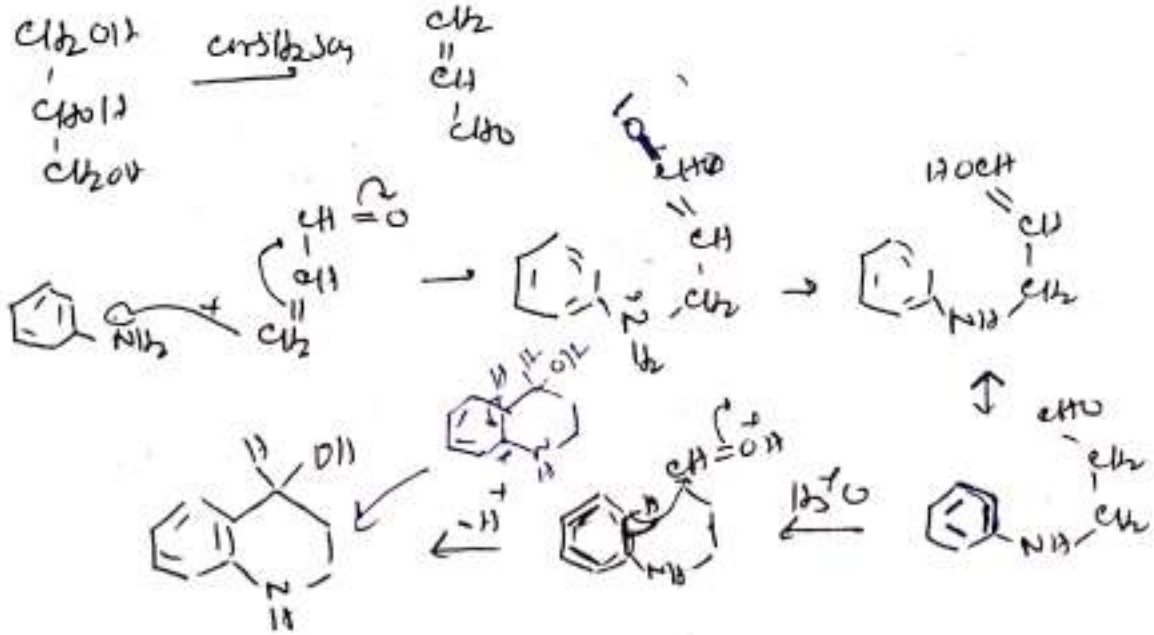
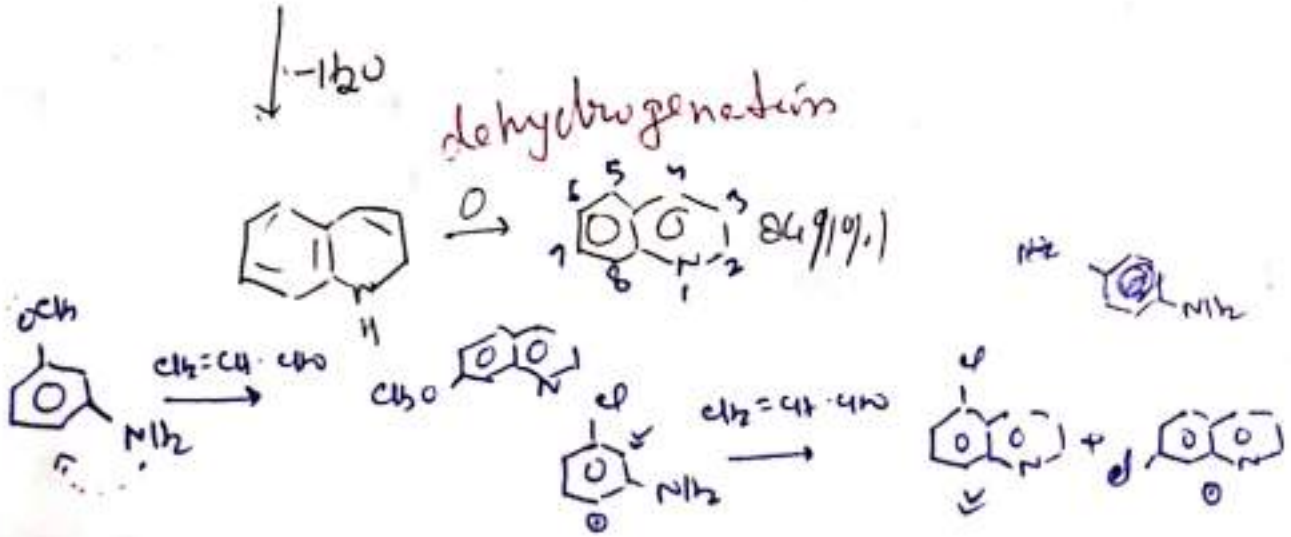
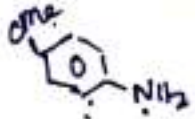
Quinoline

Skraup Synthesis → very important method, by heating a mixture of Aniline & glycerol, Conc. H_2SO_4 & nitrobenzene

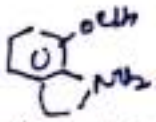
$FeSO_4$ Nitro benzene acts as oxidising agent & $FeSO_4$ makes the reaction less violent. Arsenic acid may also be used in place of Nitro benzene. Since the former is better (reaction is less violent. Mechanism is not certain. But generally believed that first step is conversion of glycerol into acraldehyde. which than undergo 1, 4 addition. Acraldehyde itself is not used since it polymerises under the condition of the experiment itself.





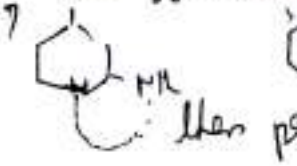


O - Substituted Aniline - 8
P - " " - 6 ✓
m - " " - 5&7

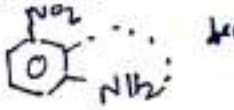


In general the Skraup Synthesis may be carried out with any primary aromatic amine in which at least one position ortho to amino gp is vacant.

Note → If strong o/p directing gp is present in the m-position eg OMe then 7-substituted quinoline is formed. If weakly o/p-directing eg Cl, then both 5&7 substituted quinoline is formed.



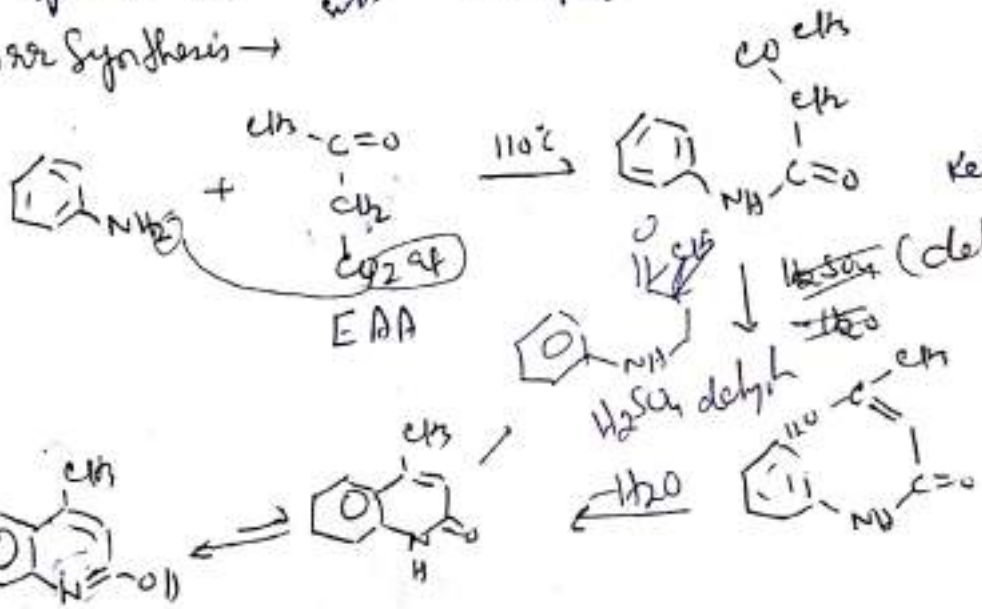
If m-substituent is m-directing then predominate product is 5-substituted quinoline.



because -I at ortho
-R at para

quinoline ring

(b) Knorr Synthesis →

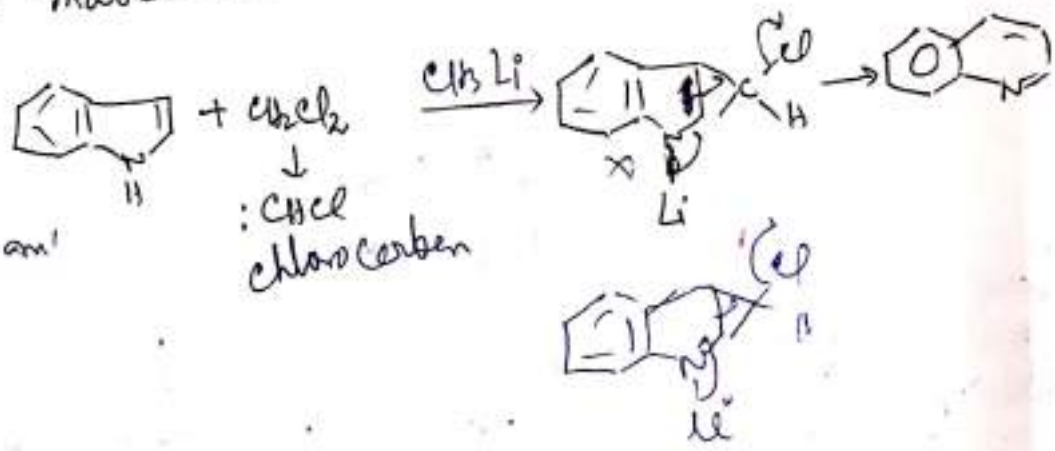


EAA

Keto Enol

(dehydration)

(c) from Indole → when CH_3Li / CH_2Cl_2



am

:CHCl
chlorocarben

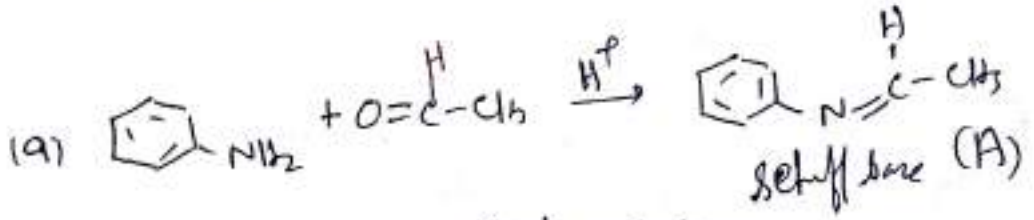
The Doebner-Miller Synthesis → closely related to Skraup Synthesis

(i) utilized an aromatic amine & proceed through intermediate formation of dehydro quinoline

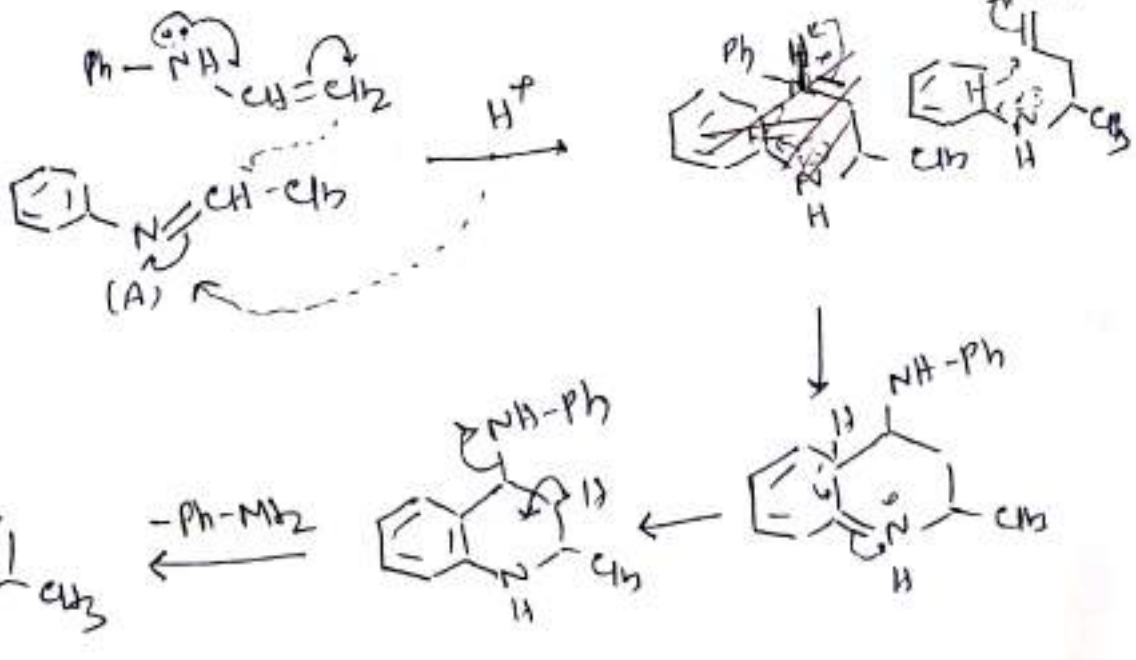
(ii) The reagent which bring dehydrogenation is different than Skraup simple synthesis.

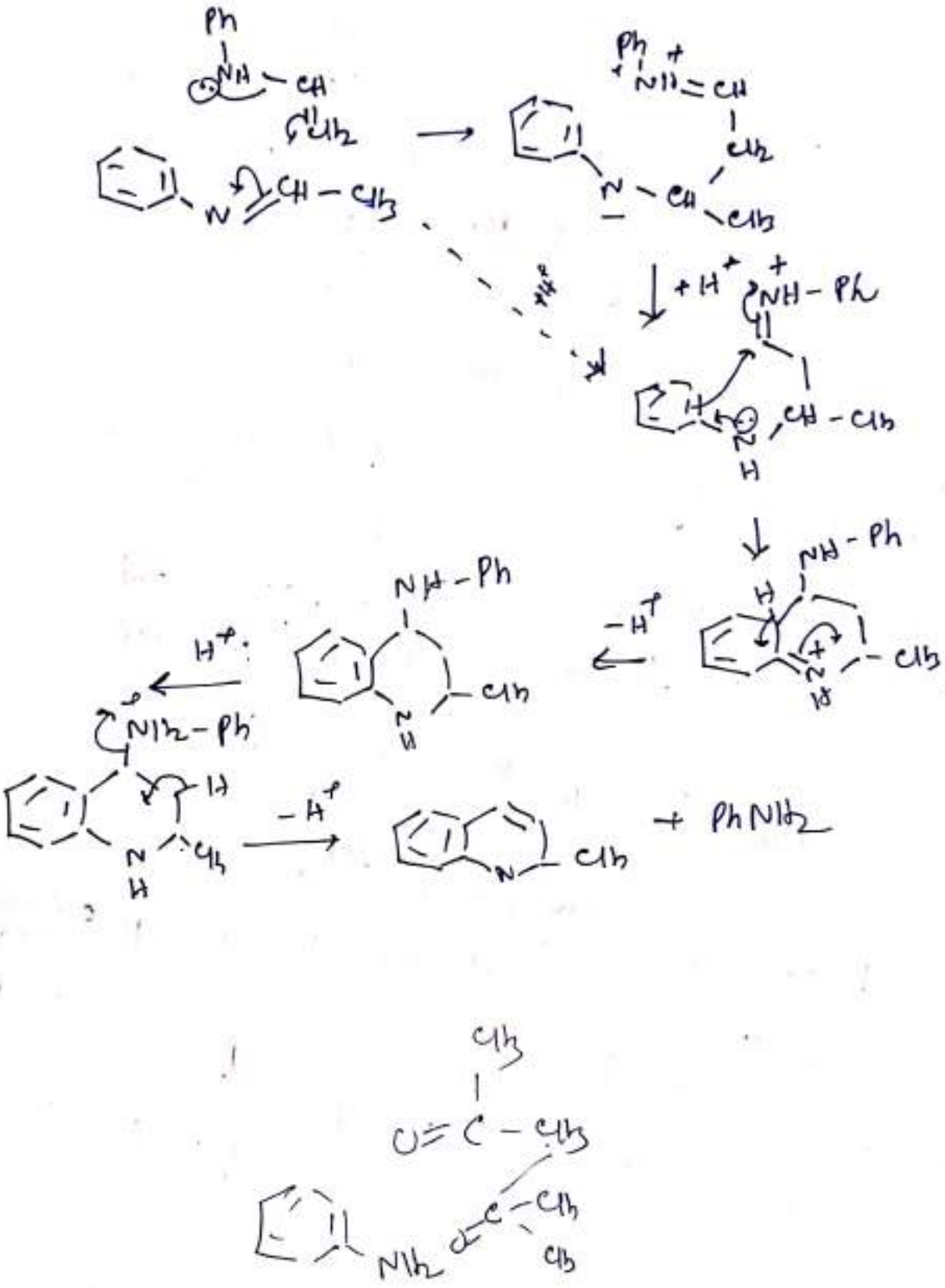
(iv) one molecule of aromatic amine & two molecule of an aldehyde are heated in presence of HCl.

(v) two molecule of schiff base (aniline + acetaldehyde) self condense to form the quinoline nucleus.

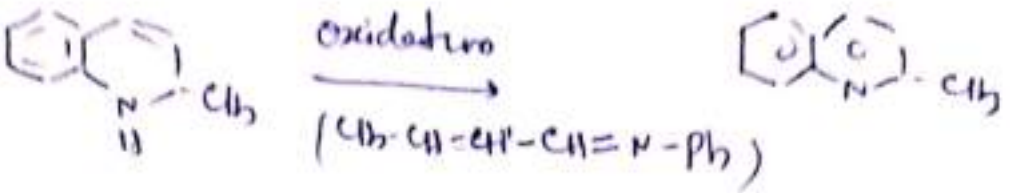
(a) 

(b) Ph-N=CH-CH3 ⇌ Ph-NH-CH=CH2 (B) (tautomerisation) (enol form of aldehyde)

(c) 



f

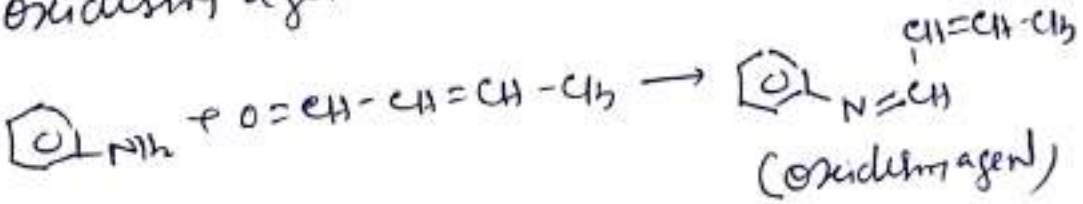


(VII) During the reaction crotanaldehyde is formed from CH_3CHO (acetaldehyde) in presence of acid

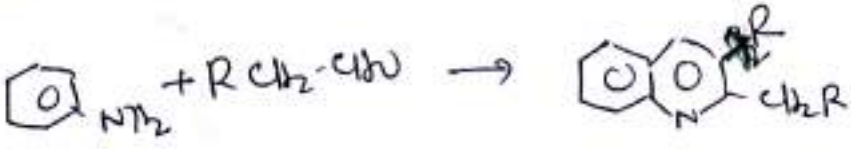
$$2\,CH_3CHO \xrightarrow{H^+} CH_3-CH=CH-CHO$$

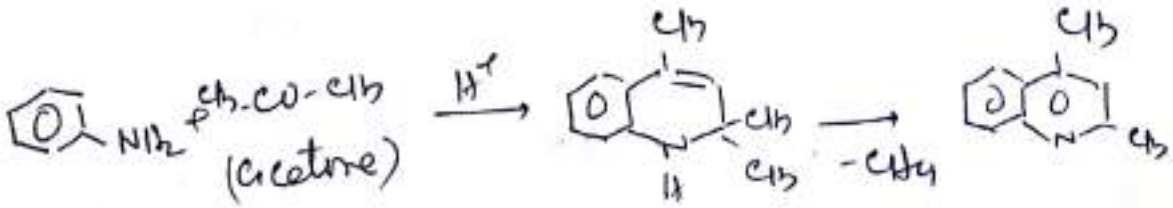
aldol followed by elimination of water

(VIII) This crotanaldehyde reacts with aniline to form Schiff base which acts as oxidising agent.

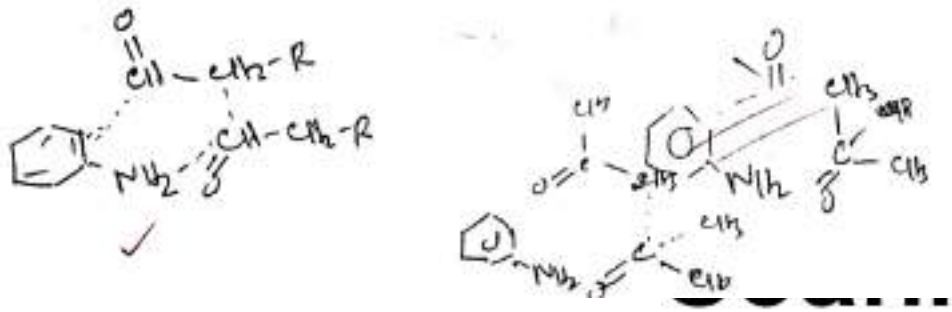


derivatives



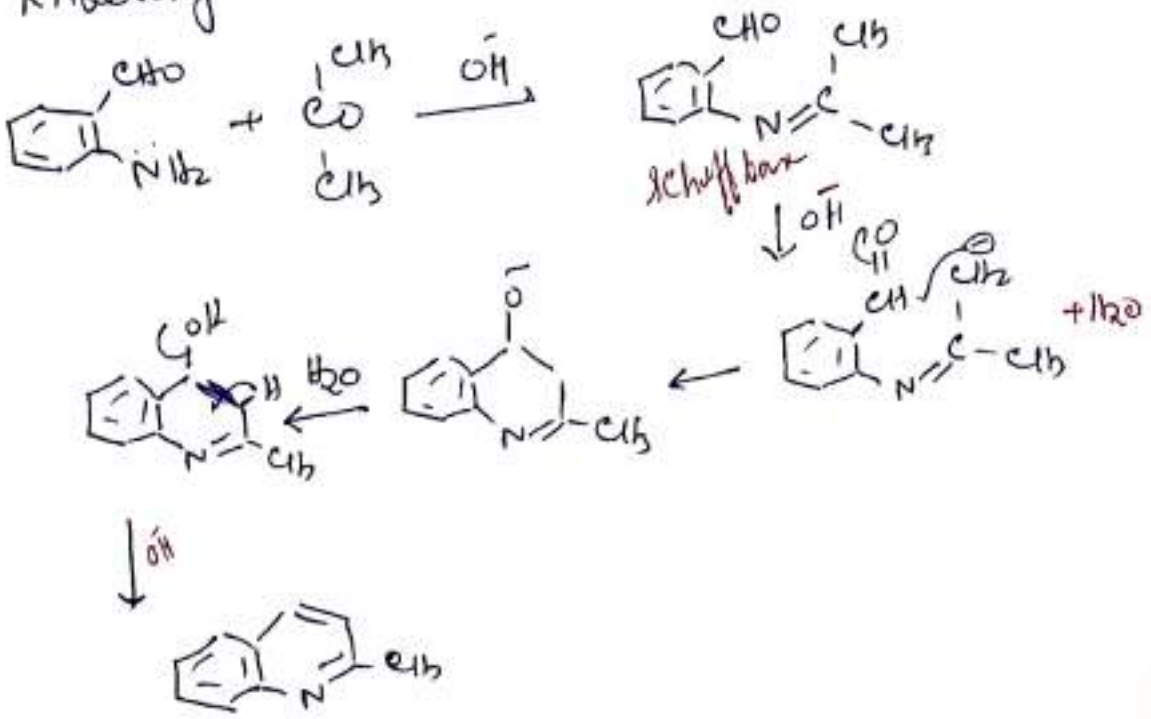


Tip

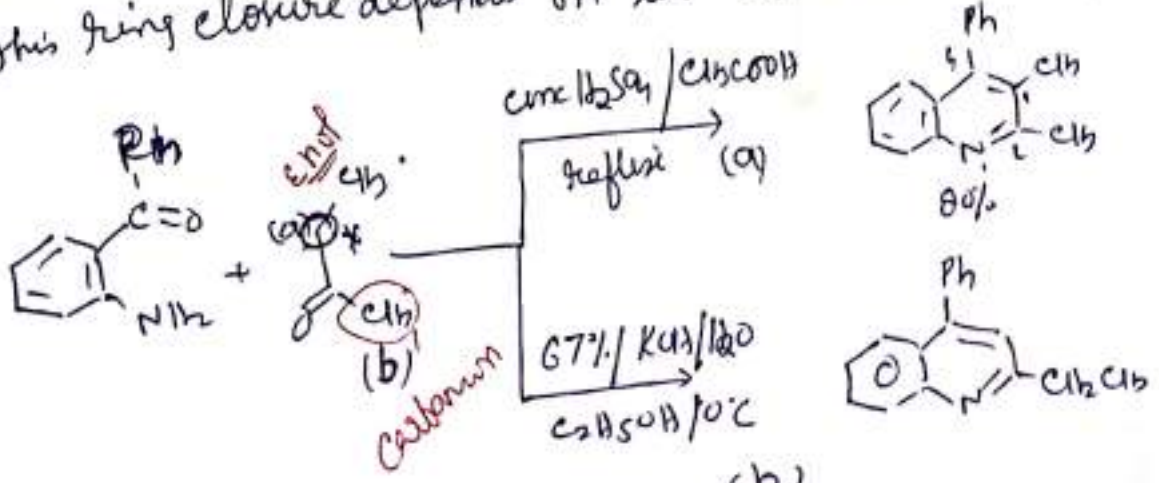


The Friedlander Syn ⟶ o-amino benzaldehyde or o-amino acetophenone is condensed with aldehyde or Ketone containing an active methylene gp in refluxing alcoholic NaOH soln in to yield QUINOLINE.

The first step is the formation of the schiff base followed by ring closure to quinoline by a Knoevenagel condensation.



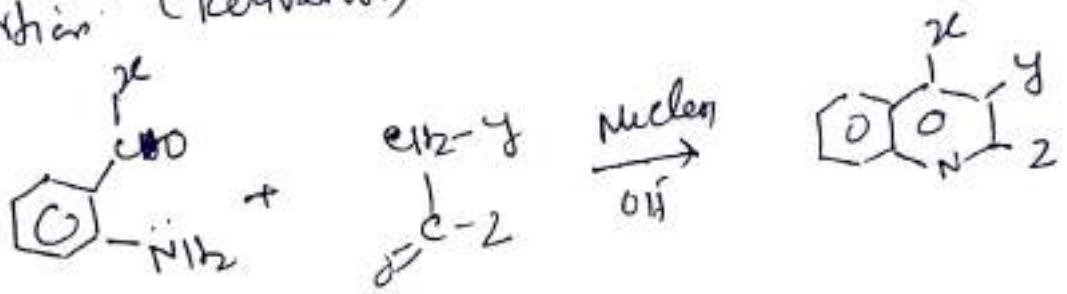
This reaction is also effective in acidic medium. This ring closure depends on the conditions employed.



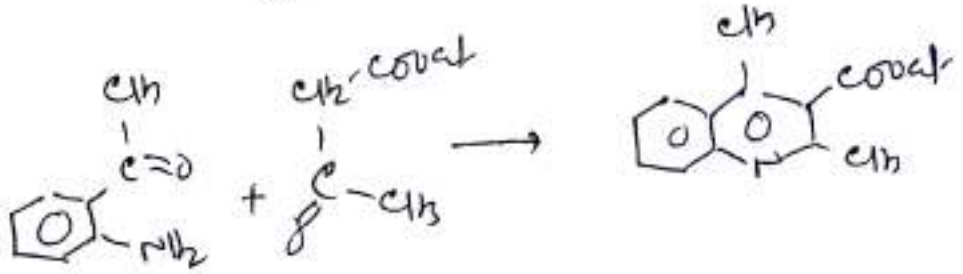
(b)

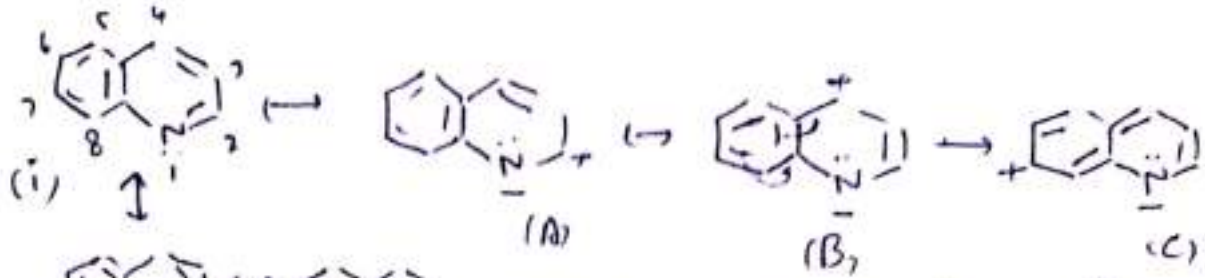
This method is particularly useful for preparation of 2 substituted quinoline derivative which is not easily accessible by other means

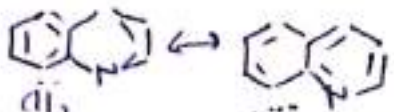
For 2 substituted quinoline the substitution is taken in aldehyde or ketone portion (Derivative)



eg



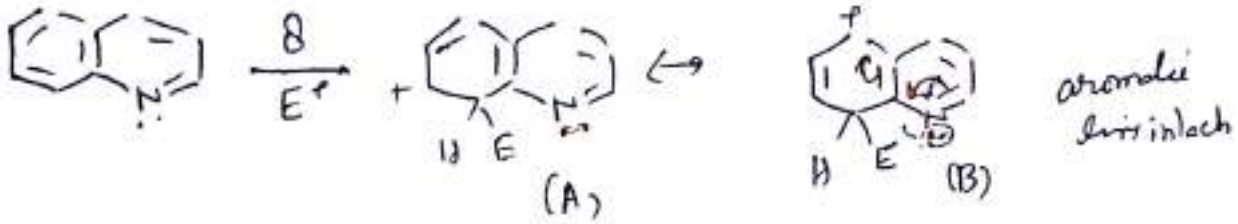


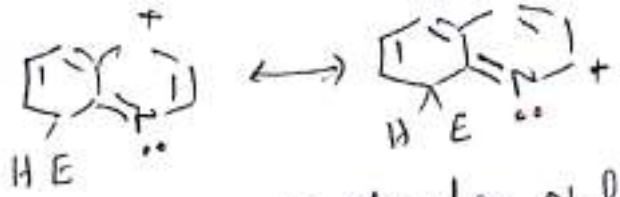


are like Kekul structure

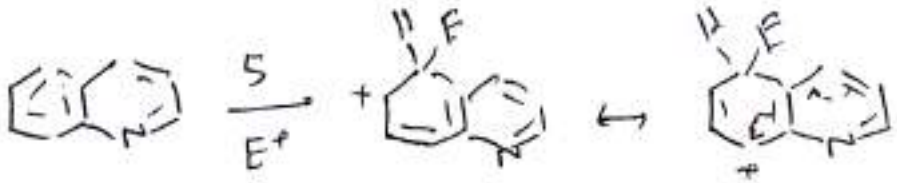
A to D are polar structure which shows electron withdrawing property of nitrogen

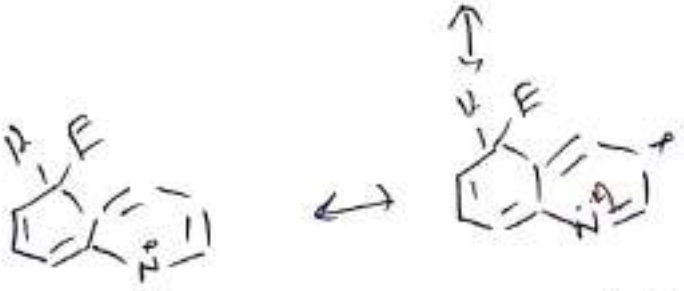
Electrophilic Substitution →





in all structure N has complet octate





Nitrogen carries +ve charge & has tendency of $\bar{e}$.

Electrophilic substitution reaction →

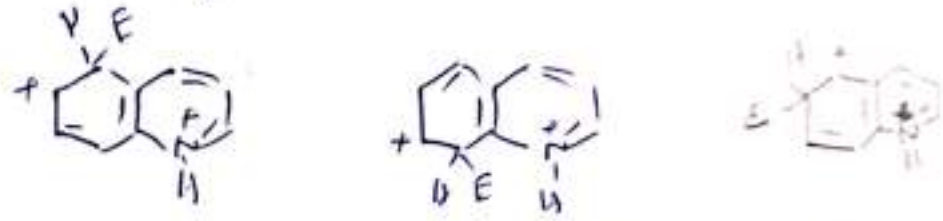
① Electron rich nitrogen atom of quinoline is the main cause for attack ~~of~~ by electrophile -

② Nitrogen atom has considerable deactivating effect on the ring towards electrophilic attack.

(3) electrophilic attack is comparable in nitro naphthalene just as the pyridine with nitro benzene

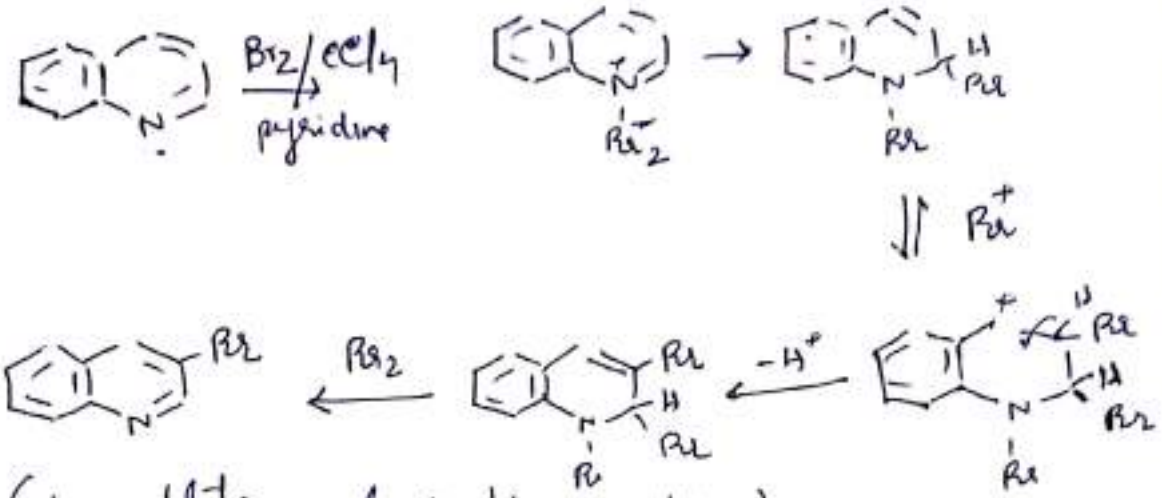
(4) electrophilic subs require severe condition though less than those in case of pyridine.

(5) attack in protonated quinoline takes place in carbocyclic ring at C-5 & C-8 position because of corresponding intermediate. (in which aromaticity of the heterocyclic ring preserved)

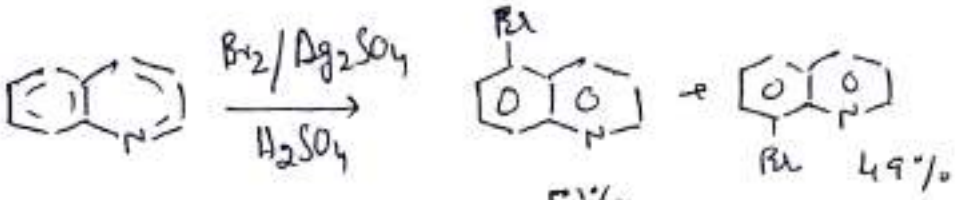


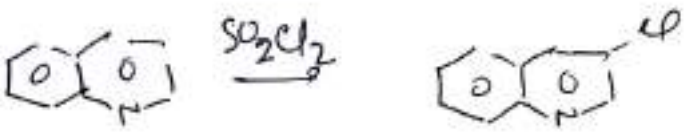
(6) As it is deficient heterocycles, quinoline is less reactive than benzene in acid solution.

Halogenation →

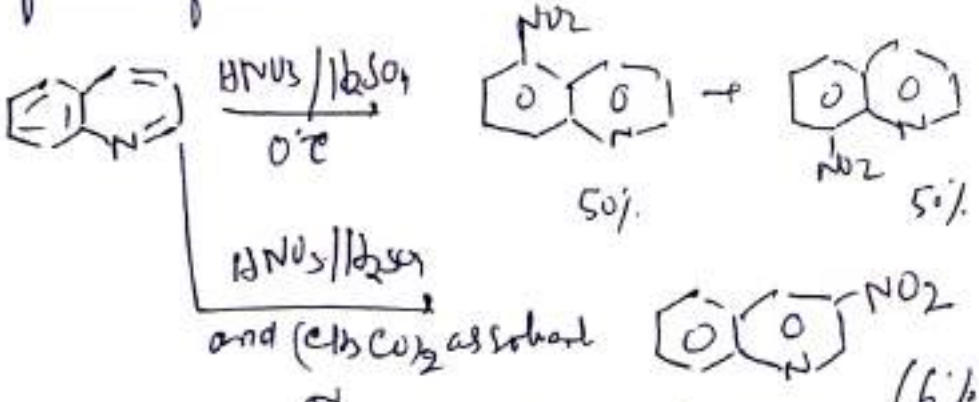


(this is (by addition-elimination reaction)





Nitration → The pyridine ring of quinoline is already π e⁻ deficient and becomes more e⁻ deficient by protonation of the ring nitrogen. Acidic electrophilic reagents thus show preference for attack in the benzene ring.

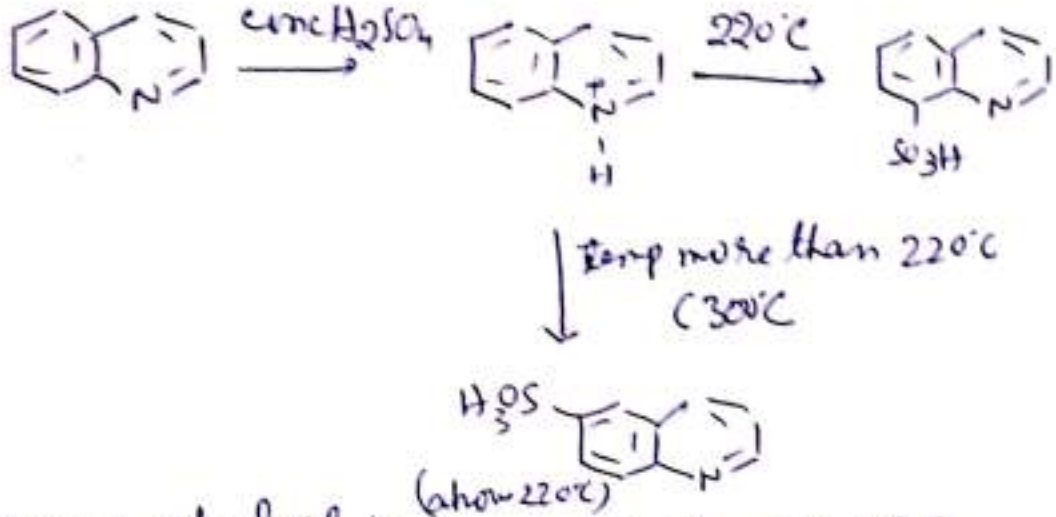


and (CH_3CO_2 as solvent

or

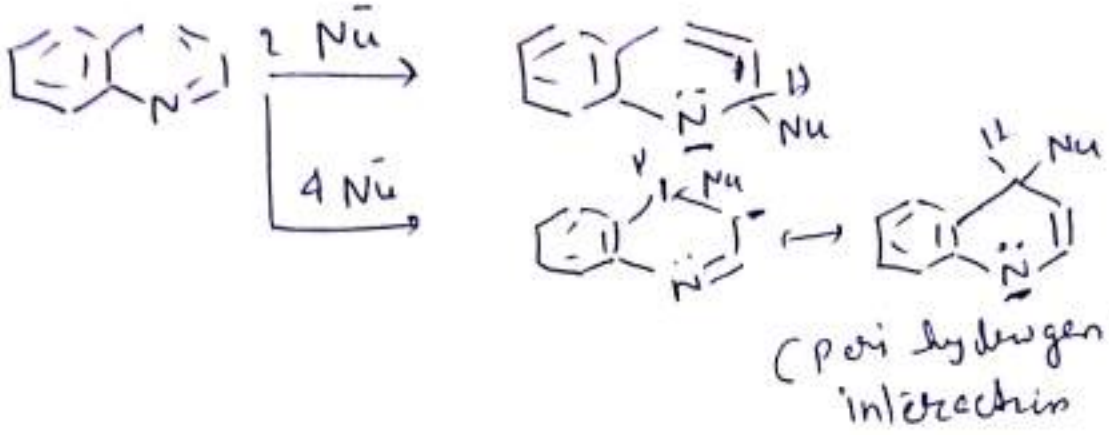
N_2O_4 (dinitrogen tetra oxide) with small quantity of 6 & 8 nitroquinoline

Sulfonation –



because at high temp, 5 & 8 isomer are rearranges to quinoline 6 sulfonic acid which is thermodynamically more stable

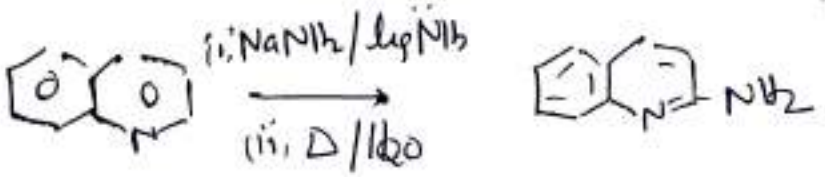
Reaction with Nucleophile –



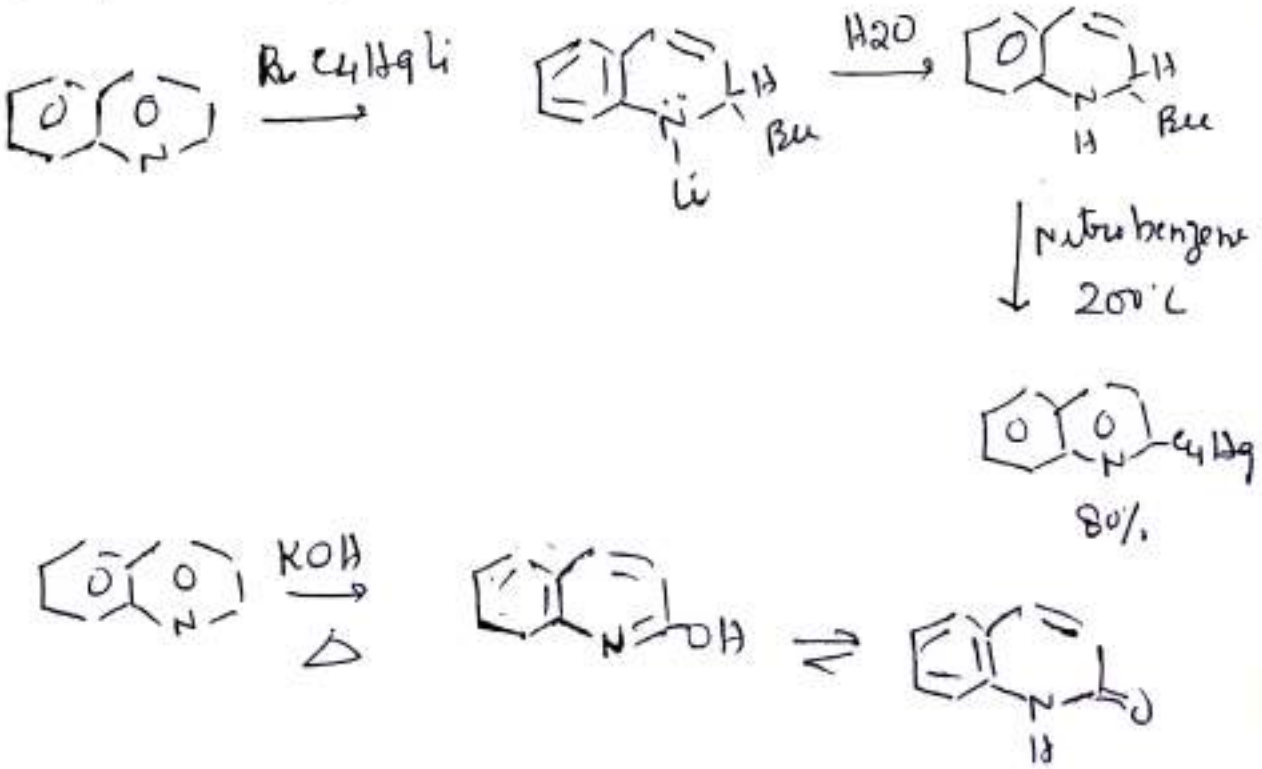
Reaction with Nucleophile - at position 2 is preferred site of attack.

If this position is occupied then add at position 4.

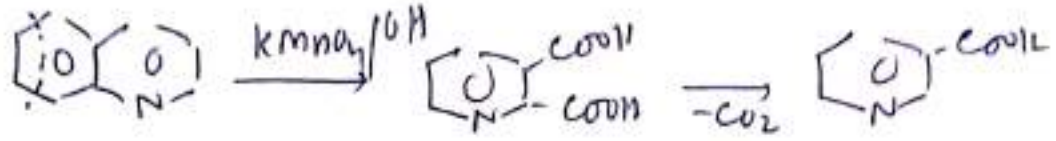
Tishitischi babin Reaction



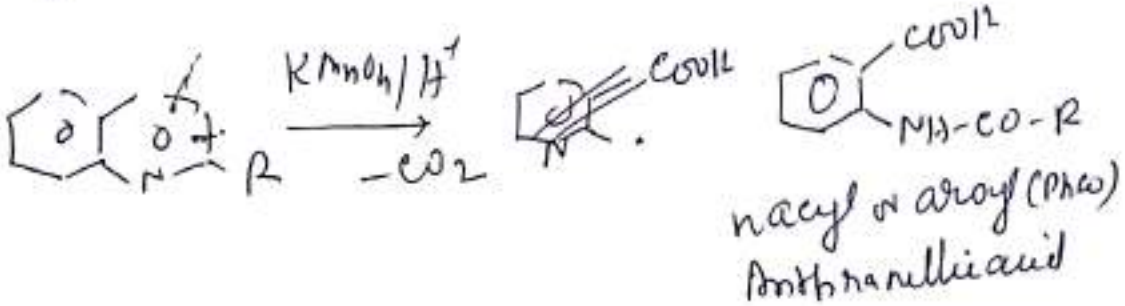
Alkyl & aryl lithium compd are also attack at the position 2 and the lithio derivative can be hydrolyzed to 2 substituted quinoline. Quaternization at the nitrogen atom reinforces the ability to react with nucleophilic reagent.



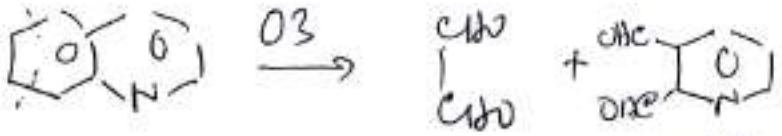
Reaction with oxidising agent.

(1) 

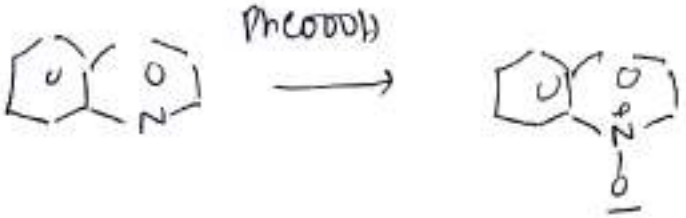
Benzene ring is oxidised because N containing ring is $\bar{e}$ deficient

(2) 

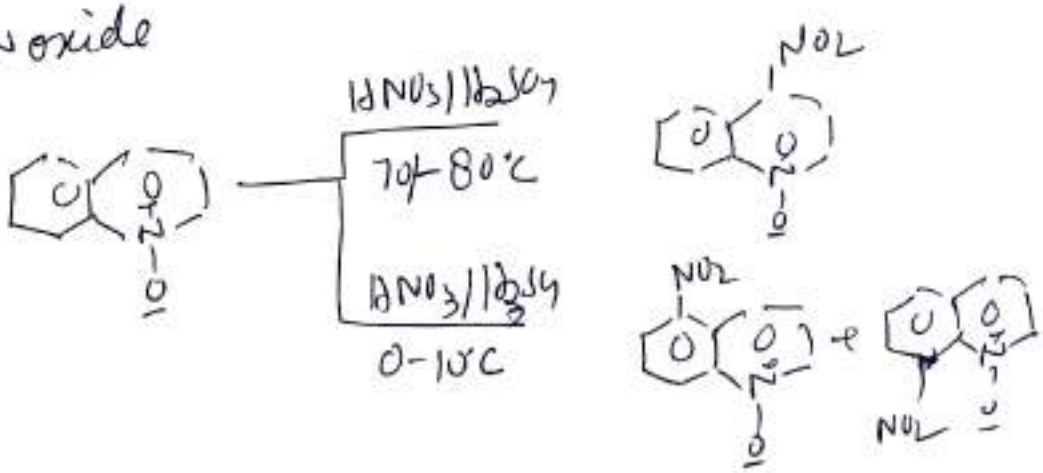
nacyl or aroyl (PhCO)
Anthranillic acid

(3) 

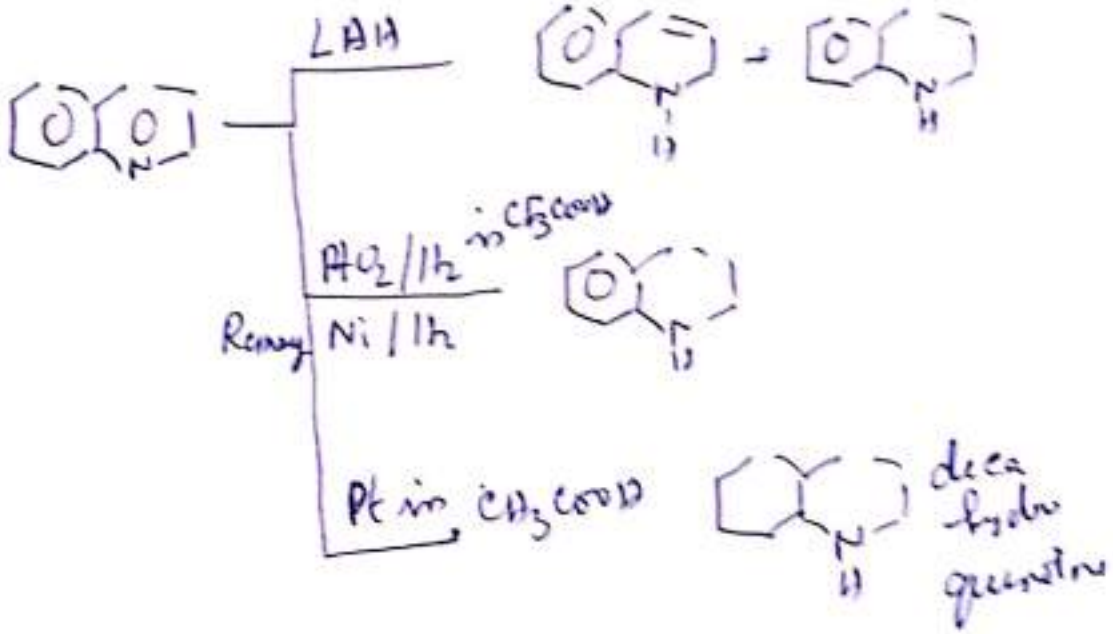
pyridine, 2,3 dicarboxy aldehyde.

(4) 

Note Quinoline N oxide shows reaction analogous to pyridine N oxide



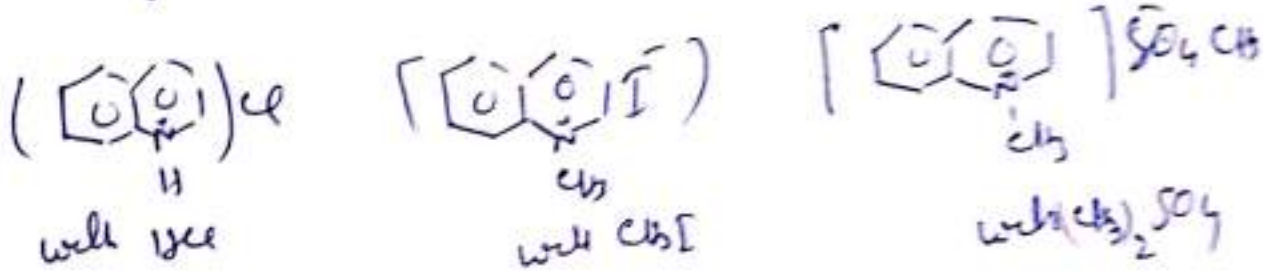
Reaction with reducing agent

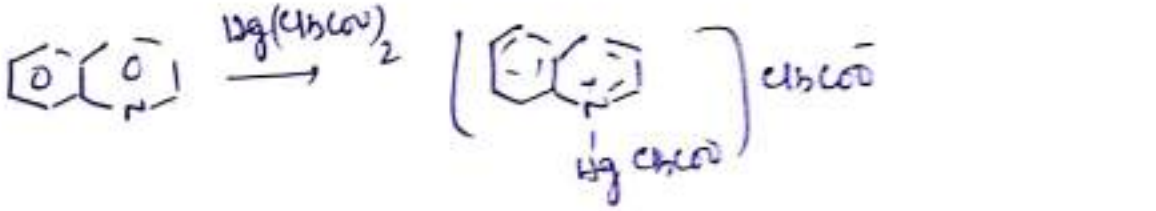


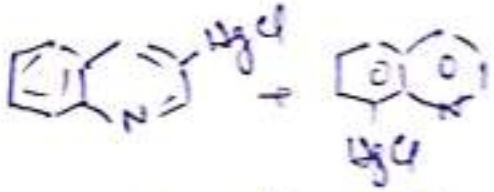
Reaction as Base

Quinoline is slightly weaker base than pyridine because ~~lone pair~~ π bond e⁻ are delocalized in two ring. So availability is less than pyridine. Nitrogen becomes more electron deficient than residual sp^2 electron's lone pair

(i) (ii) It is an tertiary base & forms salt with inorganic acids, alkyl halide, alkyl sulphate

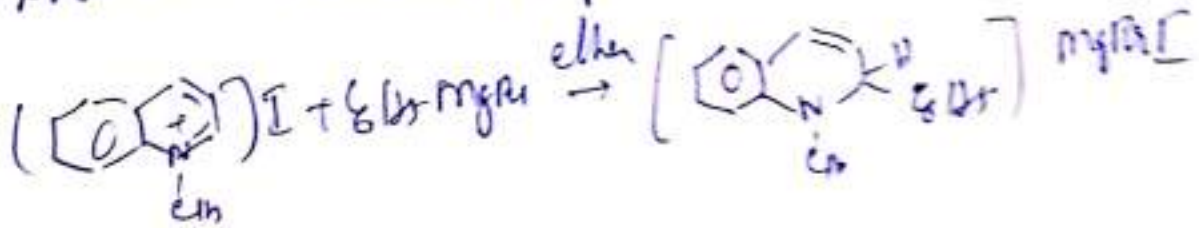


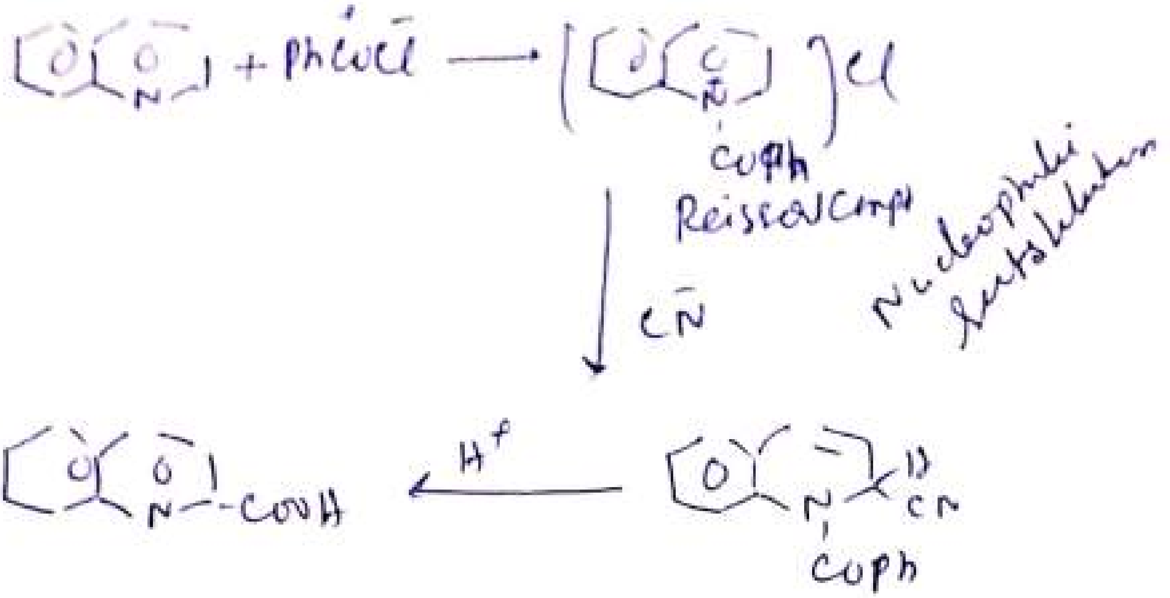




Note

The alkyl quinolinium cation is readily attack even weak nucleophile like C_6H_5MgBr (grignard reagent the resulted compd 1-methyl-2-phenyl-1,2-dihydro quinoline also known as Reissert compd.





misclenious