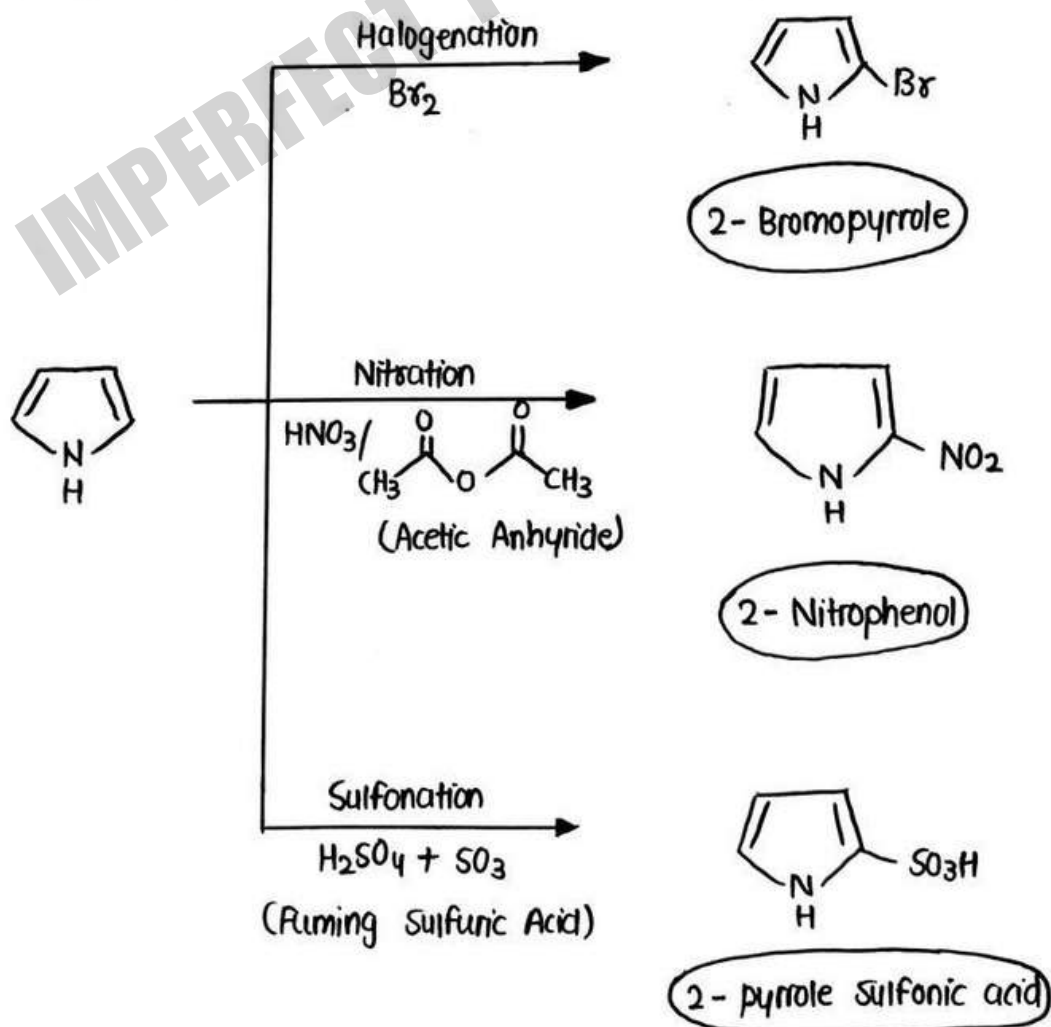
Pyrrrole due to electron-rich nature of its ring gives various chemical reactions mainly at C-2 position.

These major reactions given by pyrrole are :

- Electrophilic Substitution Reaction
- Reduction
- Riemes - Tiemann Reaction
- Oxidation

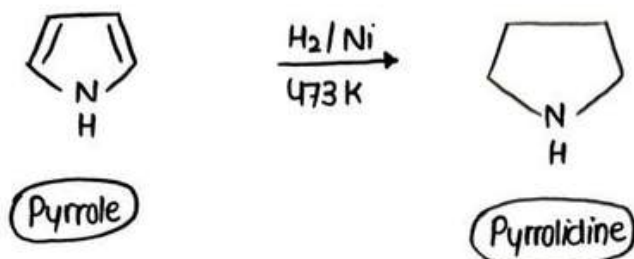
① ELECTROPHILE SUBSTITUTION REACTION

Pyrrrole undergoes substitution reaction & substitution chiefly at C-2 position.



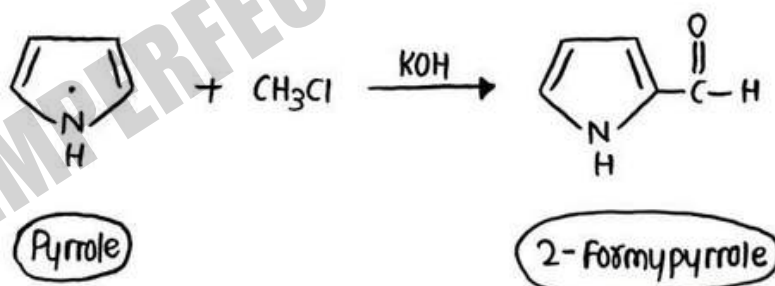
② REDUCTION

Pyrrole reduces by H_2 gas in presence of Ni at very high temperature to yield pyrrolidine.



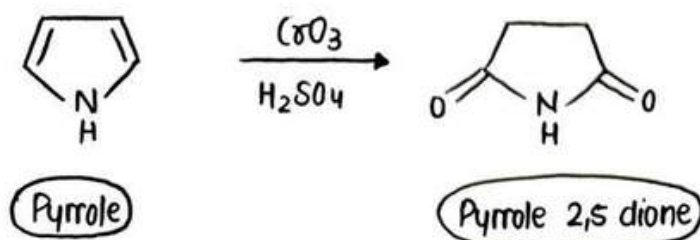
③ RIEMER - TIEMANN REACTION

In the presence of KOH, pyrrole reacts with, chloroform to produce 2-formylpyrrole.



④ OXIDATION

Pyrrole oxidises in the presence of H_2SO_4 with chromium trioxide to yield Maleicimide (Pyrrole, 2,5-dione).



MEDICINAL USES OF PYRROLE

① Core Structures in Drug Molecules

- Pyrrole is building block in many pharmaceuticals and natural products such as:
 - Atorvastatin (Lipitor) - a cholesterol-lowering drug.
 - Tolmetin - A nonsteroidal anti-inflammatory drug (NSAIDs).
 - Sunitinib - Used in Cancer therapy.

② Antimicrobial Agents

- Pyrrole derivatives show antibacterial, antifungal and antiviral activities.
- They disrupt microbial membranes or inhibit key enzymes.

③ Anti-inflammatory and Analgesic

- Many pyrrole-based compounds reduce inflammation and pain, similar to NSAIDs.
- Example - Tolmetin

④ Heme and Chlorophyll Structure

- Biologically, pyrrole units form the porphyrin ring system, found in:
 - Heme in (haemoglobin and cytochromes).
 - Chlorophyll (in plants).

FURAN

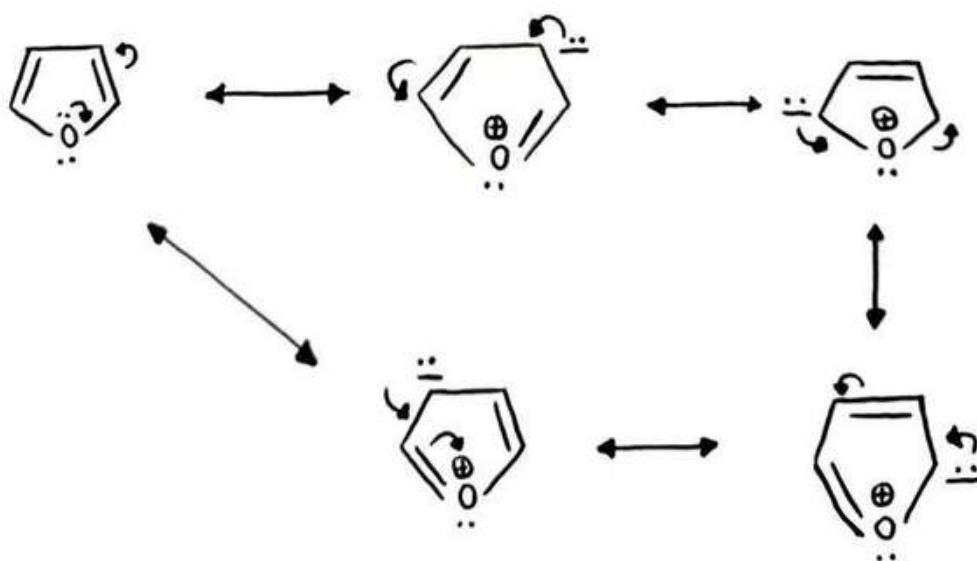
- Furan is a heterocyclic organic compound, consisting of a 5-membered aromatic ring when 4 carbon atoms & 1 oxygen atom.
- It is a colourless, inflammable volatile liquid with boiling point of 32°C .
- It is slightly soluble in water but completely soluble in many organic solvent.



furan

RESONANCE IN FURAN

Resonance in Furan helps explain its aromaticity & stability as a heterocyclic compound.



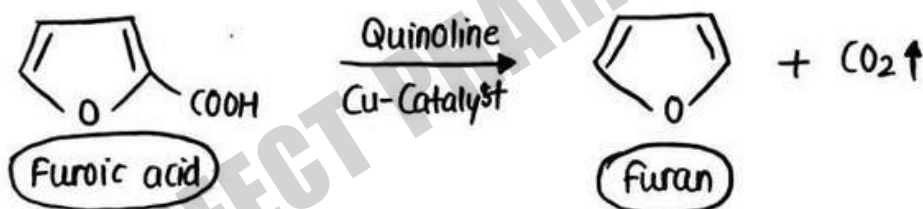
SYNTHESIS OF FURAN

Furan can be synthesized through following reactions:

- From Furoic Acid
- From 1,3 - Butadiene
- Pictet Knorr Synthesis
- From Furfural

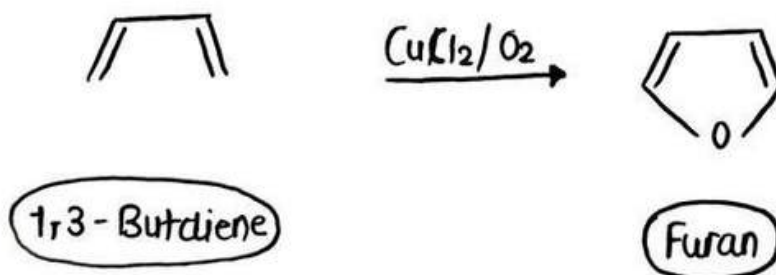
① FROM FUROIC ACID

Decarboxylation of furoic acid yields furan.



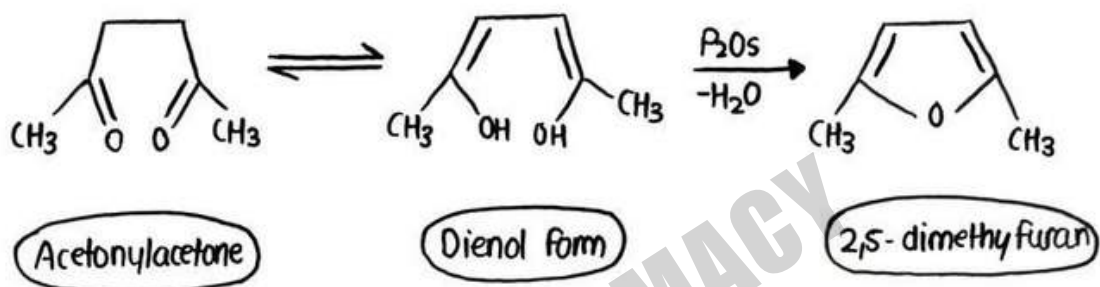
② FROM 1,3 - BUTADIENE

1,3- Butadiene yields furan by copper - catalyzed reactions.



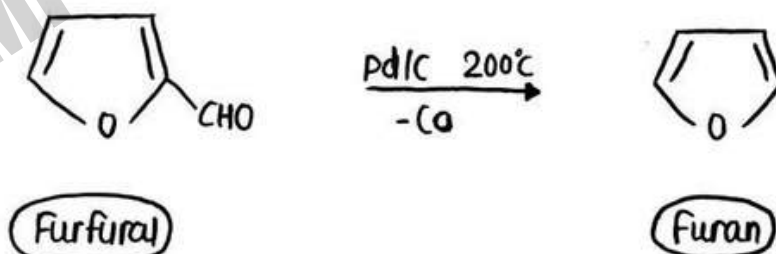
③ PAAL KNORR SYNTHESIS

1,4- dicarbonyl compound (Acetylacetone) when heated with a dehydrating agent (e.g. phosphorus pentoxide - P_2O_5) result in the formation of 2,5 dimethylfuran.



④ FROM FURFURAL

Decarbonylation of furfural yields furan in the presence of charcoal/ palladium.

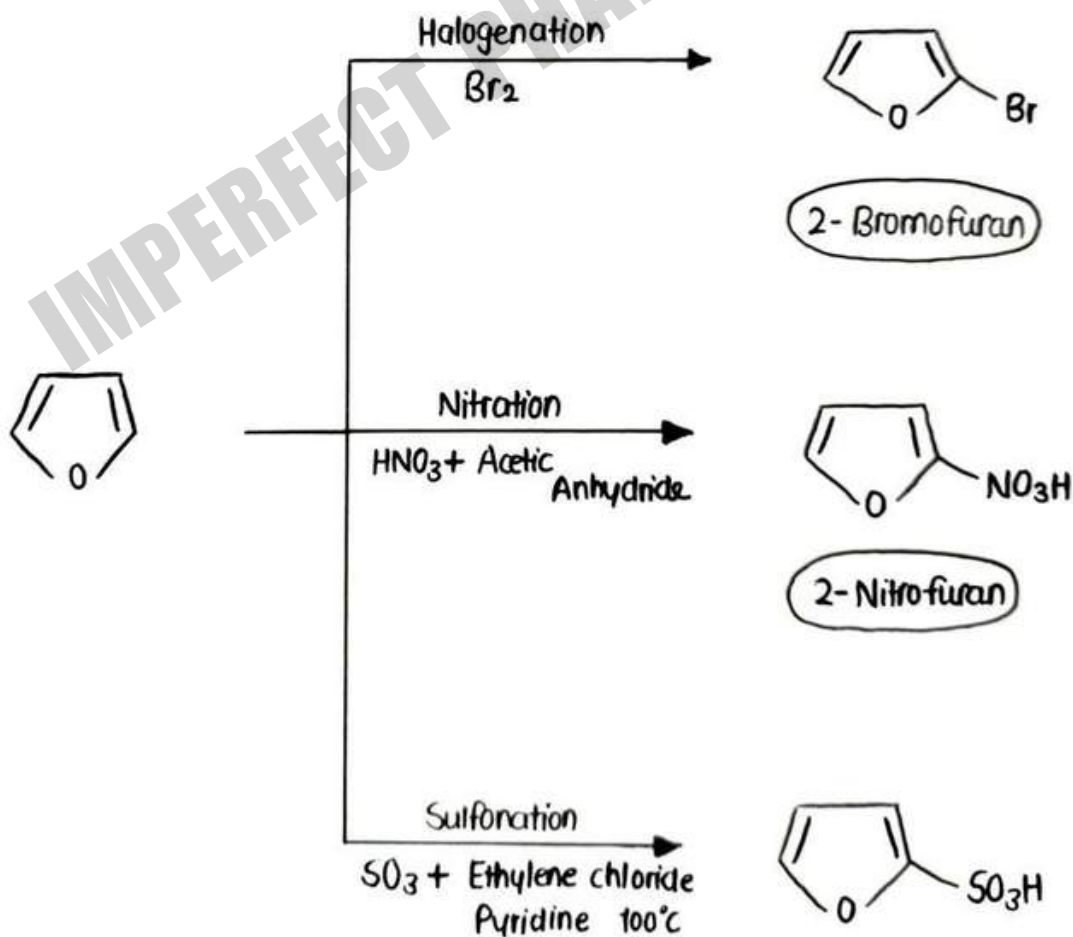


CHEMICAL REACTIONS OF FURAN

Furan undergoes various chemical reactions preferentially at C-2 position.

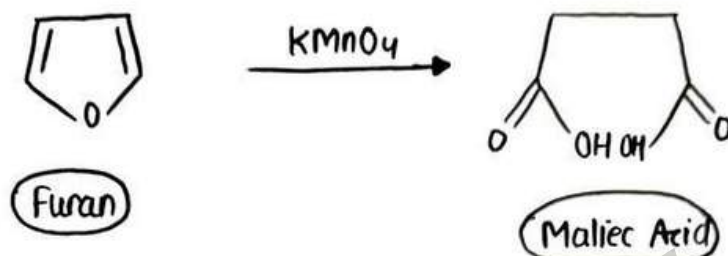
- Electrophile Substitution Reactions
- Oxidation
- Reduction
- Mercuration

① Electrophilic Substitution Reactions



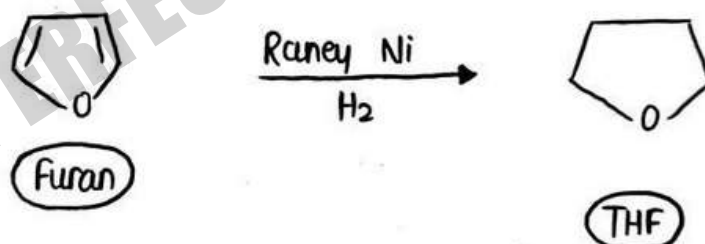
② Oxidation

Furan in the presence of strong oxidizing agents like KMnO_4 oxidized to Malic Acid.



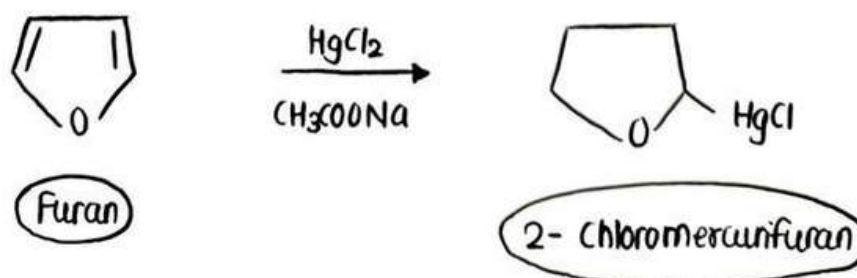
③ Reduction

Furan in the presence of nickel & hydrogen reduced into Tetrahydrofuran (THF).



④ Mercuration

Furan in the presence of Mercuric Chloride & sodium acetate gives 2-chloromercurifuran.



MEDICINAL USES OF FURAN

Furan itself is rarely used directly in medicine due to toxicity concerns, but furan derivatives are very important in pharmaceuticals.

Here are their key uses :

① Antibacterial agents

Nitrofurantoin - A furan derivative used to treat urinary tract infections (UTIs).

② Antiprotozoal Drugs

Furazolidone - Used to treat infections like giardiasis and bacterial diarrhea.

③ Antifungal Agents

Certain furan derivatives exhibit strong activity against fungal infections.

④ Anti-Inflammatory Drugs

Furan rings are present in drugs with anti-inflammatory properties (e.g. furosemide is diuretic and mild anti-inflammatory effects).

⑤ Diuretics

Furosemide - A loop diuretics used to treat edema and hypertension.

⑥ Antiviral agents

Furan - containing compounds are being developed as HIV and hepatitis inhibitors.

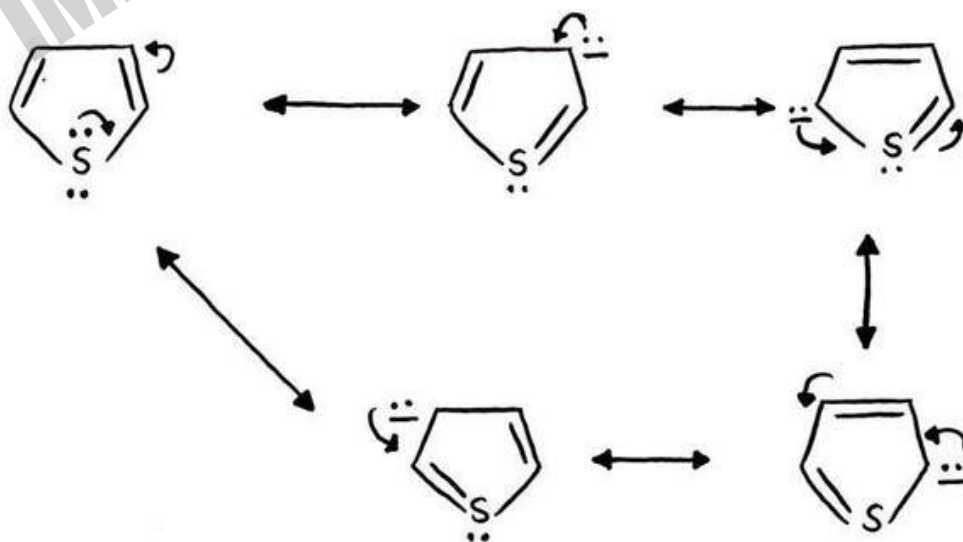
THIOPHENE

Thiophene belongs to a class of heterocyclic compounds containing a 5-membered ring made up of one sulfur as a heteroatom. It is a colourless liquid having boiling point of 84°C . It is slightly soluble in water, soluble in organic solvents.



RESONANCE IN THIOPHENE

Resonance in thiophene explain its aromatic stability, similar to pyrrole & furan.



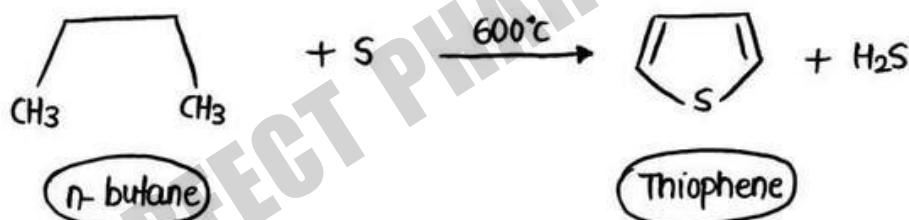
SYNTHESIS OF THIOPHENE

There are various method of preparation of Thiophene as follow :

- Industrial methods
- Paal knorr Synthesis
- From Acetylene

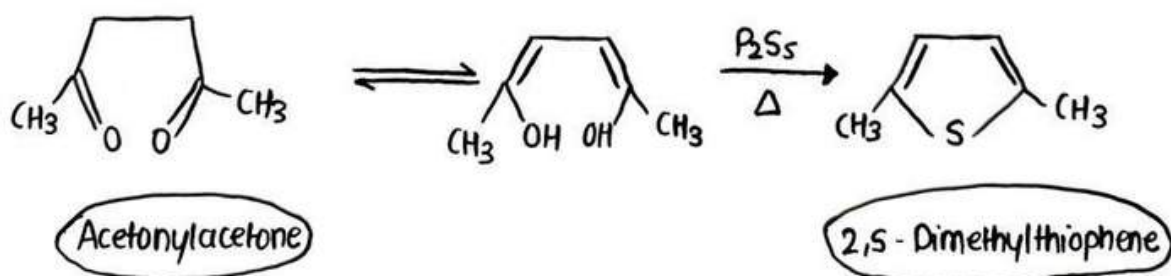
① INDUSTRIAL METHODS

Thiophene can be synthesized an industrial scale by heating n-butane & sulfur at high temperature.



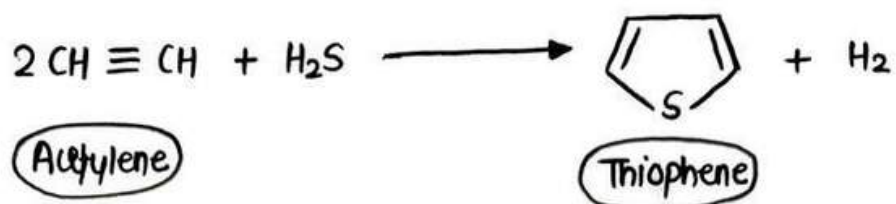
② PAAL KNORR SYNTHESIS

In this method 1,4 dicarbonyl compounds heated with phosphorus pentasulfide to give thiophene.



③ FROM ACETYLENE

Treatment of acetylene with hydrogen sulfide yields thiophene.



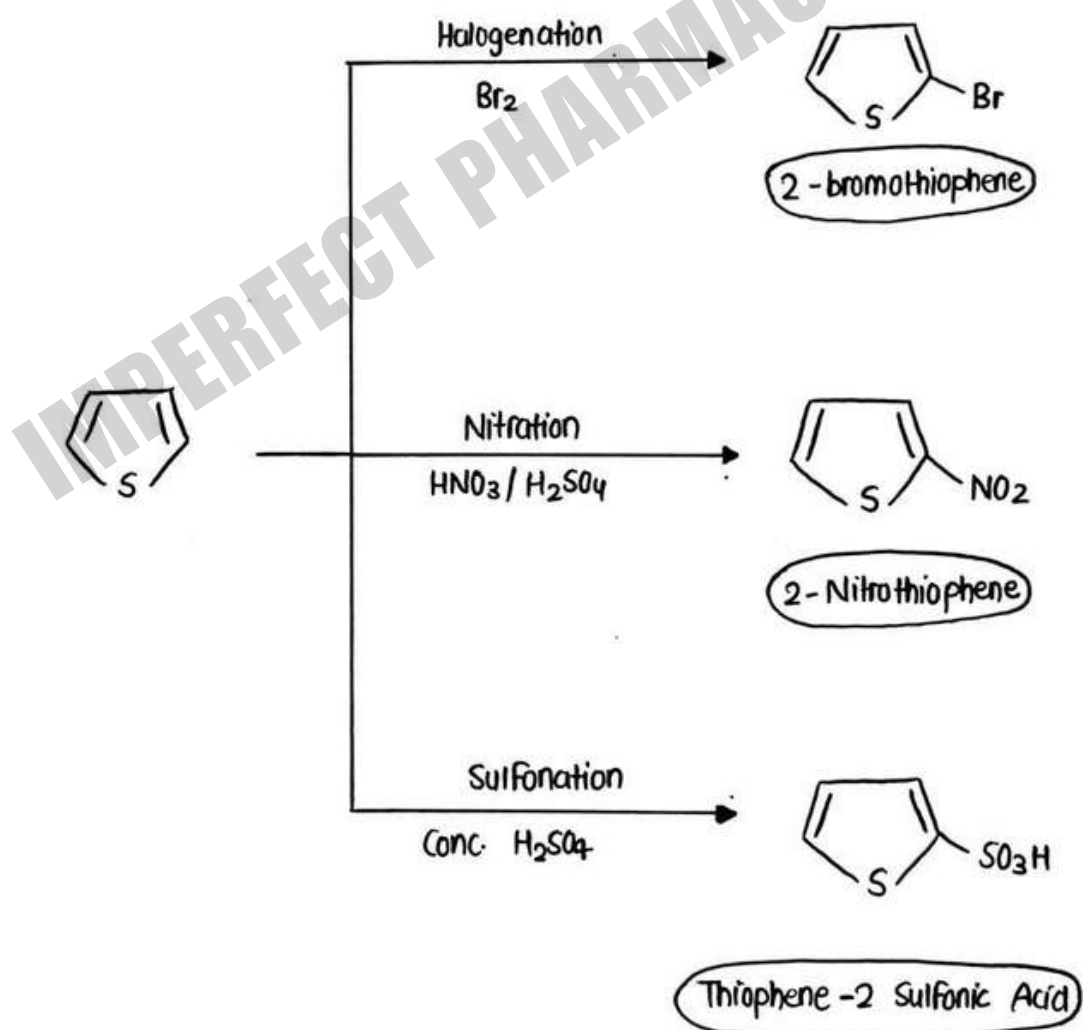
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CHEMICAL REACTIONS OF THIOPHENE

Thiophene gives following chemical reactions :

- Electrophile substitute reaction
- Mercuration
- Reduction
- Nucleophilic Substitute reaction

① Electrophilic Substitute reaction



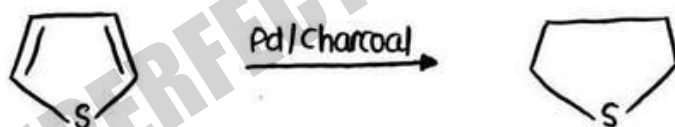
② Mercuration

Thiophene reacts with mercuric chloride in the presence of sodium acetate to give thiophene - 2- mercuric chloride.



③ Reduction

Thiophene in the presence of palladium & charcoal yields Tetrahydrothiophene.



④ Nucleophilic Substitution reaction

2-Bromothiophene, on treating with copper cyanide (CuCN) yields 2-Cyanothiophene.



MEDICINAL USES OF THIOPHENE

① Antibacterial Agents

Thiophene derivatives are used in drugs to treat bacterial infections.

② Anti-inflammatory drugs

Present in agents that reduce inflammation & pain.

③ Antidepressants

Thiophene ~~drugs~~ rings are found in certain mood-stabilizing agents.

④ Diuretics

Found in drugs like tenoxicam, a thiophene-containing NSAID.

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