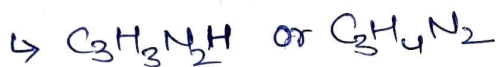
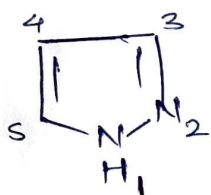


U-4. HETEROCYCLIC COMPOUND-II

SYNTHESIS, CHEMICAL REACTIONS OF AND MEDICINAL USES OF FOLLOWING COMPOUNDS -

- | | | |
|--------------|-----------------|----------------|
| 1. Pyrazole | 5. Pyridine | 9. Indole |
| 2. Imidazole | 6. Quinoline | 10. Pyrimidine |
| 3. Oxazole | 7. Isoquinoline | 11. Purine |
| 4. Thiazole | 8. Acridine | 12. Azepines |

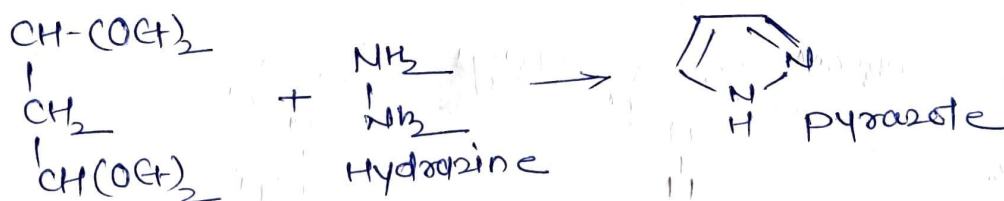
1. PYRAZOLE



↳ Weak basic

Synthesis :-

① Condensation

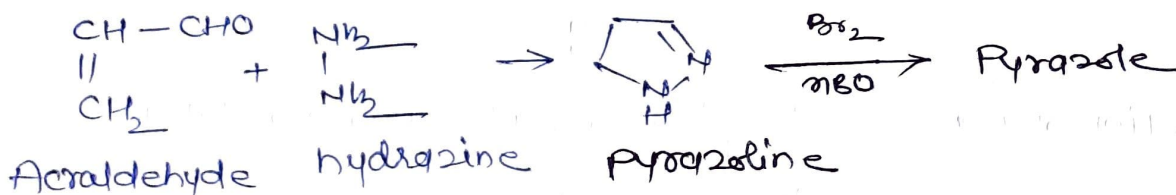


Tetraethoxy propane
(malonaldehyde diethyl acetal)

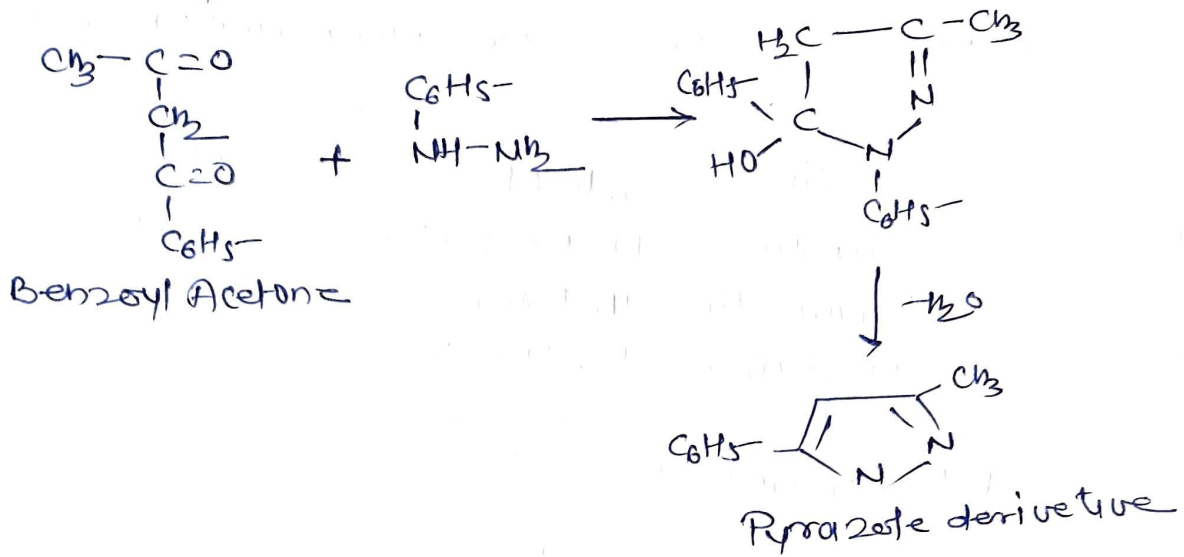
② By passing acetylene gas into cold soln of diazomethane



③ By reaction of α, β -unsaturated ald/keton with hydrazine

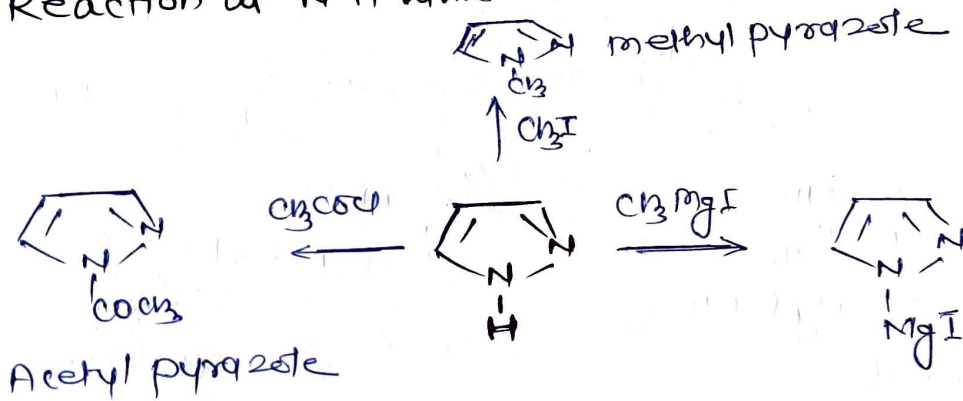


4. Know Pyrazole Synthesis

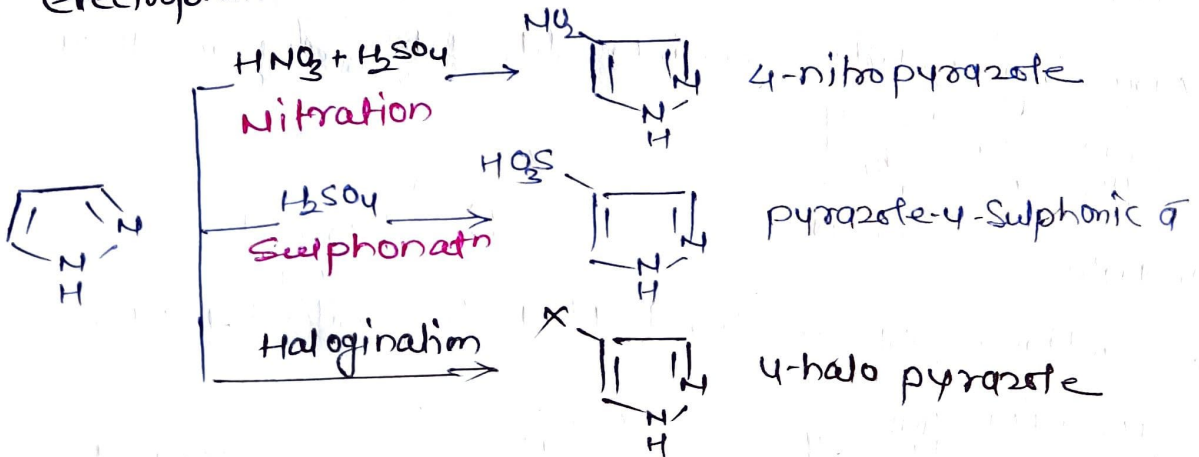


CHEMICAL REACTIONS

① Reaction at N-H atom



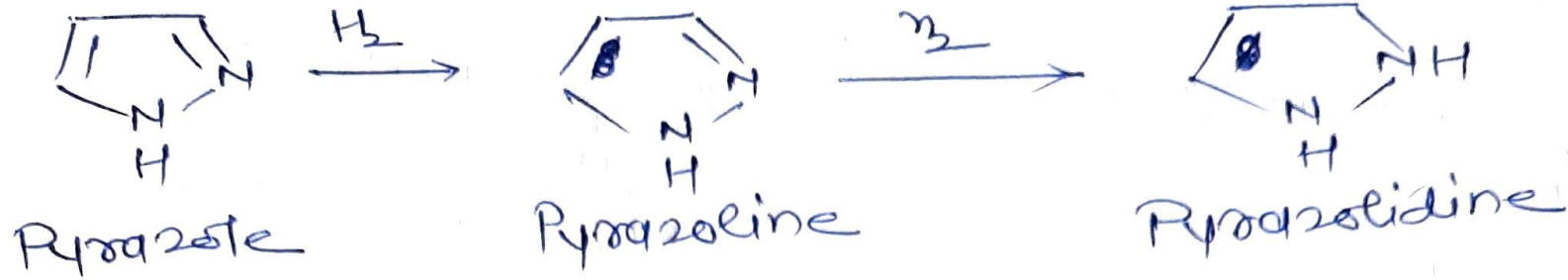
② Electrophillic Substitution Reaction - at 4 position



③ Action of Base \rightarrow Strong base on reactn gives pyrazolyl anion



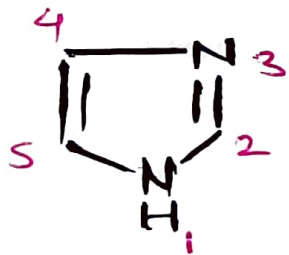
④ Reduction - gives pyrazoline & further pyrazolidine



Medicinal Uses

- # Antimicrobial \rightarrow Cefoselix - against E. coli, S. aureus.
- # Analgesic \rightarrow Phenylbutazone
- # Anticancer \rightarrow Azathioprine, Dacarbazine
- # Antioxidant \rightarrow eliminate the free radical
- # ACEIs \rightarrow lower the BP
- # Antitubercular, # MAO-Inhibitor # Diagnostic agent (Tartrazine)

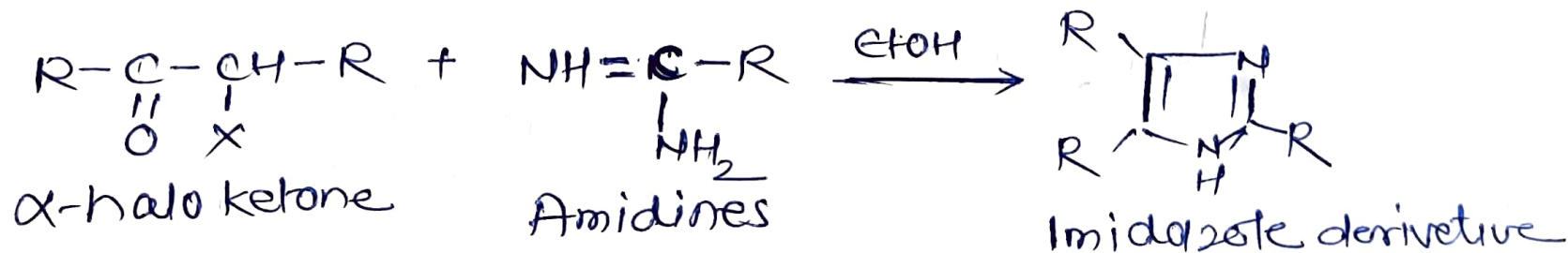
2. IMIDAZOLE



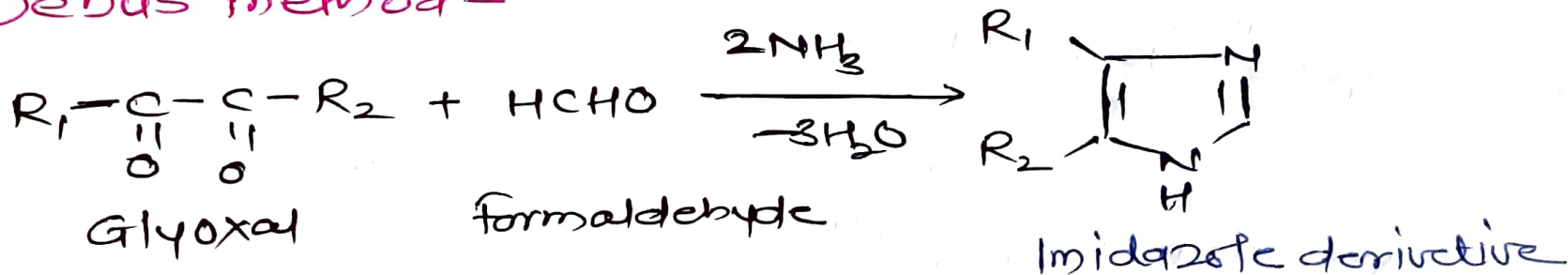
- ↳ $C_3H_4N_2 \rightarrow$ N-at 1,3,-position
- ↳ Colourless solid, soluble in water
- ↳ Mostly present in Alkaloid

Synthesis

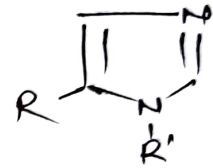
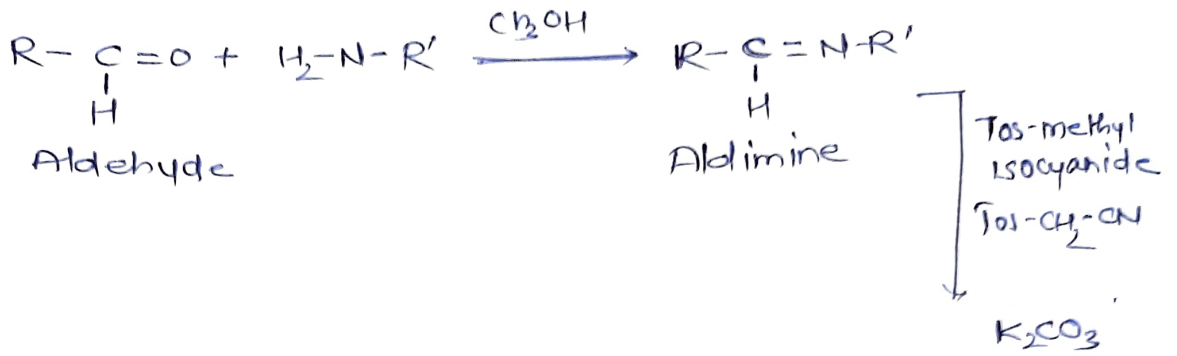
① from α -halo ketone



② Debus method -

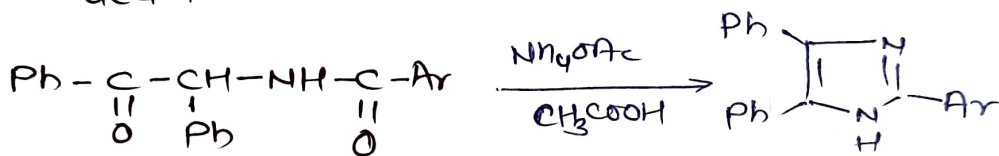


③ **Van-Leusen Synthesis** - From aldimines with tosylmethyl isocyanide

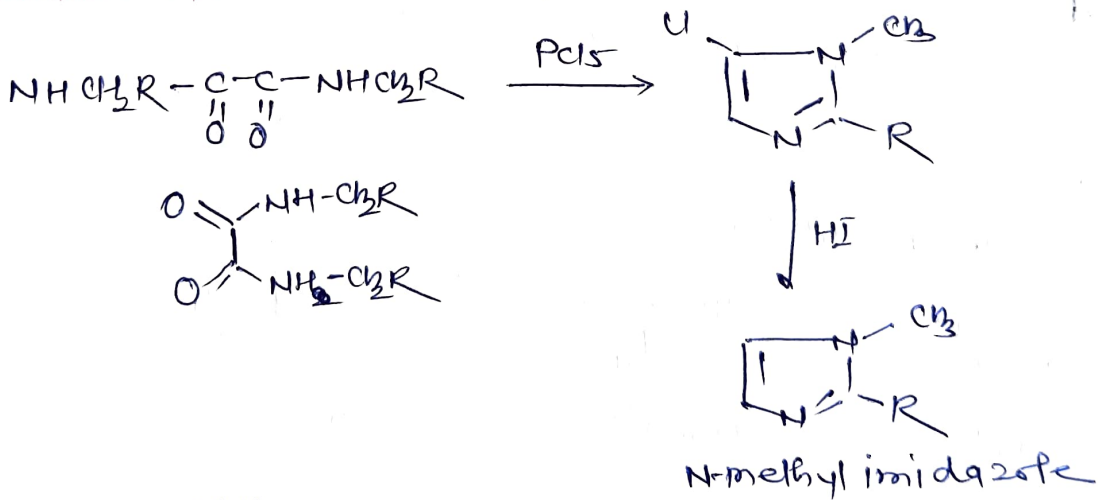


④ **Robinson-Gabriel Synthesis**

- Acylamino ketones on reaction with Ammonium acetate

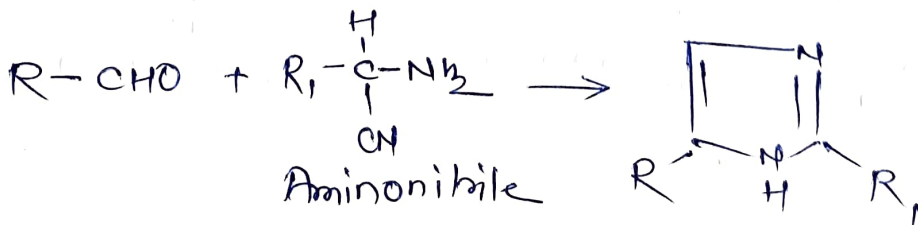


⑤ **Wittich Synthesis** - by N,N-dimethyl oxamide derivative



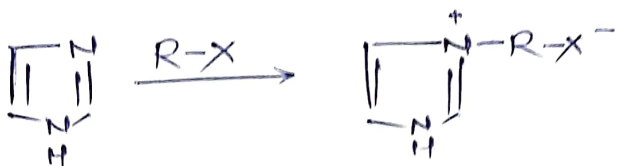
Aminonitrile

⑥ From Acetonitrile & Aldehyde

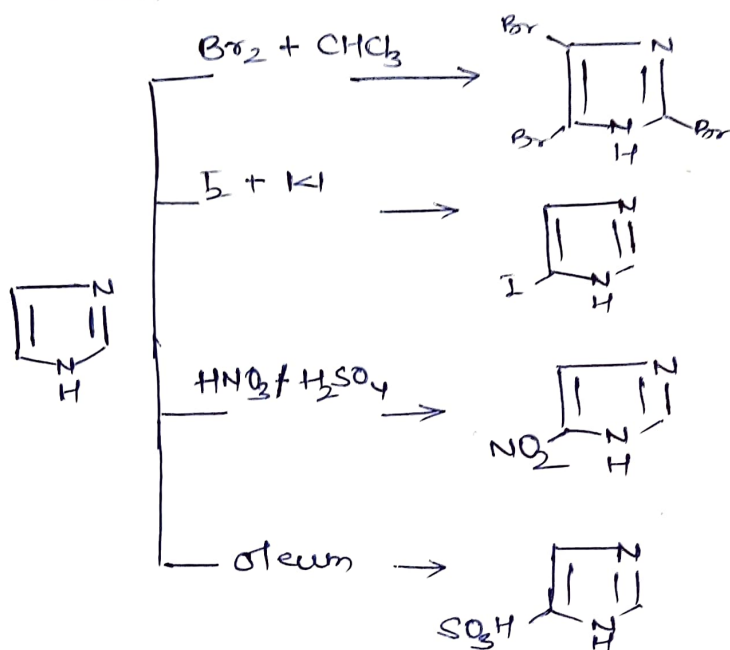


CHEMICAL REACTIONS

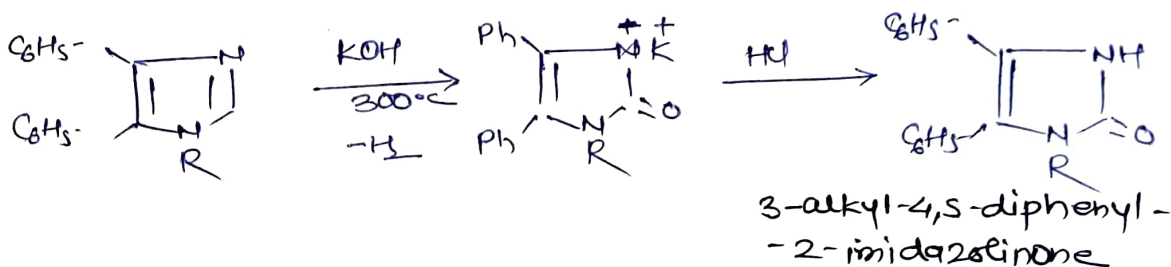
① Formation of Quaternary Salt



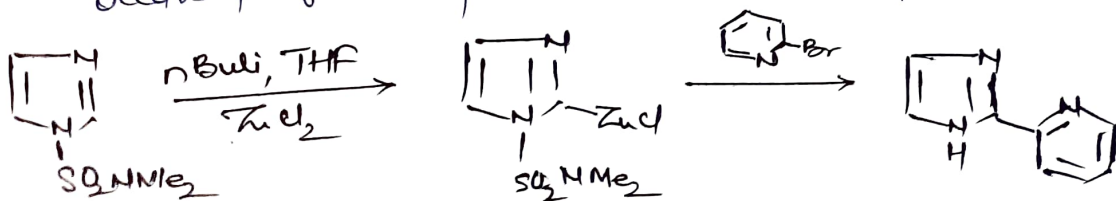
② Electrophillic Reaction at C-5 \gg at C-2



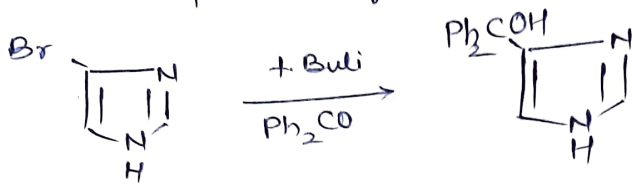
③ Nucleophilic Substitution Reactions - Generally imidazoles are often resistance to attack by ~~any~~ nucleophiles. 1-Substituted imidazole react with hydroxide ions under extreme condⁿ at $300^\circ C$



④ Direct Deprotonation - Direct deprotonation of N-alkylimidazole occurs preferentially at either C-2 or C-5 position



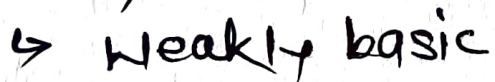
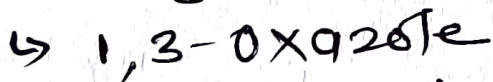
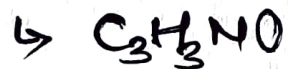
5. Metal-Halogen Exchange (Metalation) - at C-4 position.
In case for imidazole without substituent at 1-position,
two equivalents of base are required.



Medicinal Uses

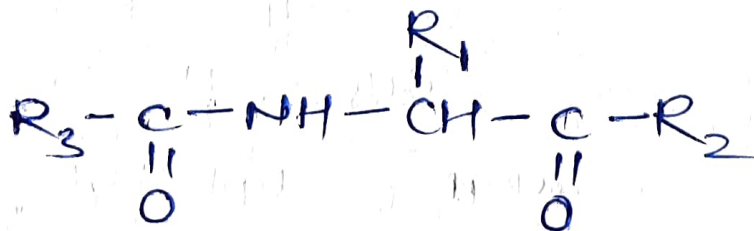
- # Anti-fungal
- # Antiprotozoal
- # Antihypertensive Agents
- # CNS Stimulants (Theophylline)
- # Anticancer (Mercaptopurine)
- # Anti-inflammatory
- # H_2 -receptor blockers

3. OXAZOLE

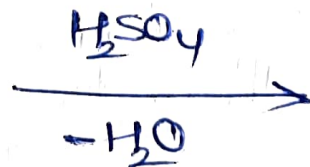


Synthesis —

① Robinson-Gabriel Synthesis

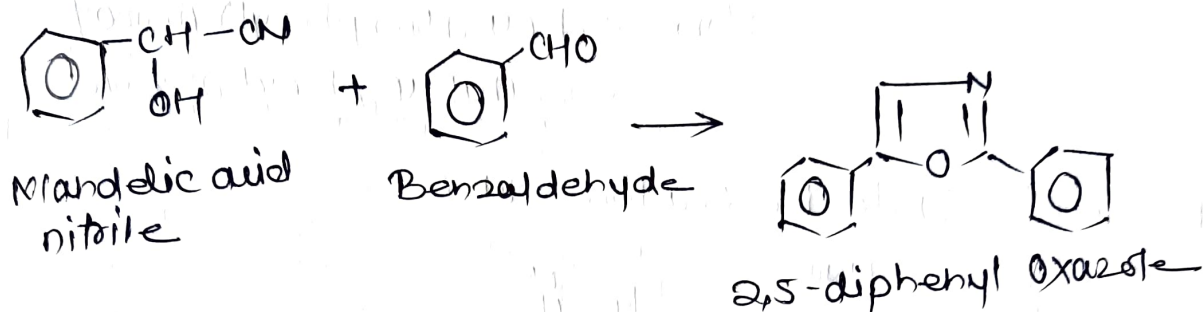
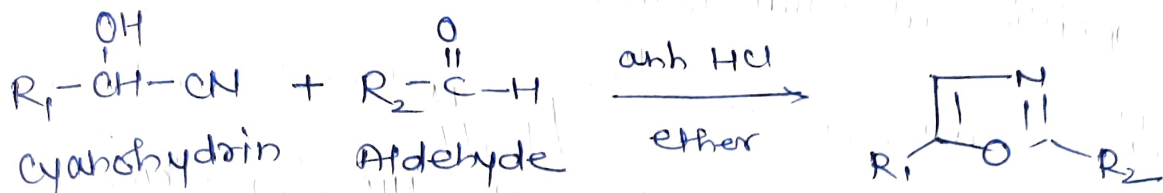


2-Acylaminoketone

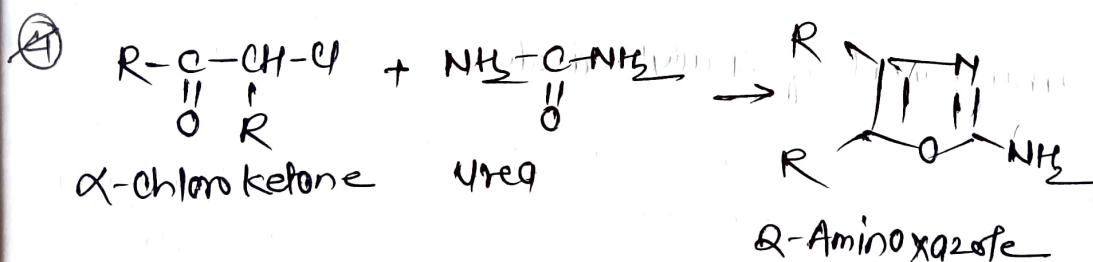
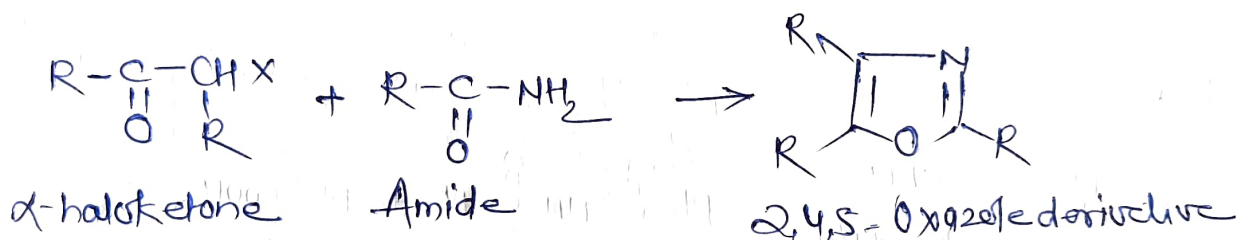


2,4,5-Oxazole
derivative

② Fischer Oxazole Synthesis

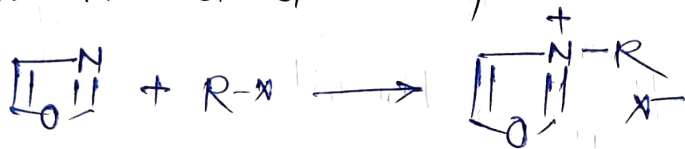


③ From α -haloketone & Amide

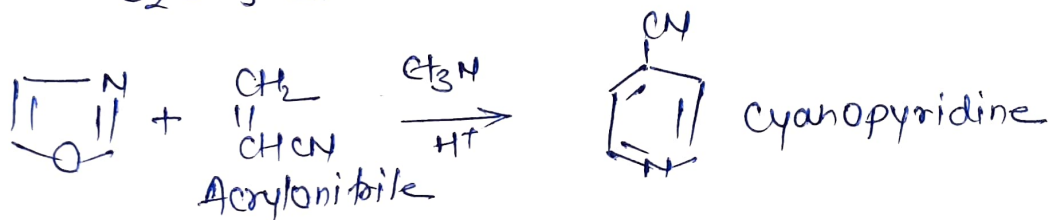


CHEMICAL REACTION

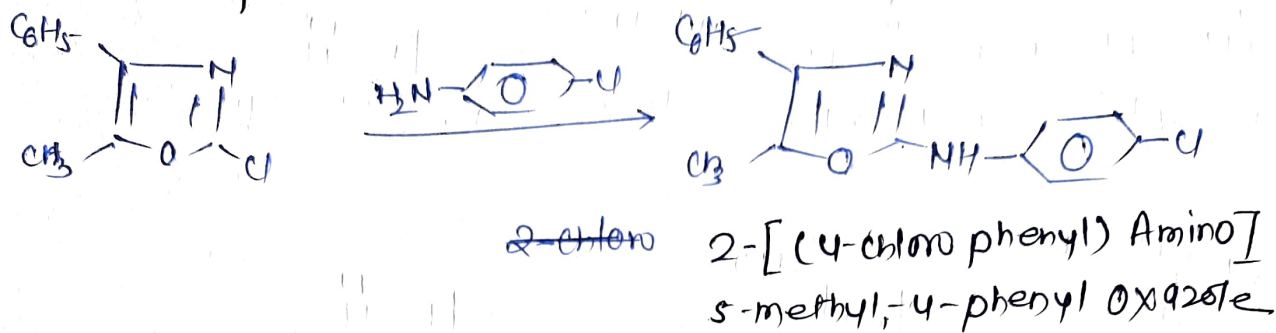
① Formation of Quaternary Salt



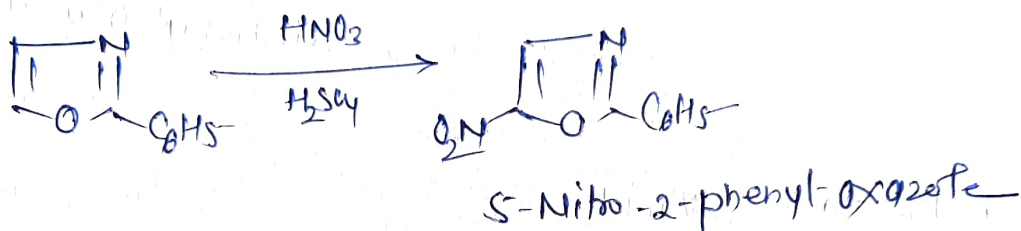
② Cycloaddition Reaction - Oxazoles are less nucleophilic at C₂ & C₅ so shows reduced aromatic character



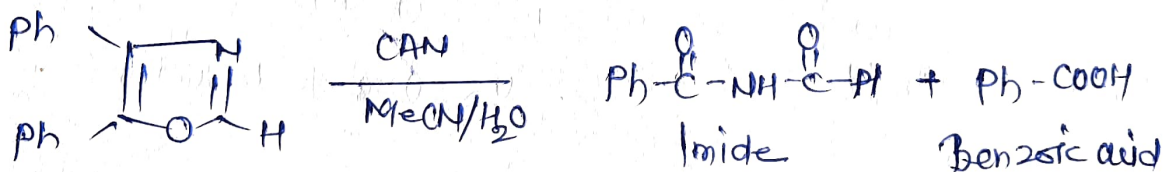
③ Nucleophilic Substitution Reaction - at C₂ position



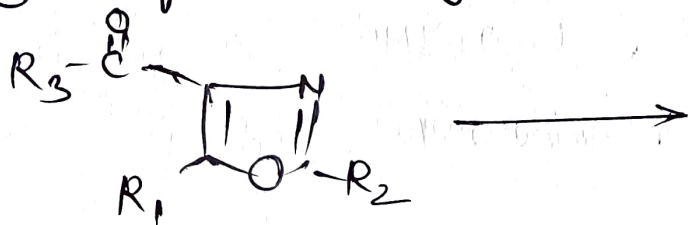
④ Electrophilic Substitution Reaction - at C₅



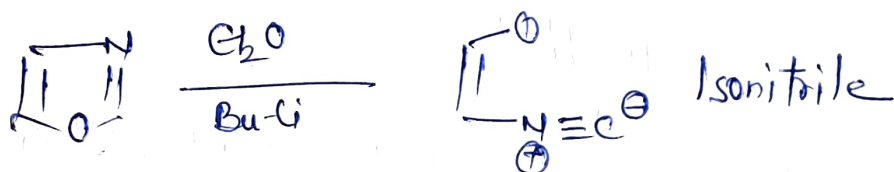
⑤ Oxidation



⑥ Conforth Rearrangement of 4-acyloxazole



⑦ Deprotonation



MEDICINAL USES

- # Antibacterials - Sulfamoxol & Sulfaguanol, Sulphaisoxazole
- # Antiplatelets - Dipyridol
- # Antibiotics - Flopristin
- # Protein kinase Inhibitor - Nilotinib

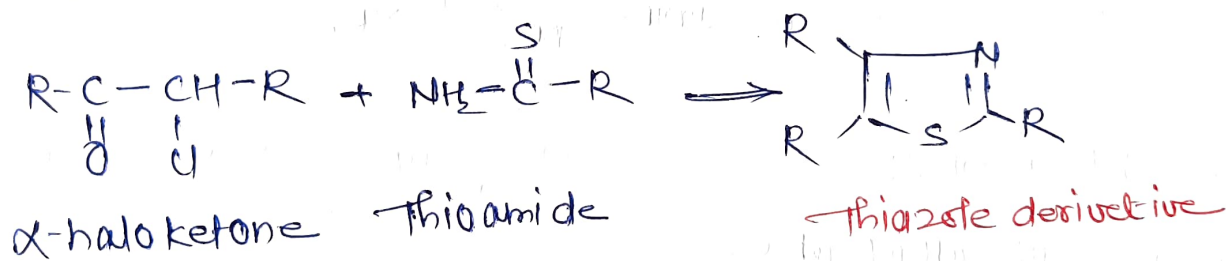
THIAZOLE



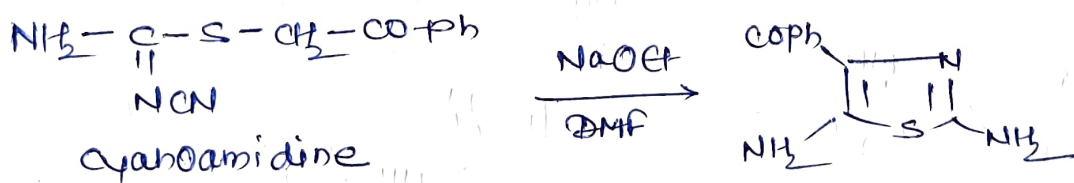
- # C_3H_3NS
- # 5-membered aromatic ring
- # Aromaticity greater than Oxazole

Synthesis :-

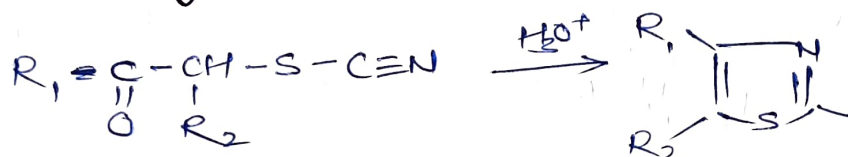
① Hantzsch Synthesis - from α -halo carbonyl compound



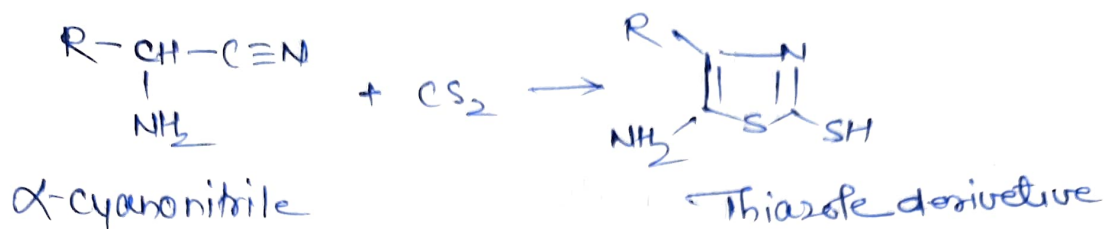
② Reaction with Cyanoamidine - 1,3 Dipolar Addition



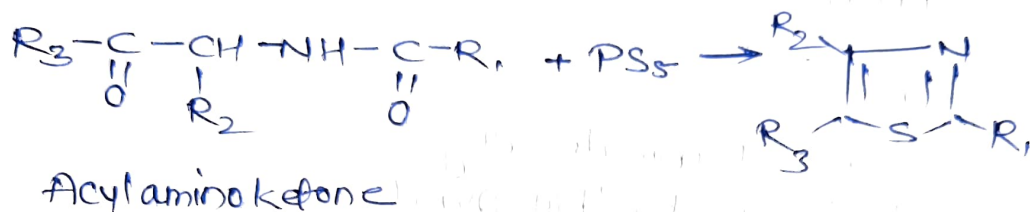
③ Rearrangement of α -thiocyanoketones



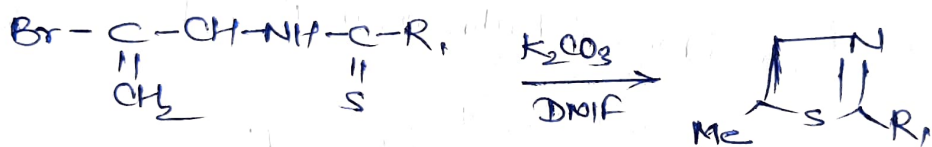
④ Cook-Heilbron's Synthesis - by α -aminonitrile



⑤ Gabriel's Synthesis

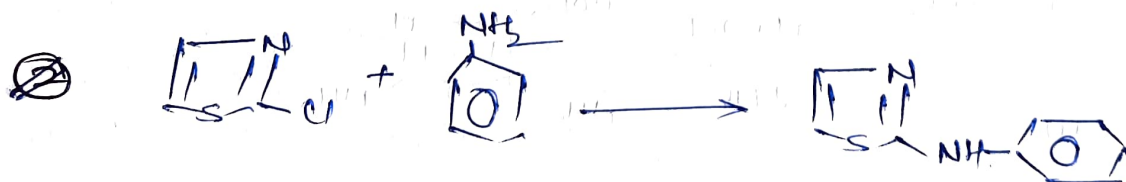


⑥ From Vinyl Bromide - by intramolecular nucleophilic substitution

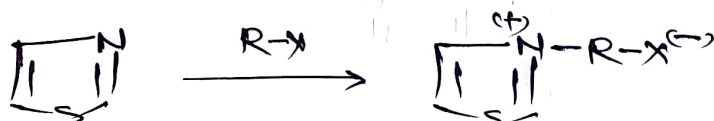


Chemical Reactions \Rightarrow

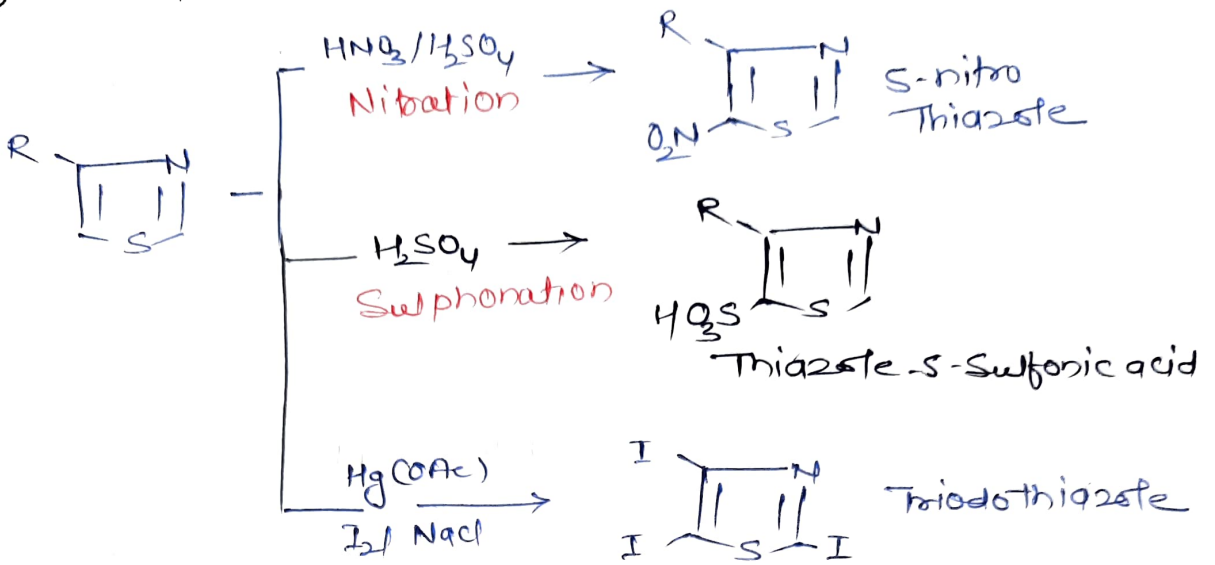
① Nucleophilic attack at C2



② Alkylation at Nitrogen



③ Electrophillic Substitution Reaction - at C5 position



Medicinal Uses

- # Antibiotic - Sulphathiazole, cefixime
- # Antinflammatory - Fenethiazole
- # Fungicidal - Combendazole
- # ~~B~~ vit B₁ - Thiamine
- # Respiratory stimulant - Amiphenazole
- # Anti HIV - Breca Navir
- # Antihypertensive - Alagebrinium
- # Thyroid inhibitor - Aminethiazole



5. PYRIDINE



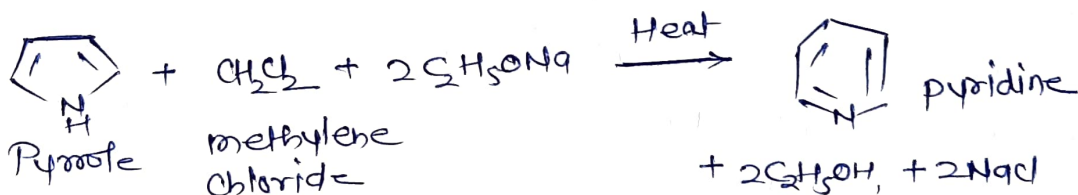
- ↳ C_5H_5N
- ↳ Six membered heterocyclic aromatic compound
- ↳ present in no. of natural compounds like pyridoxine, nicotinic acid, nicotine, etc
- ↳ Basic in nature

Synthesis:-

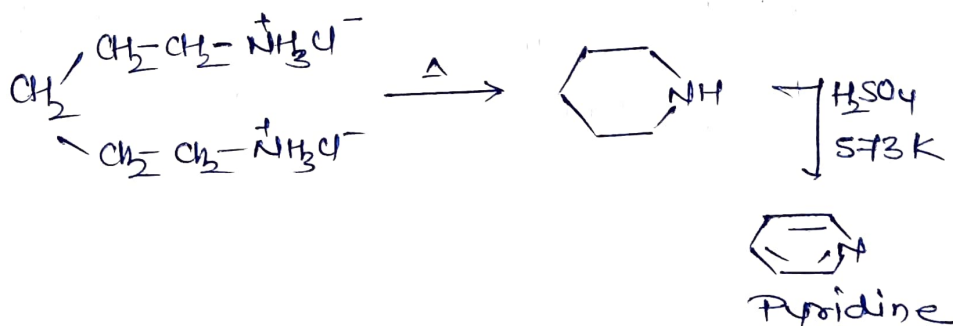
① from Acetylene



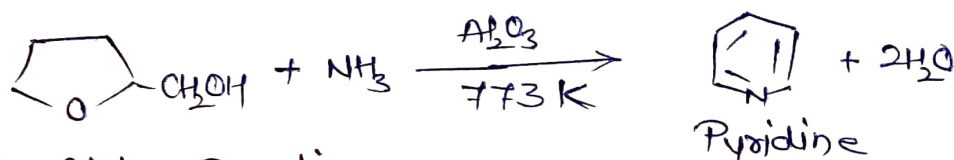
② from Pyrrole



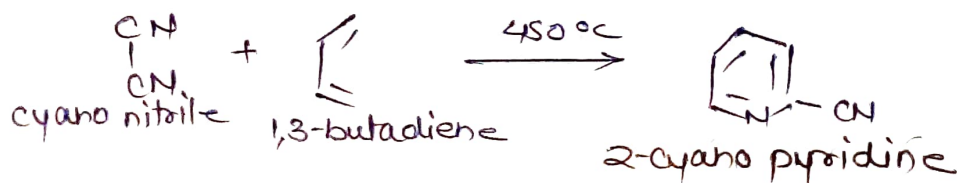
③ from Pentamethylene Diamine hydrochloride



④ from Tetrahydrofurfuryl alcohol

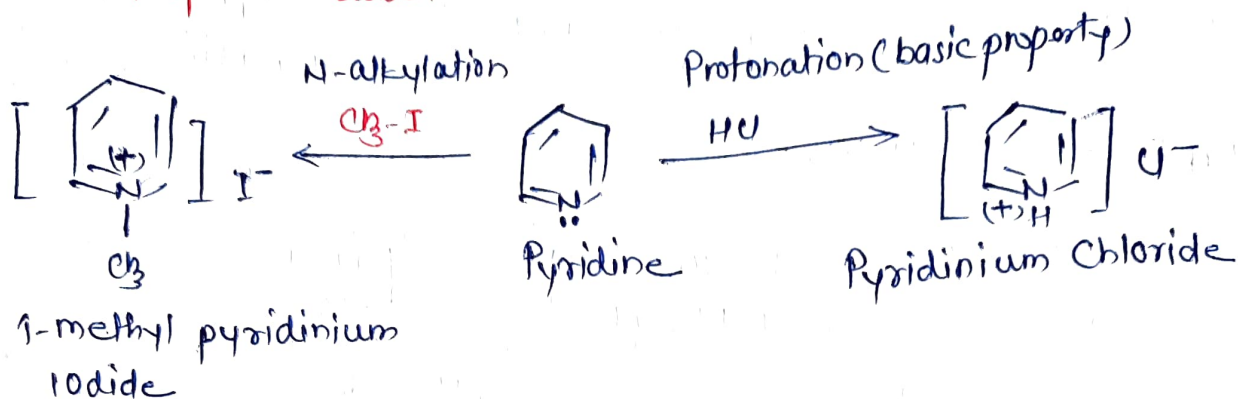


⑤ Diels-Alder Reaction

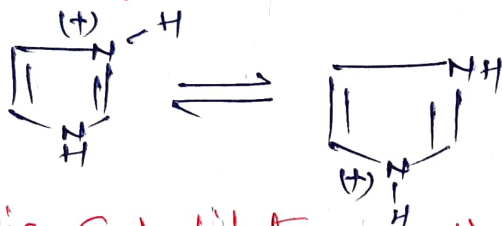


CHEMICAL REACTIONS

① Electrophilic addition to N atom.

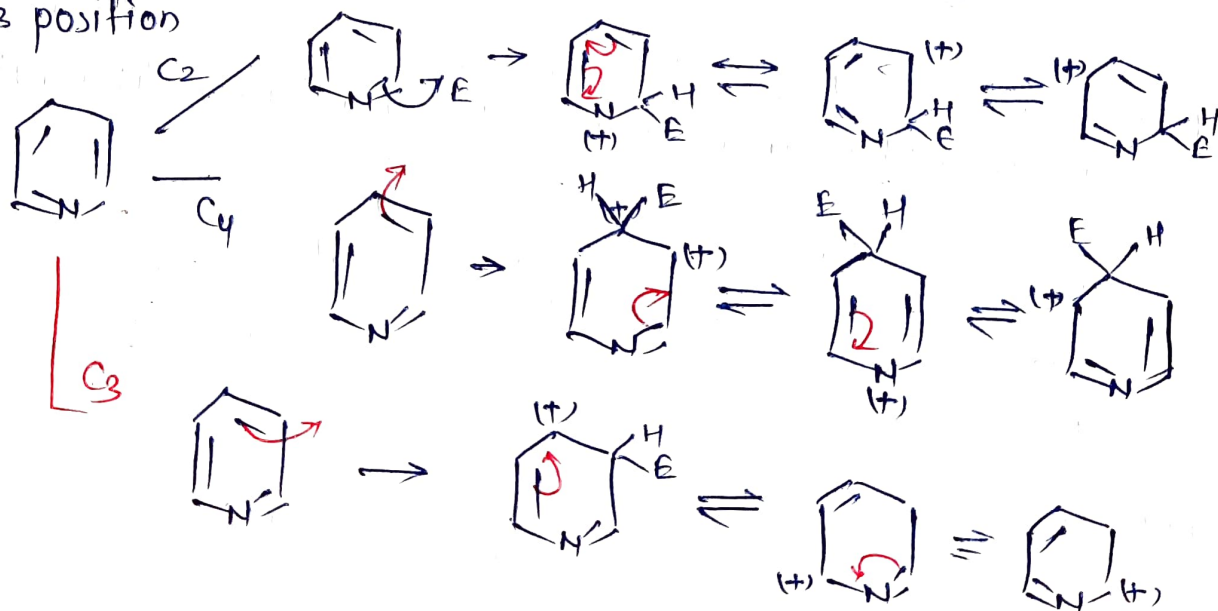


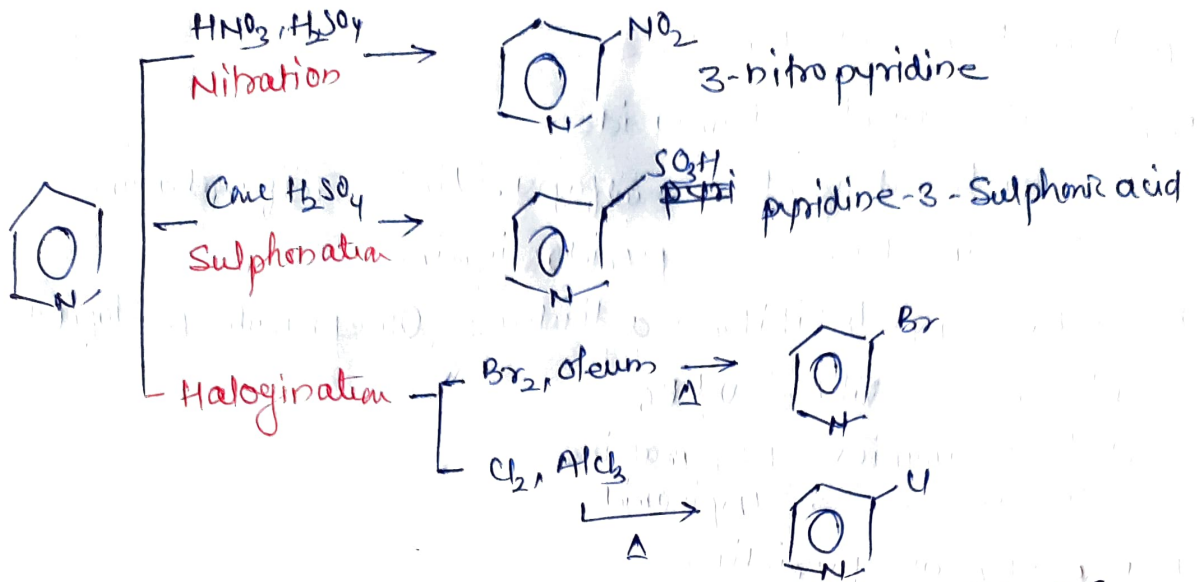
✳ Imidazole, 100 times more basic than pyridine due to delocalization of electron



② Electrophilic Substitution Reaction = at C₃ position

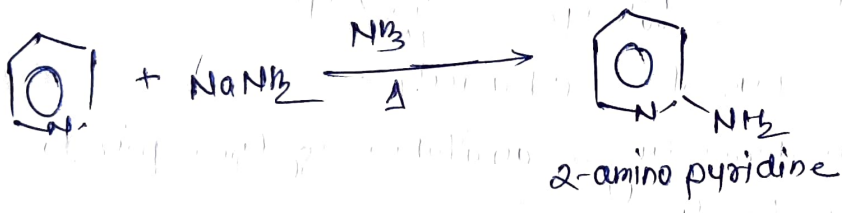
At C₂ & C₄, generate N⁺ that is less stable so favoured at C₃ position



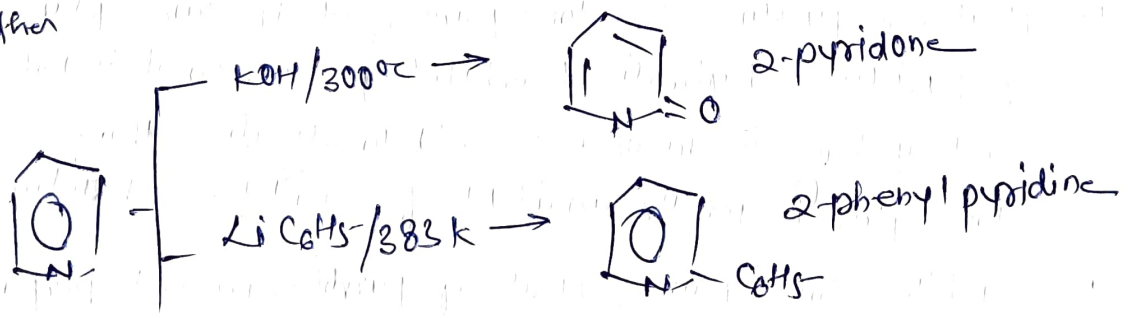


③ Nucleophilic Substitution Reaction - At C₂ position > C₄

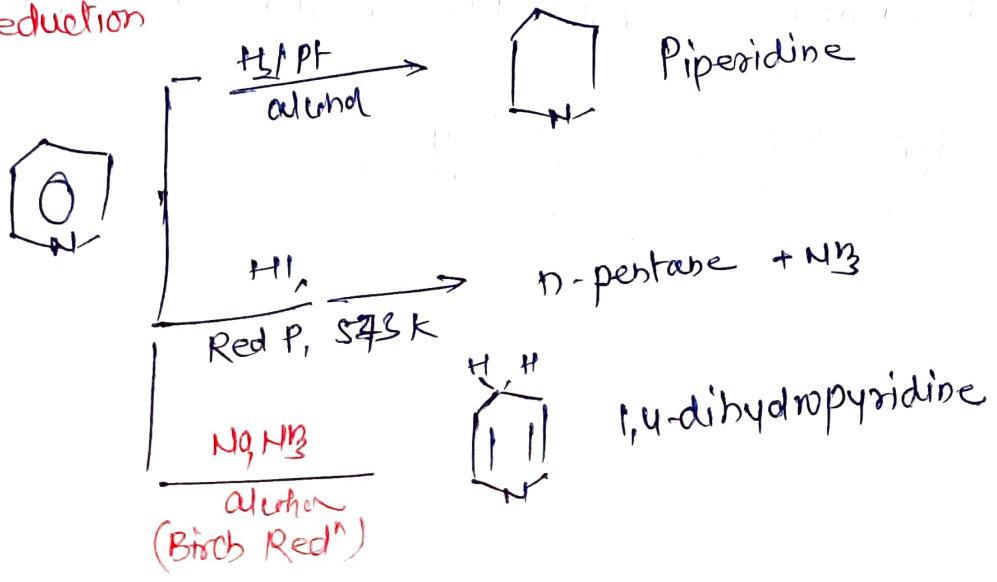
① Chichibabin Reaction



② Other



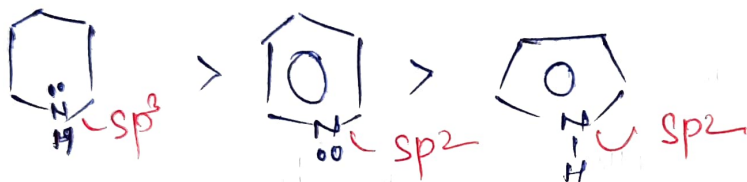
④ Reduction



Medicinal Uses of Pyridine

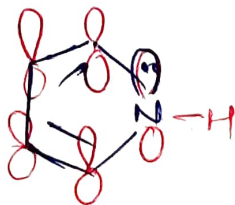
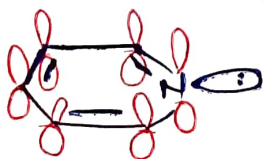
- ① Antituber agent - Isoniazide
- ② Antibacterial agent - Sulfapyridine, Sulfasalazine
- ③ Anticholinesterase \rightarrow pyridostigmine
- ④ Proton pump Inhibitors (anti ulcer) - Omeprazole, pantoprazole
- ⑤ Vitamins \rightarrow Vit B₂, Vit B₆
- ⑥ Antihistaminics - Mepyramine
- ⑦ Anticholinergic \rightarrow Tropicamide

Basicity of Pyridine

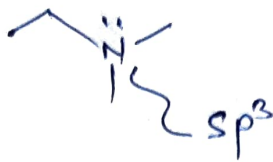


pyridine $>$ pyrrole (basicity)

- \hookrightarrow Basicity is depending on availability of lone pair to reaction or donation
- \hookrightarrow N-atom of pyridine has lone pair of e⁻ in same plane of pyridine hybridized orbital plane, so it is not participating in resonance or delocalization thus lone pair is readily available for acid base reaction.
- \hookrightarrow while lone pair of N-atom of pyrrole present perpendicular to plane of hybridized orbital & participate in resonance & not readily available for reaction



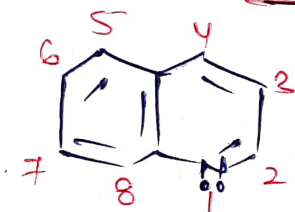
pyridine < piperidine or Aliphatic amine



- ↳ More electro -ve
- ↳ More s-character
- ↳ e^- closely held toward N-atom
- ↳ Less available for reaction
- ↳ So lesser basic than aliphatic amine

==: ==

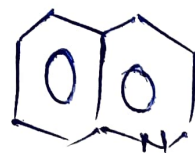
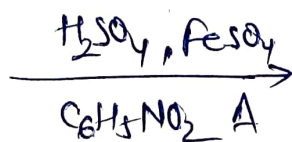
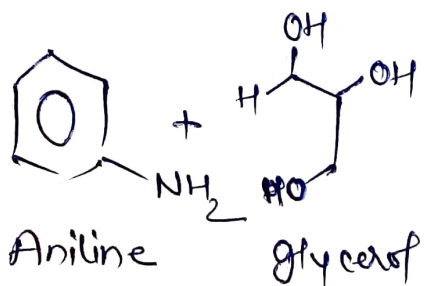
6. Quinoline



- ↳ fused aromatic heterocyclic compound
- ↳ 1-aza naphthalene
- ↳ benzo(b)pyridine
- ↳ weak base

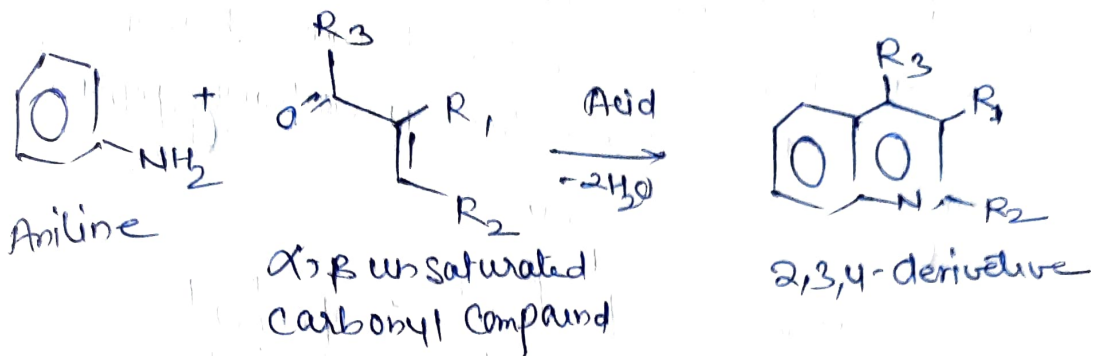
Synthesis -

① Skraup Quinoline Synthesis

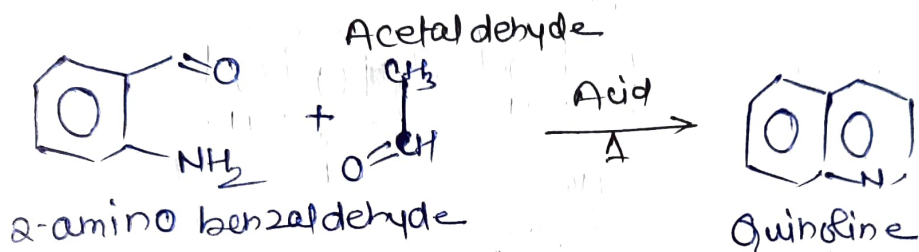


Quinoline

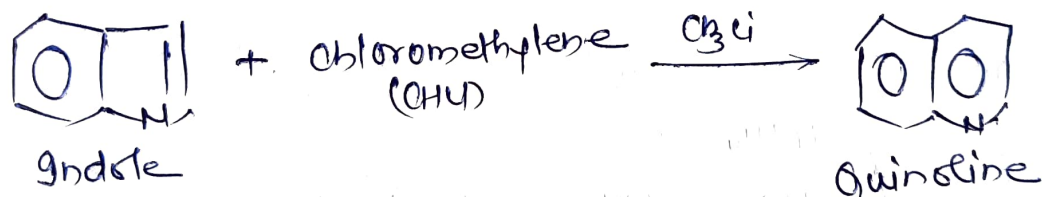
② Doebner-Miller Synthesis



③ Friedlander Synthesis

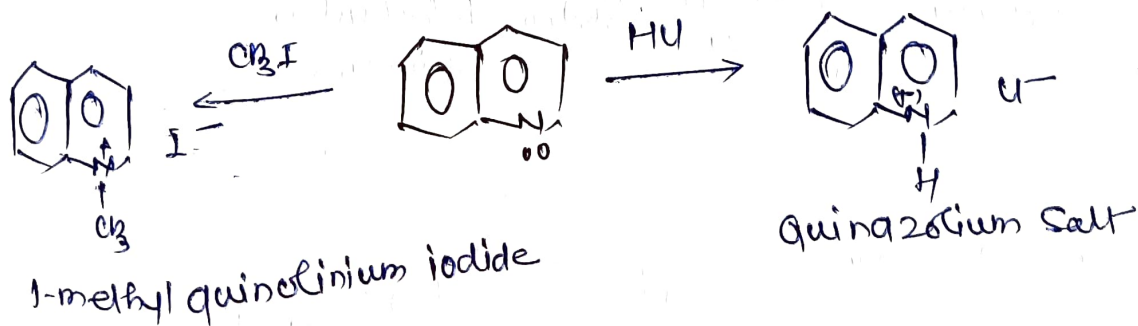


④ from indole



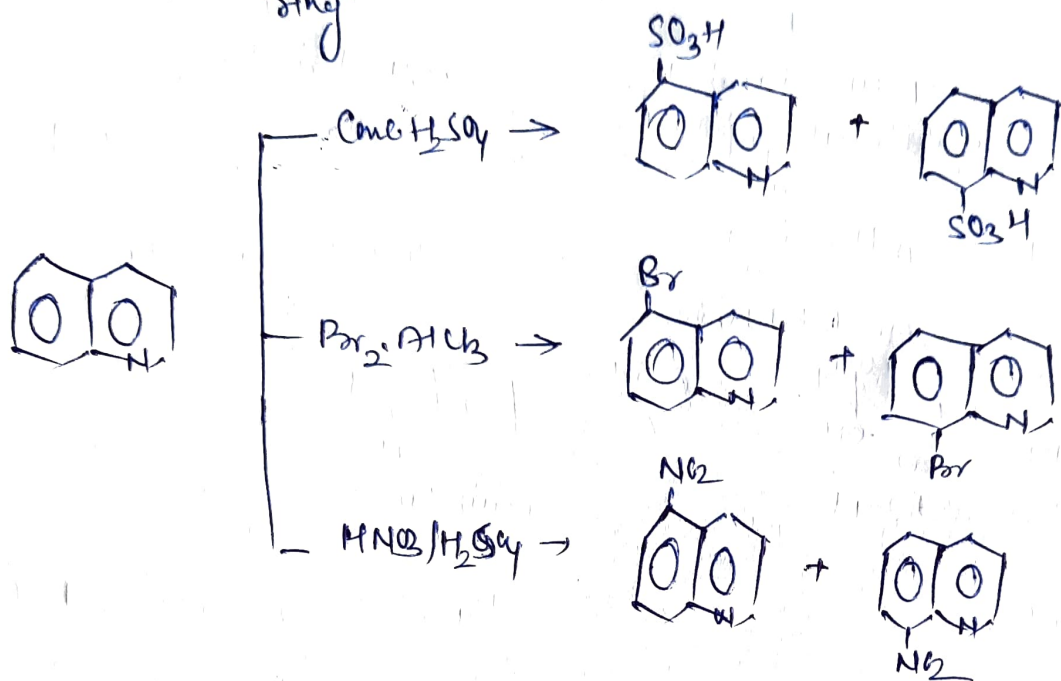
Chemical Reaction

① Electrophilic addition N-atom

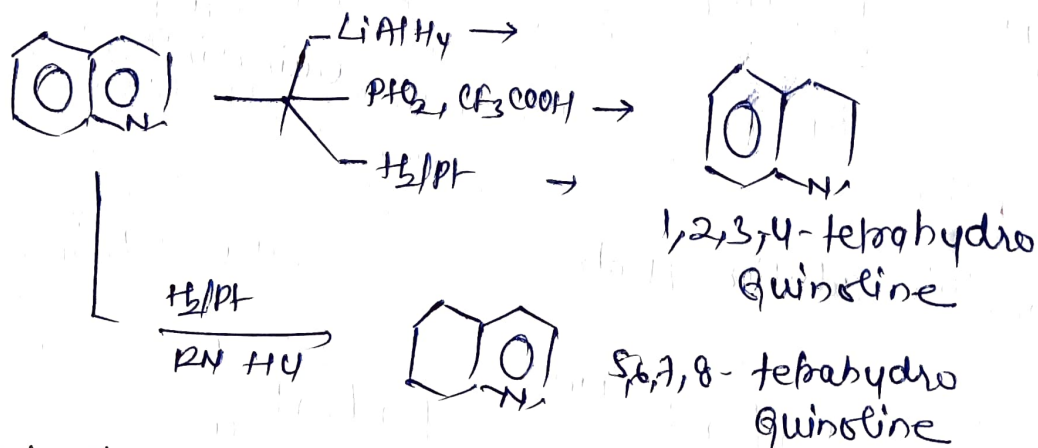


② Electrophilic Substitution Reaction

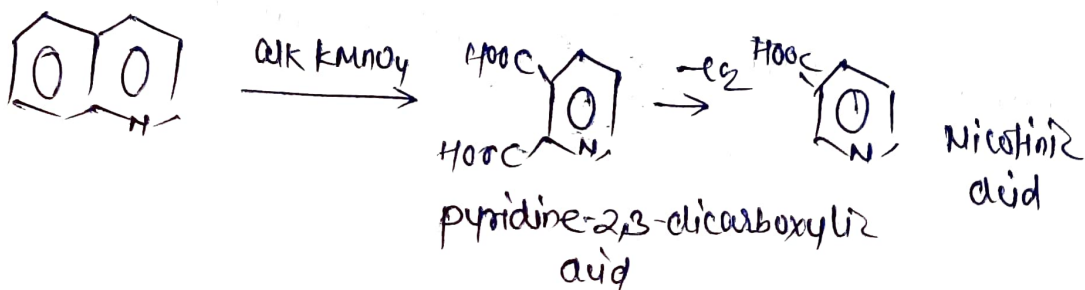
↳ Occurs at C5 & C8 position because benzene ring has more e⁻ rich than N-containing pyridine ring



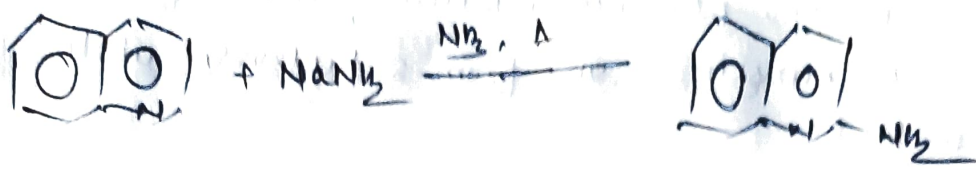
③ Reduction



④ Oxidation



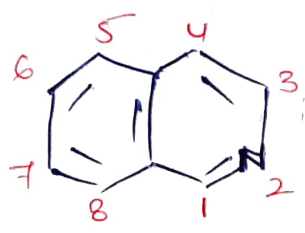
⑤ Nucleophilic Substitution - at C2 position



Uses -

- ① Antimalarial - Quinine, Cinchonine, Primaquine
- ② Antiprotozoal - Quinacrine
- ③ Anesthetic - quinaldine
- ④ Anti HIV - Saquinavir
- ⑤ Anti UTI - norfloxacin

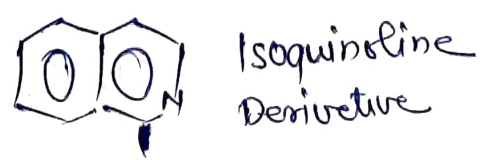
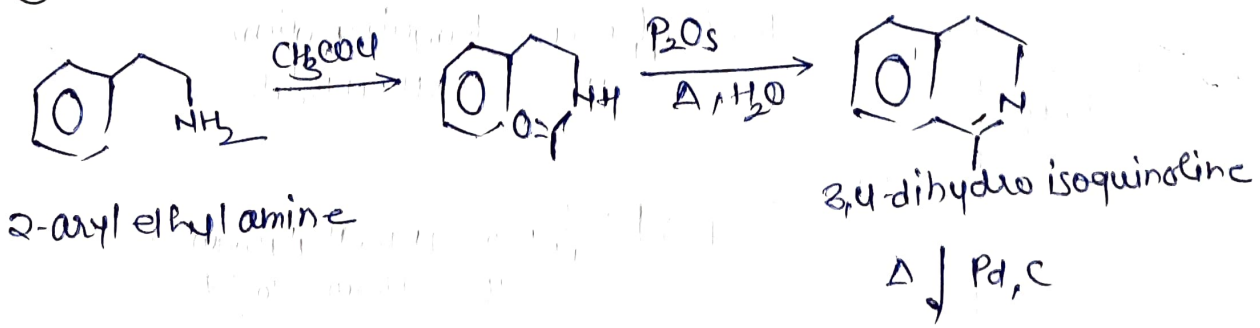
7. ISOQUINOLINE



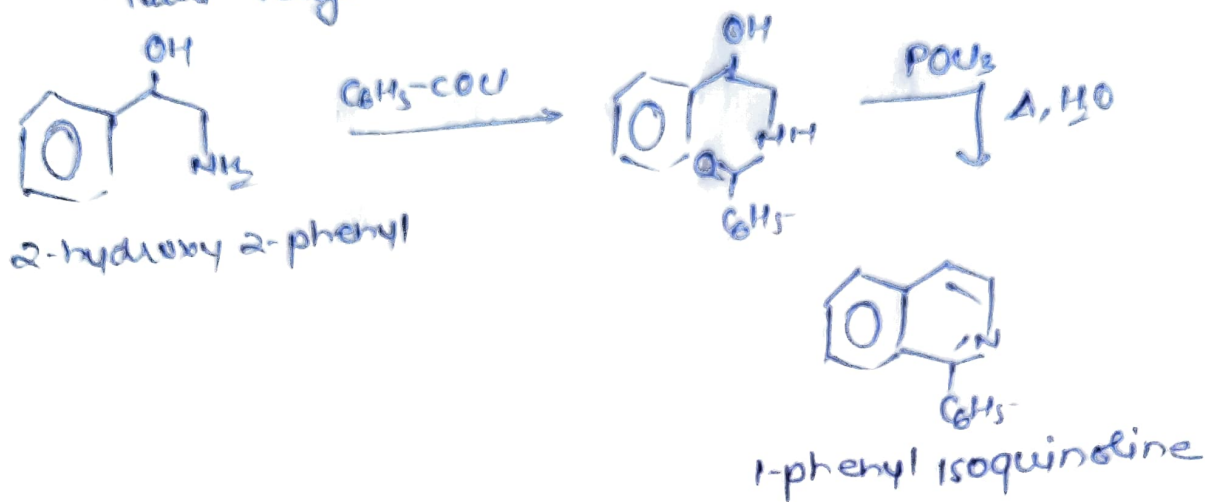
- 2-quinazolinone
- Benzo [c] pyridine
- Aromatic ring, all atom sp²
- weak base

Synthesis

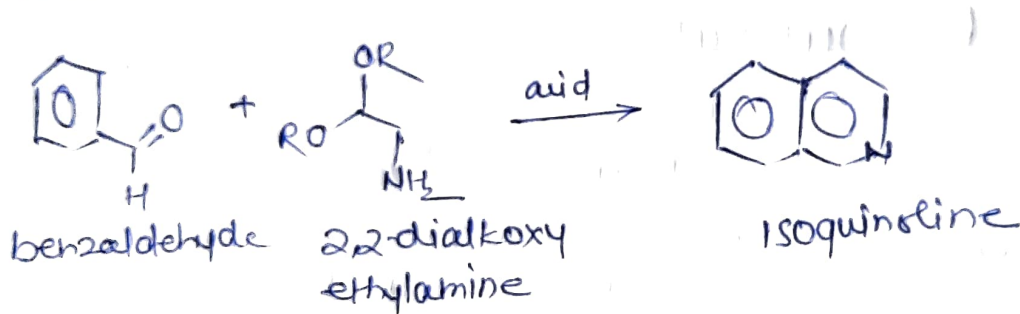
① Bischler-Napieralski Isoquinoline synthesis



② The Pictet-Gams Synthesis
 → Modified Bischler-Napieralski method, - direct fully
 aromatic isoquinoline syn. from 2-hydroxy-substi-
 tuted reagent

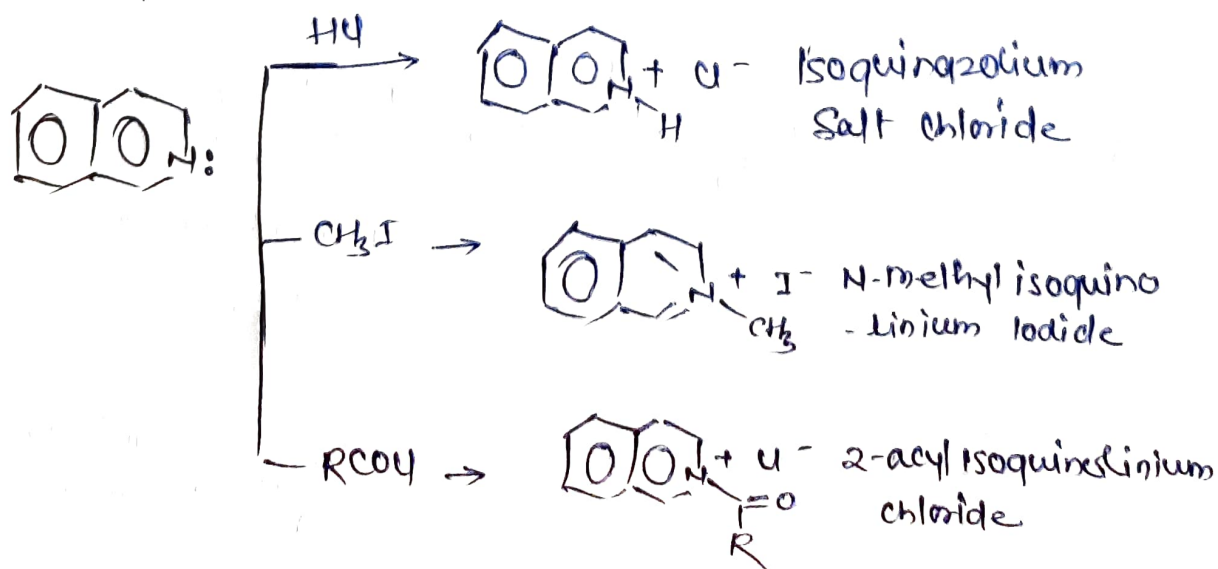


③ Pomerantz-Fritsch Synthesis

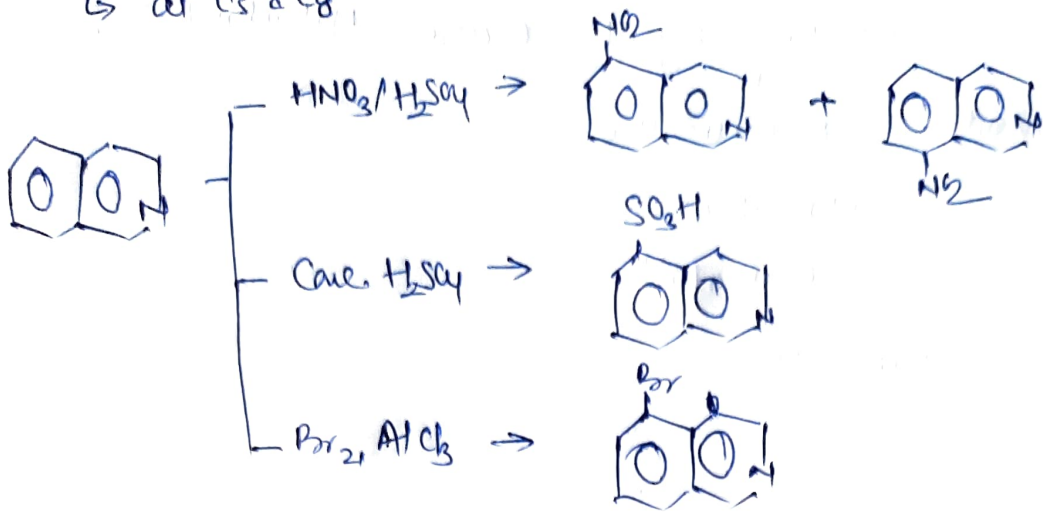


Chemical Reaction

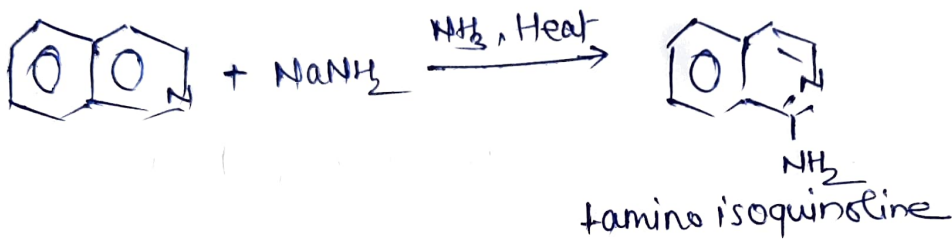
① Electrophilic Addition to N-atom



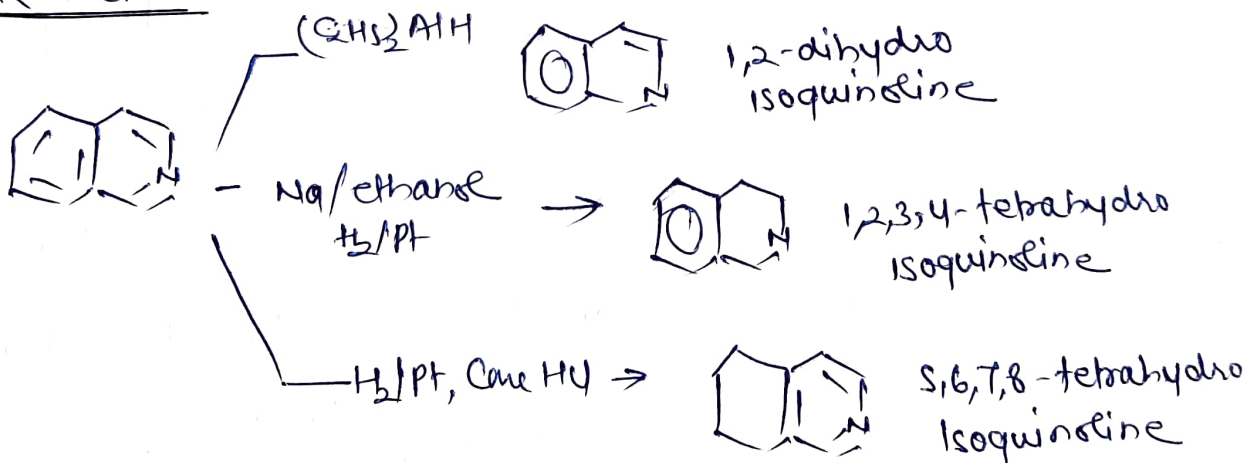
② Electrophilic Aromatic Substitution
 ↳ at C5 & C8



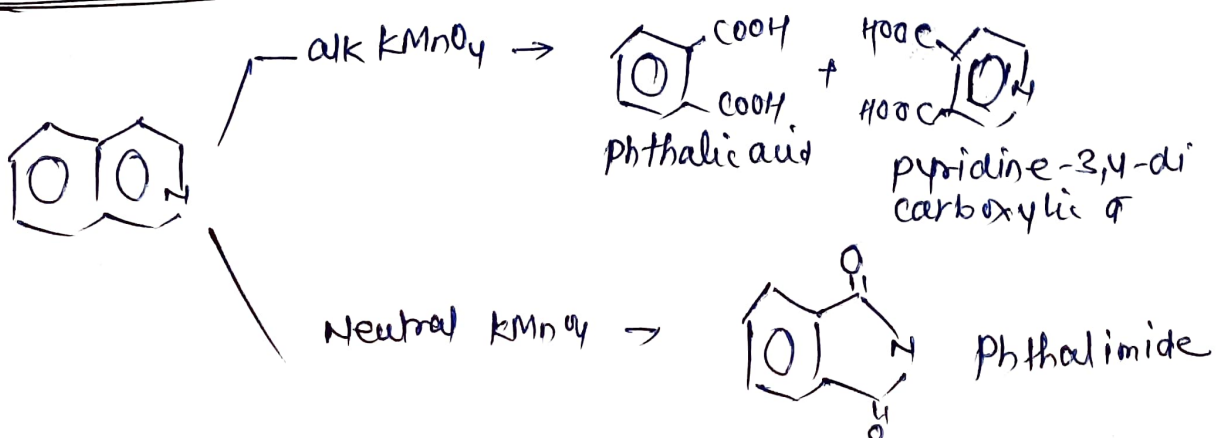
③ Nucleophilic Substitution - at C9 position



④ Reduction



⑤ Oxidation



Medicinal Uses -

- # Neuromuscular blocking Agent - Curare Alkaloid
 - # Antispasmodic - papaverine
 - # Antitussive - Noscapine
 - # Antihypertensive - Quinopril,
 - # Vasodilator → papaverin
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