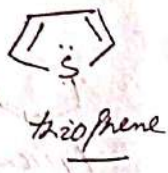
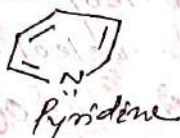


Heterocycles

Heterocyclic compounds can also be aromatic since for the application of Hückel's rule what one needs is a ring of atoms, all with unhybridized 'p' orbitals, in a planar arrangement in order that the 'p' orbitals overlap in a continuous ring. Thus e.g. the heterocyclic compounds are all aromatic. Pyrrole, furan and thiophene in fact represent 1-hetero-2,4-cyclopentadienes and contain a butadiene unit bridged by a heteroatom bearing lone electron pairs. In electronic structure, these three compounds are similar to cyclopentadienyl anion.

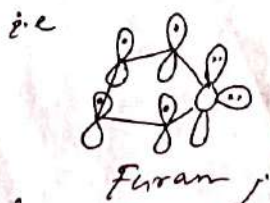
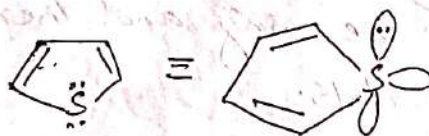
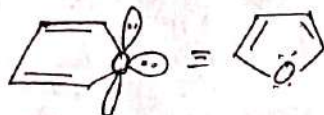


In pyrrole only four π e's are contributed by the carbon atoms of the ring. To make an aromatic sextet the sp^2 hybridized nitrogen then contributes two electrons. Pyrrole is far less basic than pyridine ($pK_b = 8.8$). Because these apparently unsh-



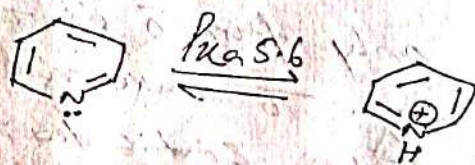
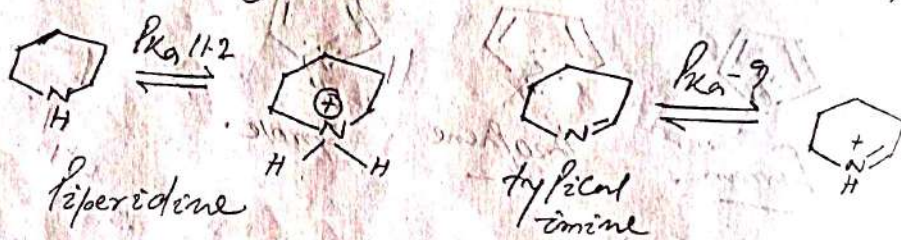
ared e's are in the aromatic π cloud, these are not readily available for bonding with a proton.

Both furan and thiophene have two pairs of e's on the heteroatom and therefore, combine the structural features of pyrrole and pyridine. One pair of e's is in the six-electron π -system and other lies in the plane of the ring.

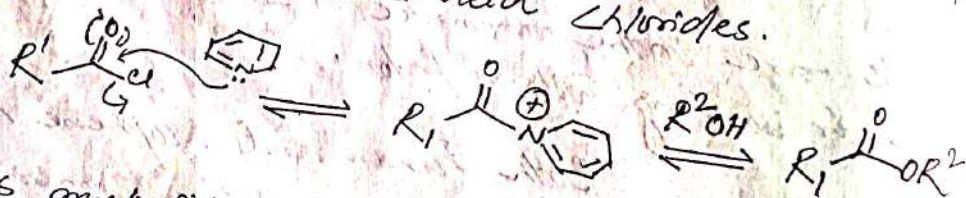


Pyridine

The nitrogen atom in the pyridine ring is planar trigonal with the lone pair in the plane of the ring, making it an imine. Most of the imines, however, are unstable intermediates in carbonyl group reactions but in pyridine we have a stable imine - ^{stable} because of its aromaticity. All imines are more basic than saturated amines and pyridine is a base with a pK_a of 5.5. This means that the pyridinium ion is about as strong an acid as a carboxylic acid.



Pyridine is a reasonable nucleophile for carbonyl group and is often used as a nucleophile catalyst in acylation reactions. Esters are often made in pyridine solution from alcohols and acid chlorides.

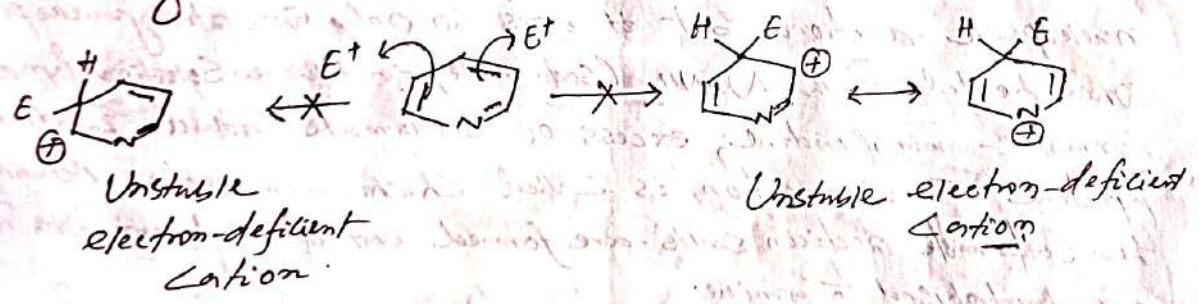


Pyridine is nucleophilic at the nitrogen atom, because the pair of electrons on nitrogen cannot be delocalized around the ring. They are in an sp^2 orbital orthogonal to the p orbitals in the ring and there is no interaction between orbitals.

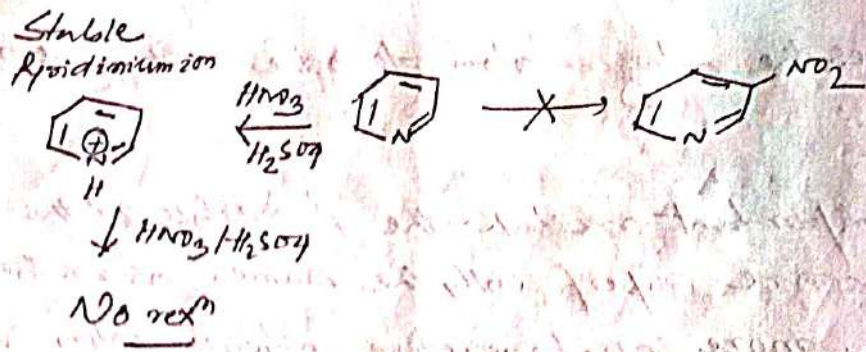
* What does the nitrogen atom do to the rest of the ring of Pyridine:

The important orbitals - the p orbitals of the aromatic system are superficially the same - as in benzene, but the more electronegative nitrogen atom will lower the energy of all orbitals. Lower-energy filled orbitals mean a less reactive nucleophile but a lower-energy LUMO means a more reactive electrophile. This is a good guide to the chemistry of Pyridine. It is less reactive than benzene in electrophile-aromatic substitution rxn, but nucleophilic substitution reactions, which is difficult for benzene, comes easily to Pyridine.

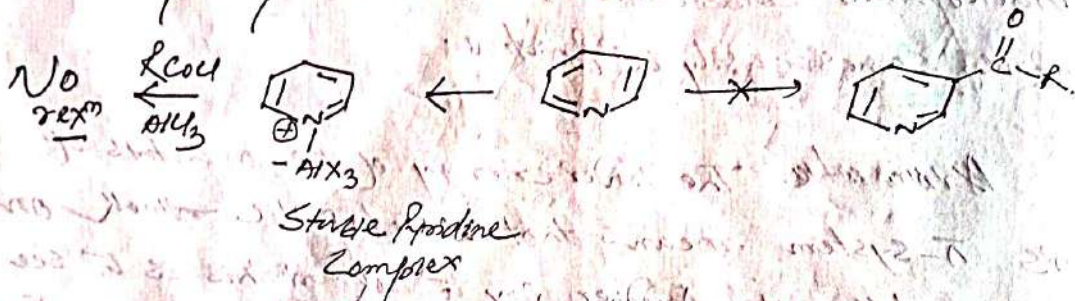
Aromaticity The lower energy of the orbitals of Pyridine's π -system means that electrophilic attack on the ring is difficult. Another way to look at this is to see that the nitrogen atom destabilizes the cationic would-be intermediate, especially when it can be delocalized onto nitrogen.



An equally serious problem is that the nitrogen lone pair is basic and reasonably good nucleophile - this is the basis for its role as a nucleophilic catalyst in acylations. The normal reagents for electrophilic substitution reactions, such as nitration, are acidic. Treatment of Pyridine with the usual mixture of HNO_3 and H_2SO_4 merely protonates the nitrogen atom. Pyridine itself is not very reactive towards electrophiles; the pyridinium ion is totally unreactive.

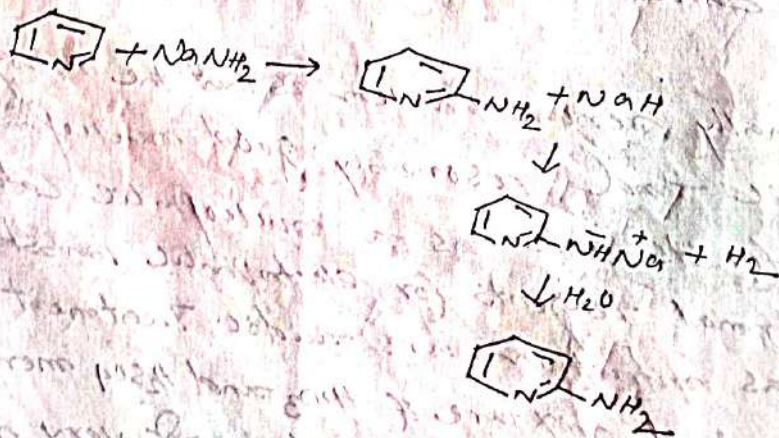


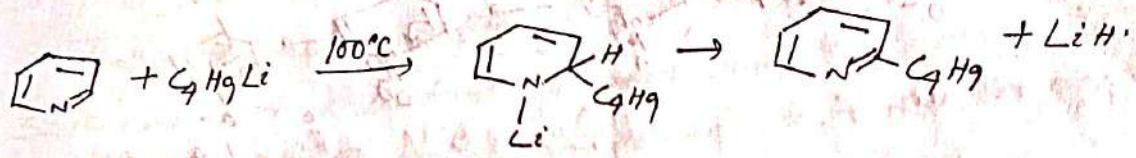
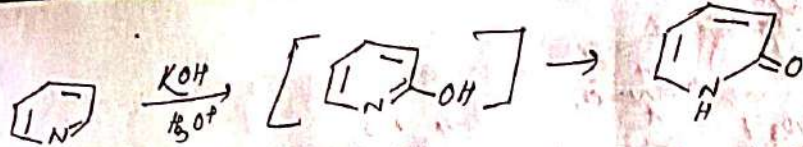
Other reactions, such as Friedel-Crafts acylations, Lewis acids and these too react at nitrogen. Pyridine is a good ligand for metals such as Al(III) or Sn(IV) and once again, complex with its cationic nitrogen. Completely unreactive towards electrophiles.



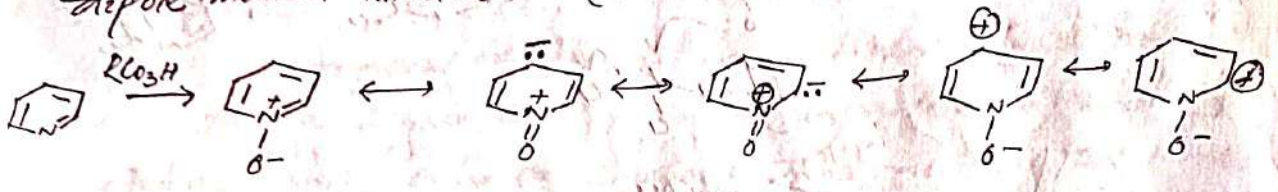
Nucleophilic Substitution reaction:

In addition to electrophilic reactions, pyridine undergoes nucleophilic reactions, but it does so only with strong nucleophiles. When heated with NaNH_2 (sodamide) in toluene solution, pyridine forms 2-aminopyridine; excess of sodamide produces 2,6-diaminopyridine. This reaction is called Chichibabin reaction. Actually sodamide sodium salts are formed, but on treatment with water are hydrolysed to amine.

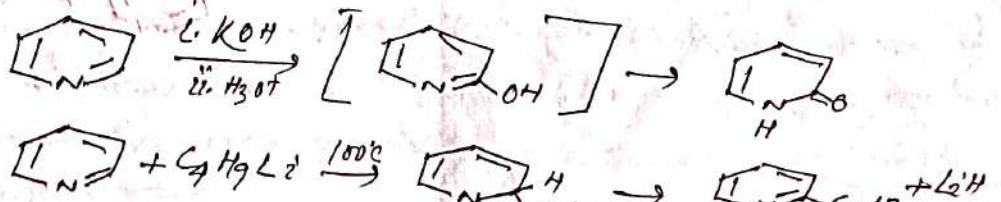
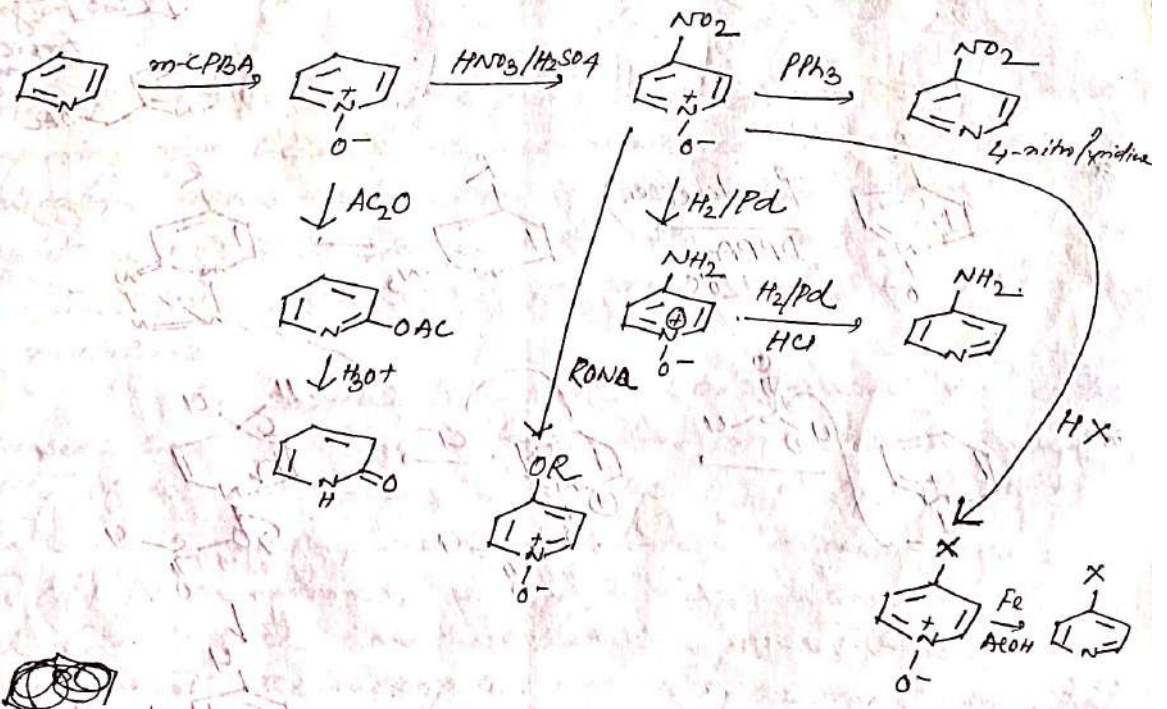




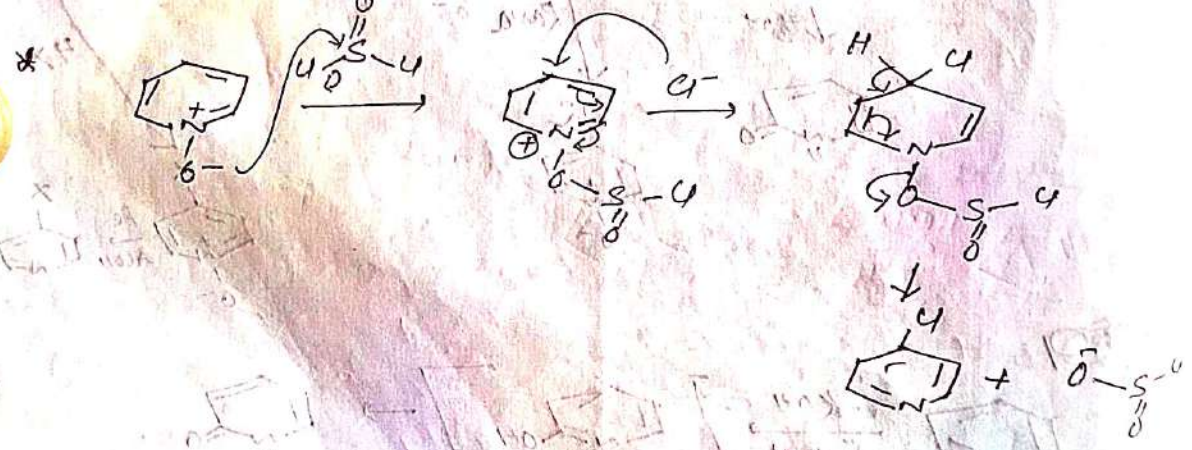
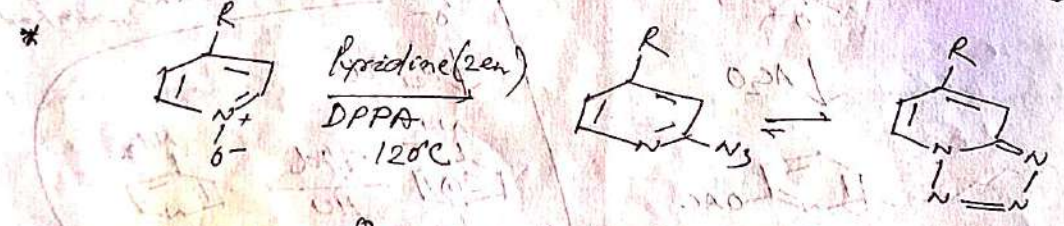
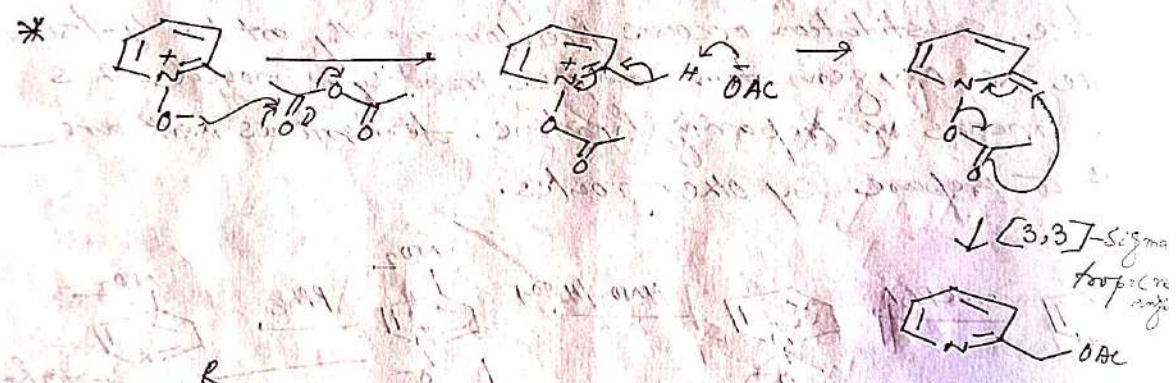
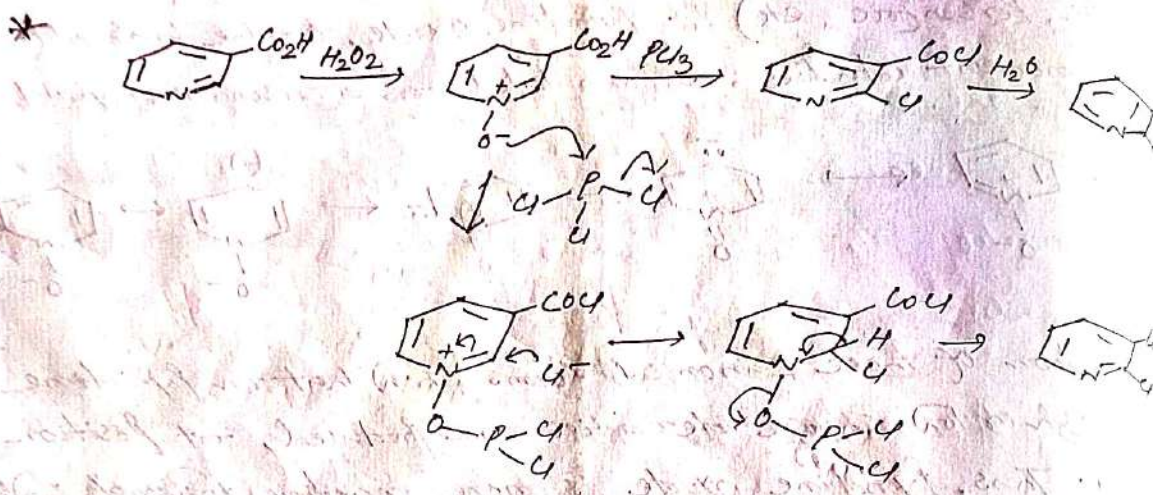
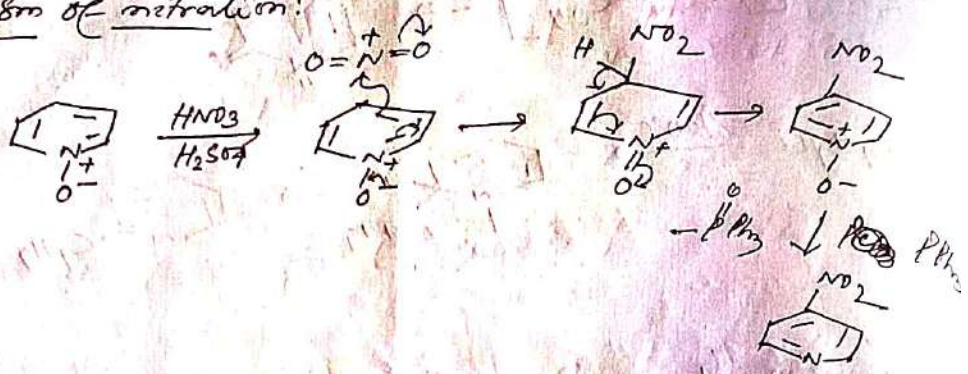
* Pyridine-2-oxide: Pyridine is oxidized by Pero acid (Peracetic, Perbenzoic, etc) to Pyridine oxide, on the basis of dipole moment studies, is formulated as a resonance hybrid.



Examination of these canonical forms show that in Pyridine oxide, high or low charge densities are produced at position 2 and 4. Thus, Pyridine oxide is more reactive towards both electrophilic and nucleophilic reagents than Pyridine itself. In practice, substitution occurs predominantly at the 4-positions and since the oxygen atom may be readily removed, this offers a means of preparing Pyridine derivatives that are difficult to prepare by other routes.



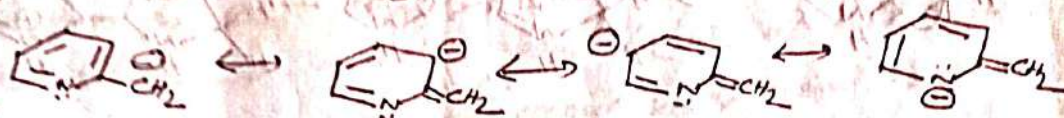
Mechanism of nitration:



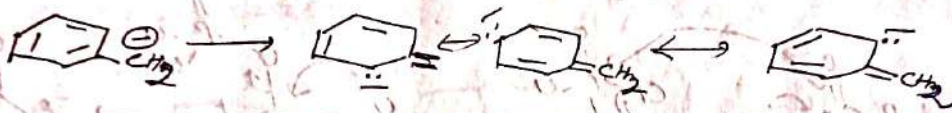
* 2-picoline is more acidic than toluene. pK_a 11.0 vs 11.4

Ans:

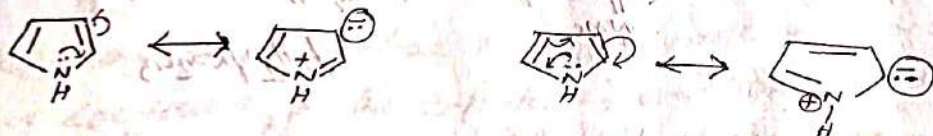
The enhanced acidity of the hydrogen atoms of an alkyl side chain at α -positions is again due to the delocalization of negative charge in the intermediate anion onto the ring, particularly onto the electronegative nitrogen atom.



However, the removal of proton from toluene ($-CH_3$ group) gives only a higher energy anion (conjugate base) with negative charge only on carbons. This acidity of toluene lower than 2-picoline.

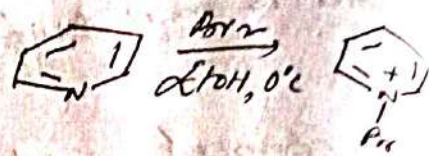
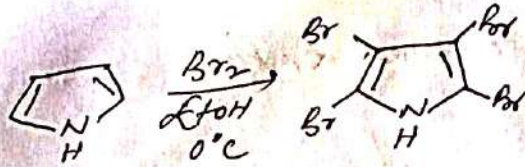


Pyrole and thiophene:

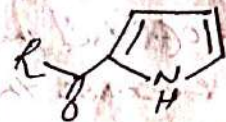
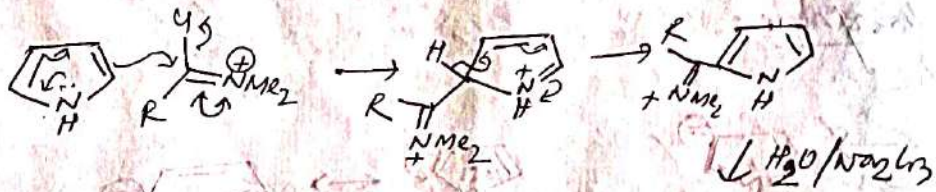
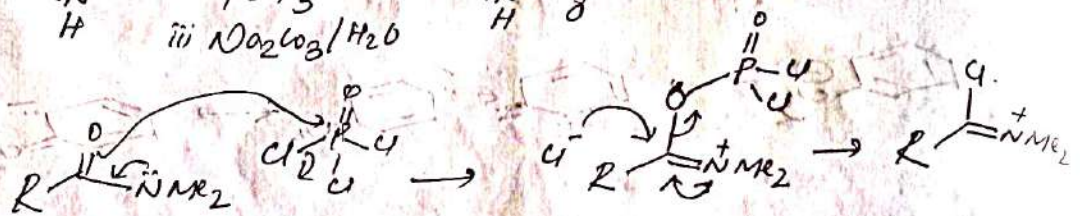
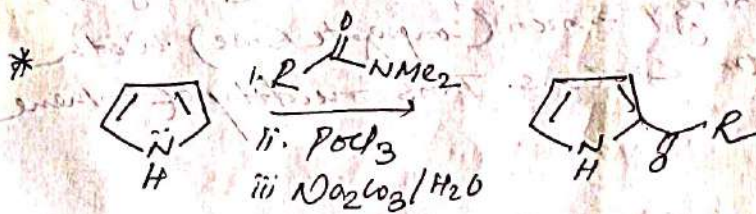
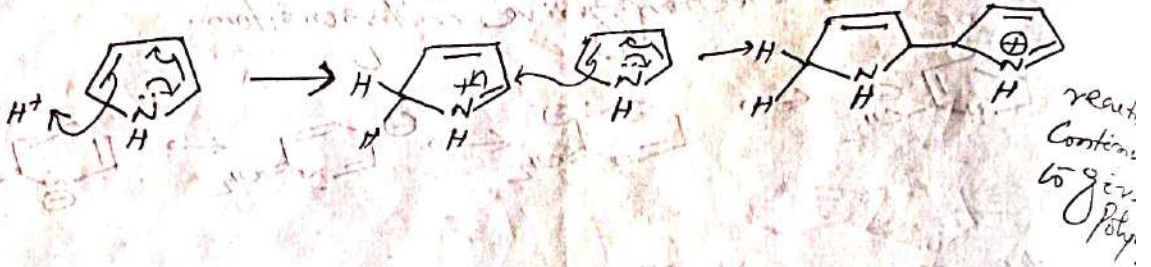


The delocalization of the lone pair can be drawn equally well to any ring atom because the five-membered ring. All the delocalization pushes electrons from the nitrogen atom into the ring and we expect the ring to be electron rich at the expense of the nitrogen atom. Thus HOMO should go up in energy and the ring become more nucleophile.

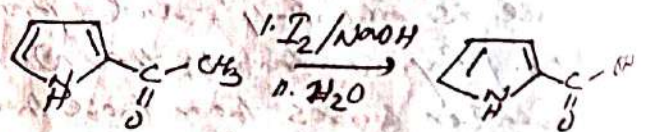
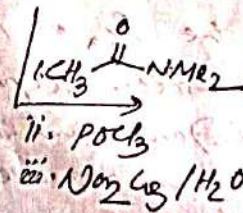
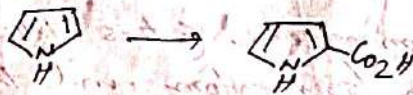
An obvious consequence of this delocalization is the decreased basicity of the nitrogen atom and the increased acidity of the 'NH' group. In fact, the pK_a of Pyrole acting as a base is about -4, and protonation occurs at carbon below pH 4. By contrast, the NH proton can be removed by much weaker bases than those that can remove protons on normal secondary amines. The nucleophilic nature of the ring means that pyrole is attacked by electrophiles. Reaction with bromine requires no Lewis acid and leads to substitution at four free positions. Contrast ~~pyrole~~ pyridine's reactivity with bromine: it reacts just once, at nitrogen.

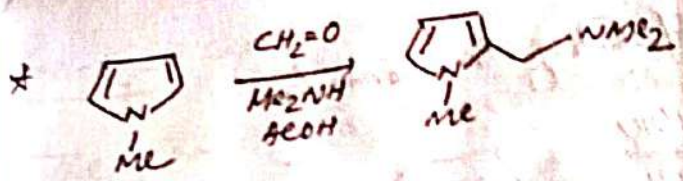


In the presence of strong acid, pyrrole forms polymers.



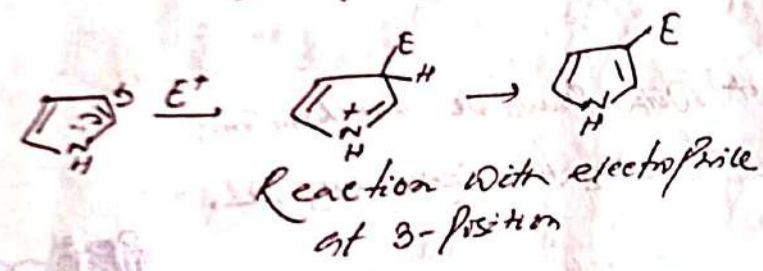
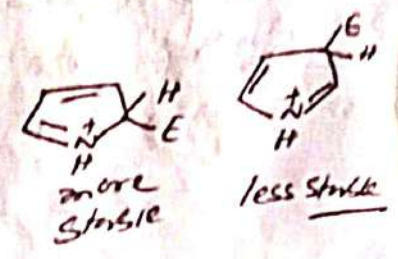
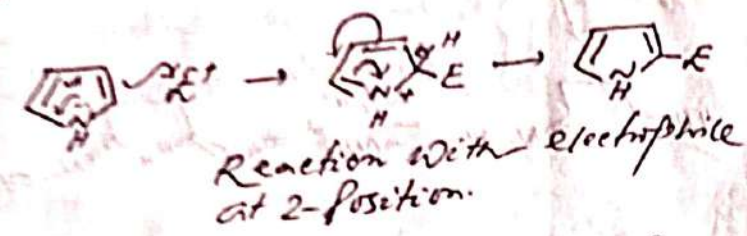
* How would you carry out the following conversion:



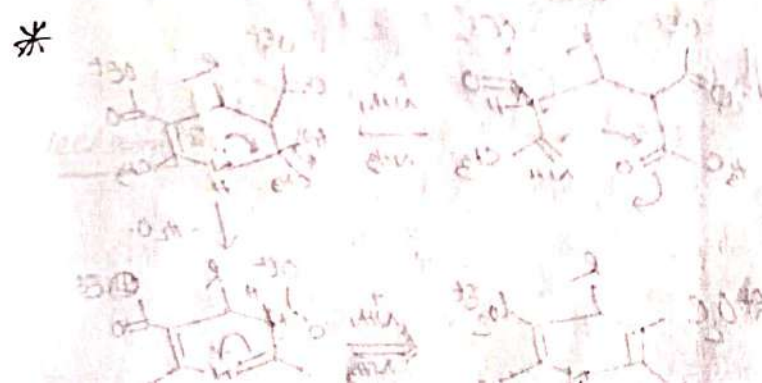


* Substitution of Pyrrole at 2- and 3- Position (reason):

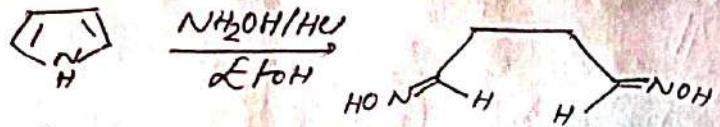
The mechanism for both 2- and 3- substitutions looks good and we will draw both, using a generalized E⁺ as the Electrophile. Both mechanisms can occur very readily. Reaction in the 2-position is somewhat better than in 3-position but difference is small.



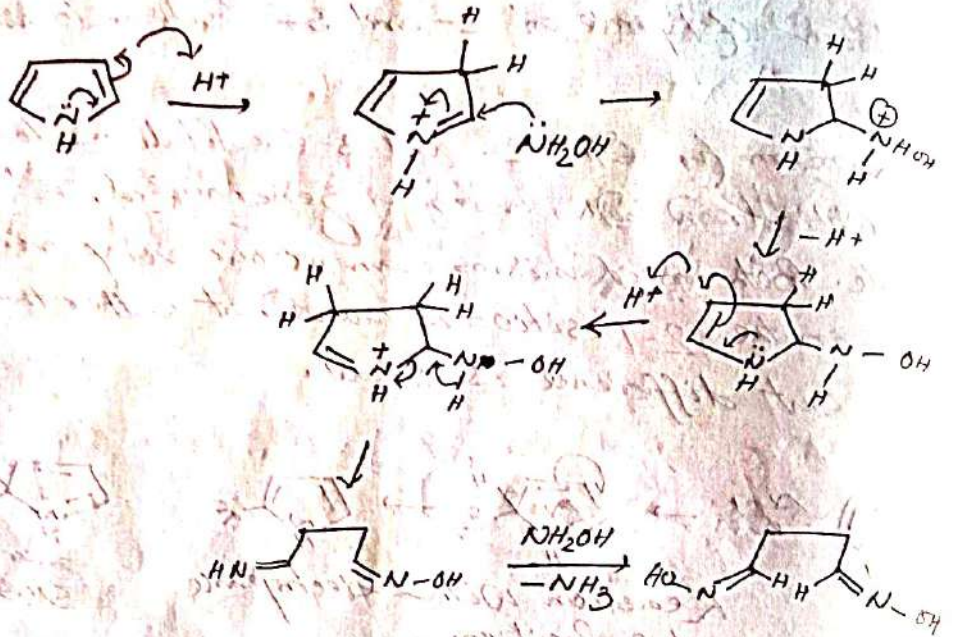
Calculations show that the HOMO of Pyrrole does indeed have a larger coefficient in the 2-position, and one way to explain this result is to look at the structure of the intermediates. The intermediate from attack at the 2-position has a linear conjugated system. In both intermediates the two double bonds are, of course conjugated with each other, but only in the first intermediate are both double bonds conjugated with N⁺. The second intermediate is cross-conjugated, while the first has a more stable linear conjugated system.



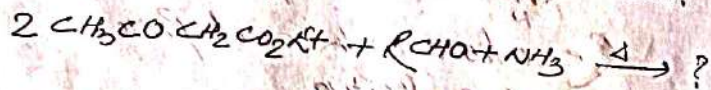
* Give the mechanism of the following transformation:



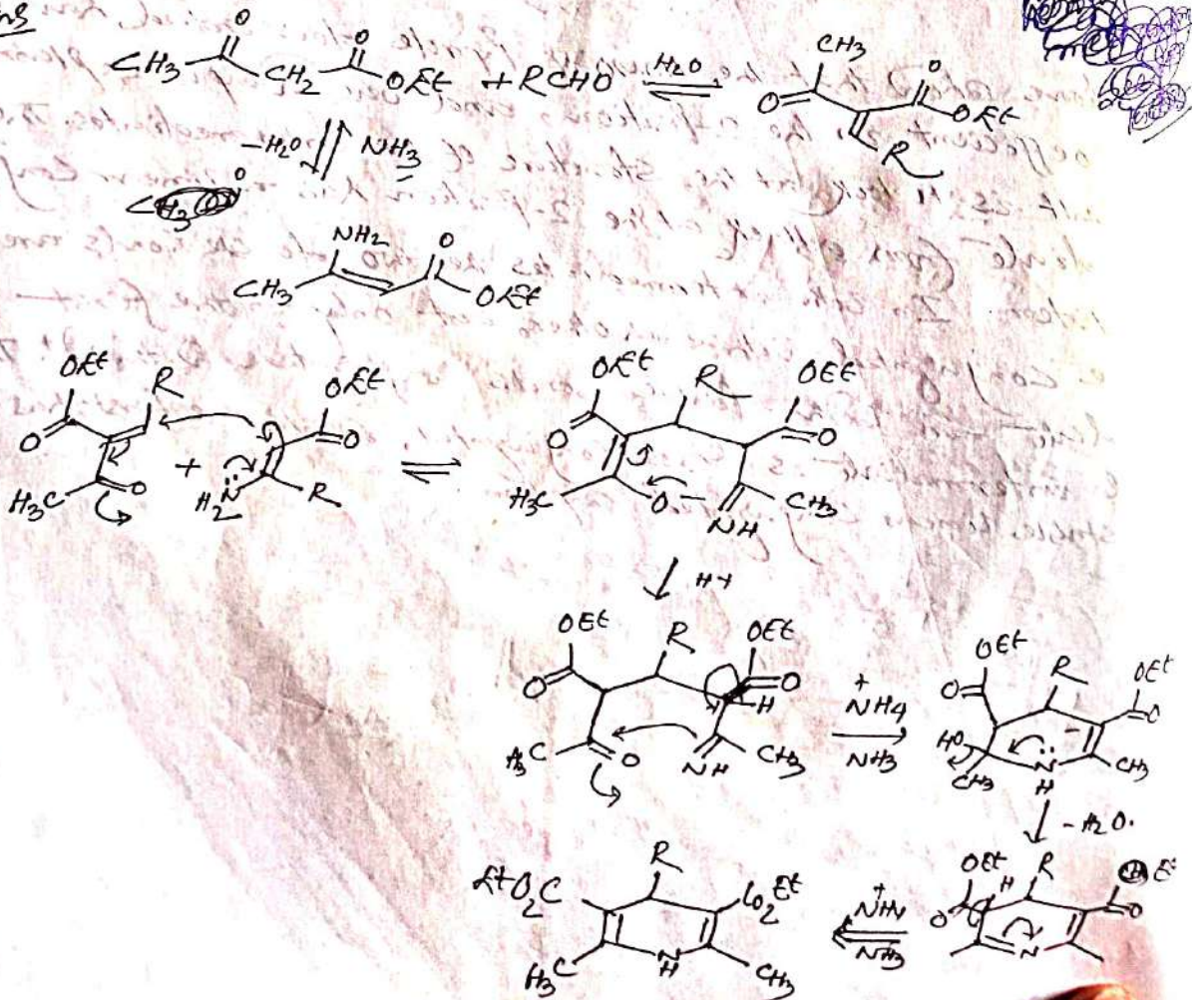
Ans:



* Predict the product with plausible mechanism:

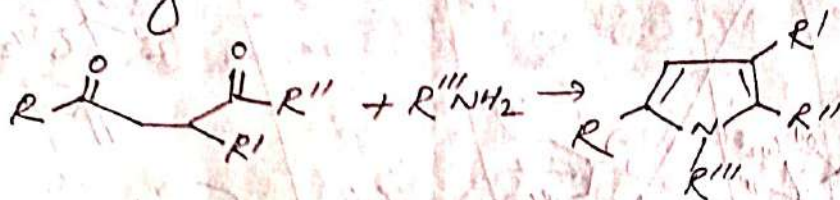


Ans:



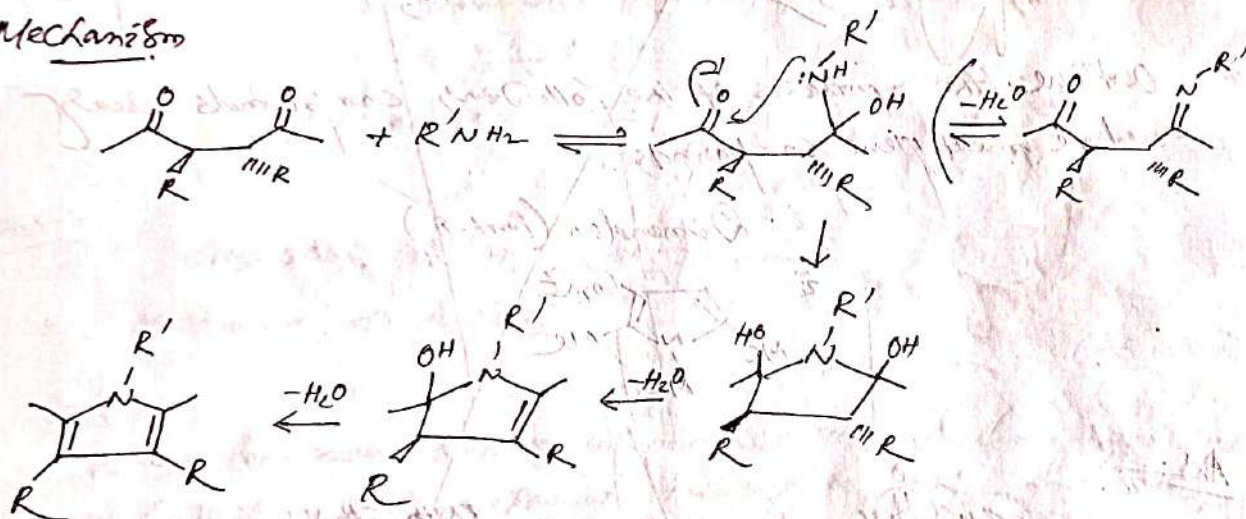
Paal-Knorr Synthesis:

The Paal-Knorr Pyrolysis is the condensation of a 1,4-dicarbonyl compound with an excess of primary amine or ammonia to give a pyrolysis.



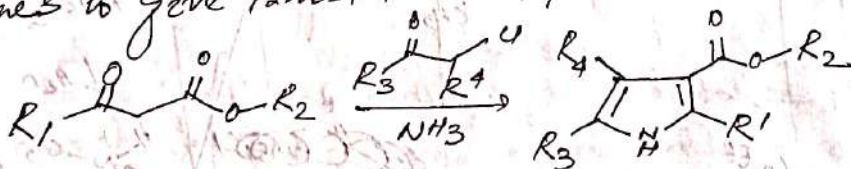
The reaction can be conducted under neutral or weakly acidic conditions. Addition of a weak acid such as acetic acid accelerates the reaction, but the use of amine/~~acid~~ or ammonium hydrochloride salts or reactions at $pH < 3$ lead to furan as main product.

Mechanism

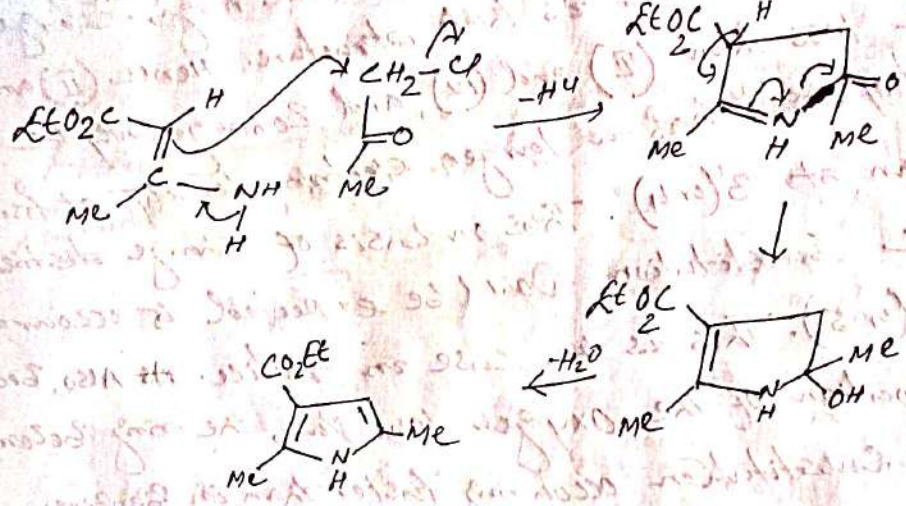
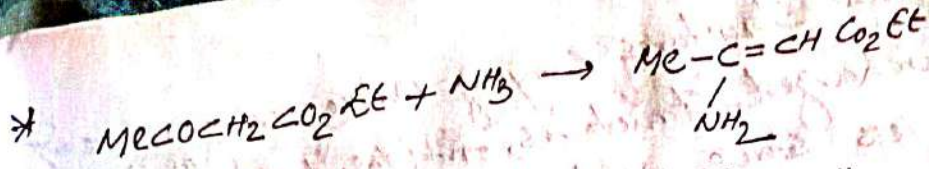


Hantzsch Synthesis

The Hantzsch Pyrolysis is the chemical reaction of β -ketoesters with ammonia (or primary amines) and α -keto ketones to give substituted pyrolysis.

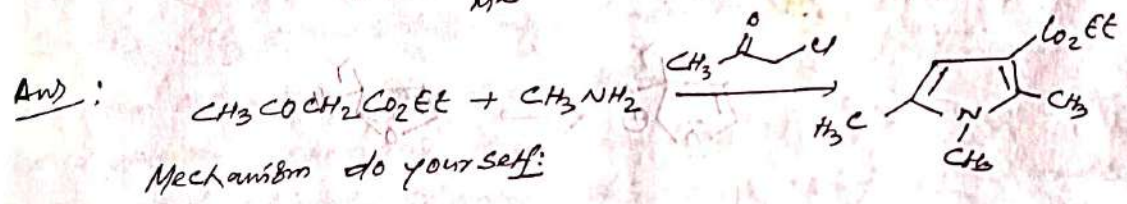
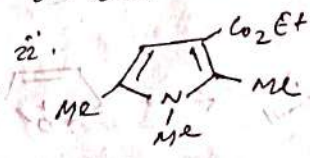


Mechanism:



* Outline the synthesis of the following compounds using active methylene compounds:

i. Dimendone (Part-1)



* When potassium pyrrole is heated with chloroform and KOH or NaOEt, ring expansion takes place, the product being 3-chloropyridine



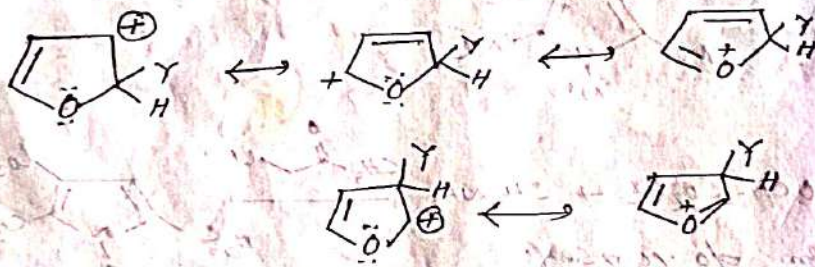
Furan

Furan has a resonance energy of $71.1-96.2 \text{ kJ/mol}$, and is best represented as a resonance hybrid of contributing structure I-V. As we have seen, to be aromatic, a monocyclic molecule must be a planar (anti) π -electron molecule. Hence to provide six- π -electrons for the ring system, one of the lone pairs of e's of the oxygen atom is involved



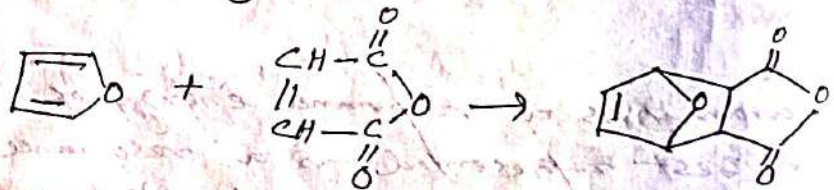
As we know, Canonical Structures carrying unlike charges are the larger. So stable as uncharged structures, and the larger the charge separation, the less stable is that structure. Hence (II) and (V) contribute less than (III) and (IV), and consequently the resonance hybrid has a larger electron density at position 2 (or 5) than at 3 (or 4). Thus on basis of charge distribution electrophilic substitution would be expected to occur at position 2 (or 5). This is the case in practice. Also, because of the donation of the oxygen lone pair, the ring behaves activated, substitution occurring faster than in benzene.

Alternatively, if we consider the contributing structures of the intermediate carbonium ion (α -complex) then there are three for α - and two for β -substitution.

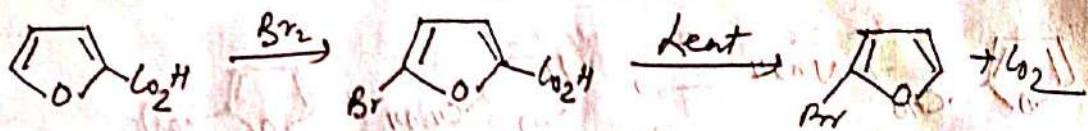


Reactions

Furan, b.p. 32° turns green on moistening with HCl . It behaves chemically as an aromatic compound but in some ways it behaves as a 1,3-diene. Thus, it is less aromatic than thiophene and pyrrole, and is the one of these to undergo the Diels-Alder rxn.

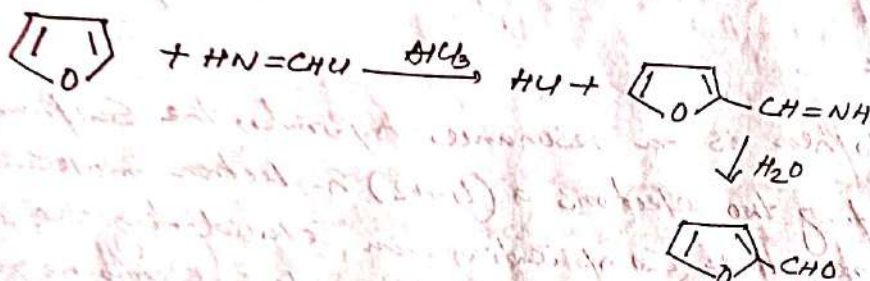
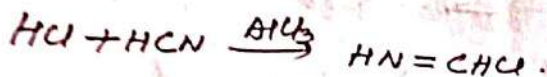
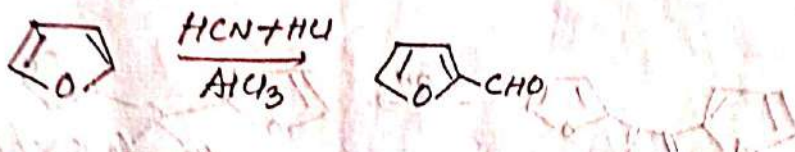


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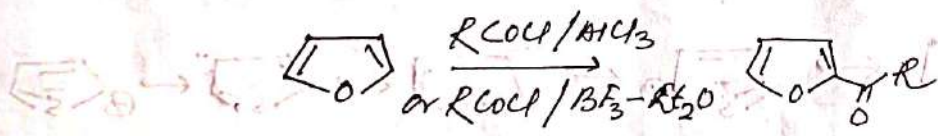


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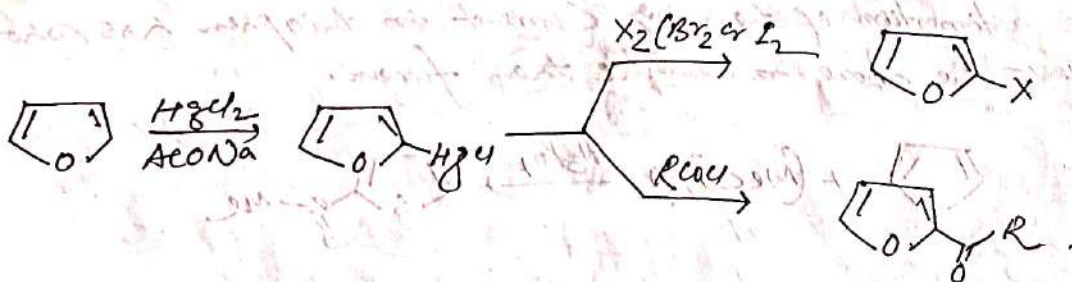
Furan undergoes the Gattermann reaction to form Furfural.



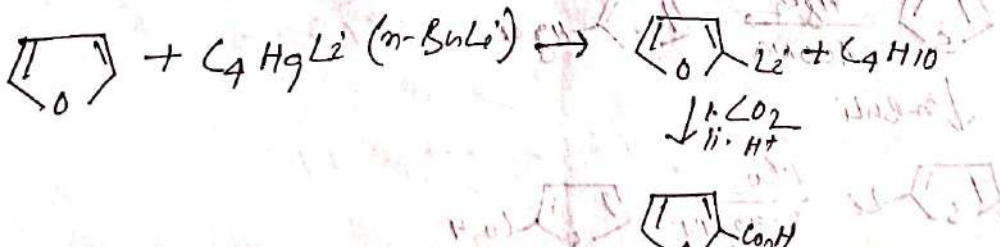
Since $AlCl_3$ attacks the ring, Friedel-Crafts reactions are best carried out with stannic chloride as catalyst. In any case, alkylation reactions with furan lead to polymers, but acylation with acid chloride or anhydrides with stannic chloride as catalyst gives 2-acyl derivatives. A better catalyst for the reaction with anhydrides is BF_3 in ether.

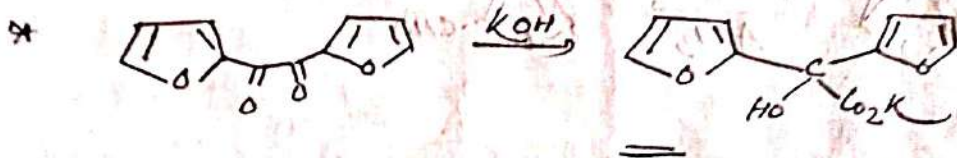
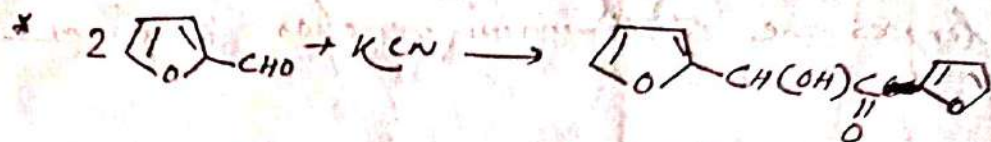


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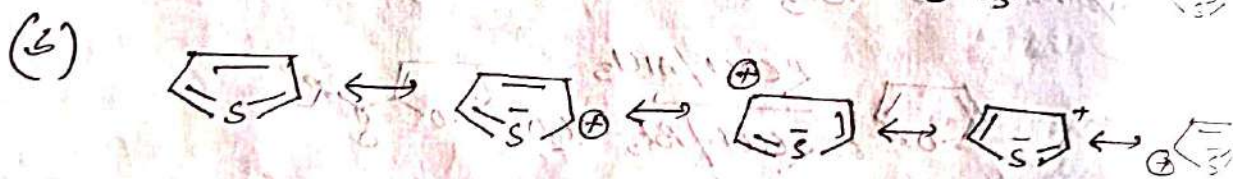
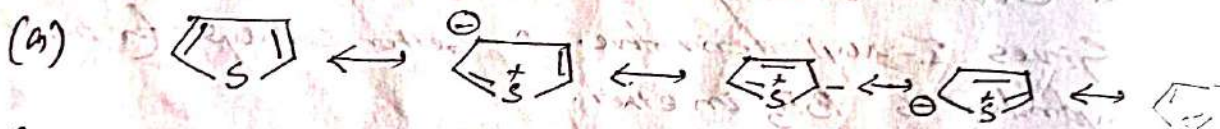
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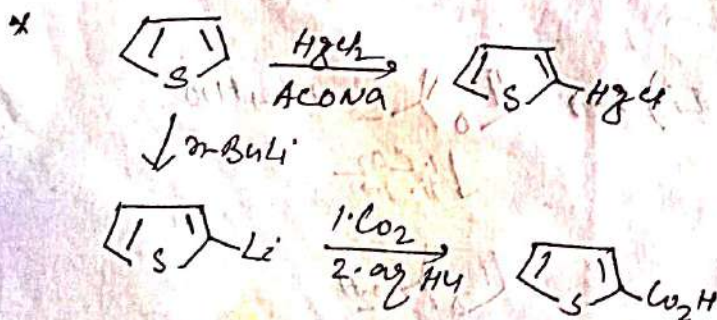
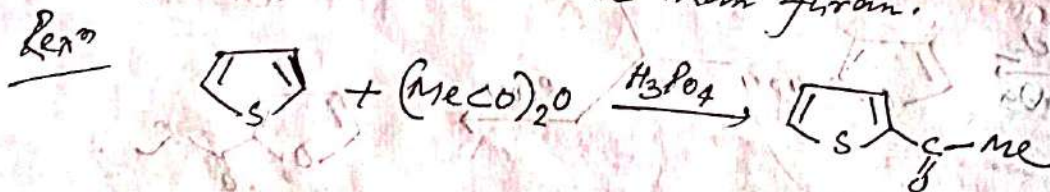


Thiophen.

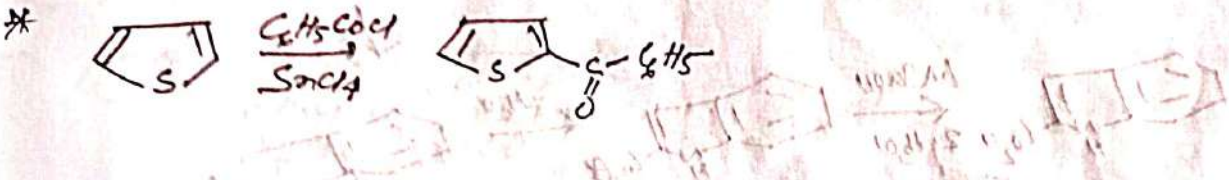
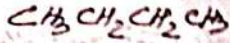
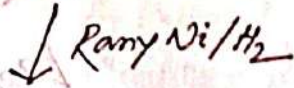
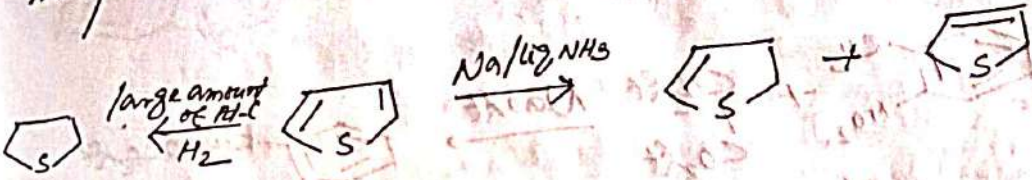
Thiophen is a resonance hybrid, the Sulfur atom contributing two electrons a (4n+2) π electron molecule. There are some complications in elucidating the structure of thiophene. Sulfur is less electronegative than oxygen (or nitrogen) and can also use 3d orbitals (if needed). Hence more canonical forms are possible for thiophen than for furan and pyridine. In group (a), the sulfur atom uses p-orbitals; in group (b) it also uses d-orbitals.



The estimation of the ring current in thiophen has shown it to be more aromatic than furan.

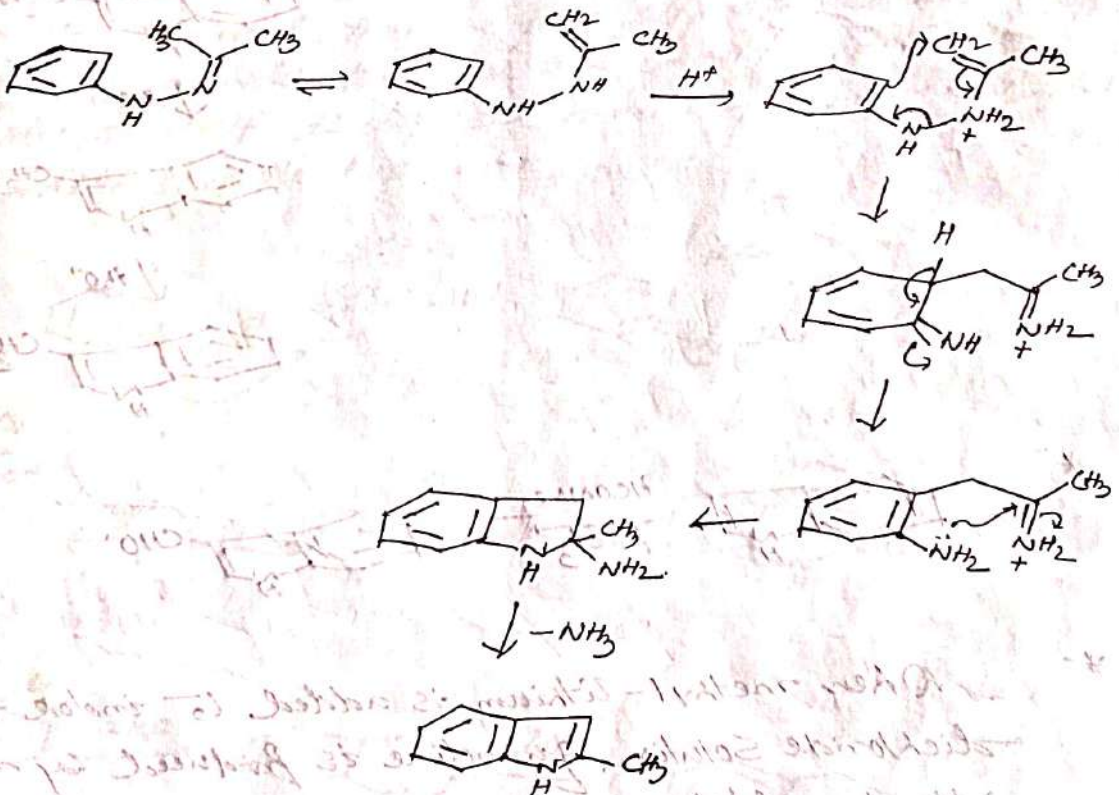


* Thiophene does not undergo

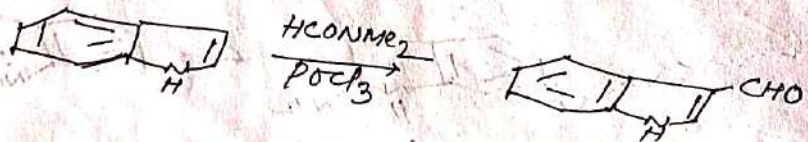
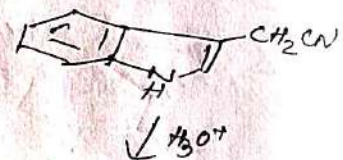
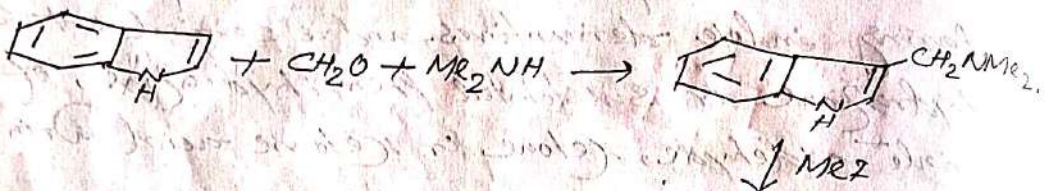
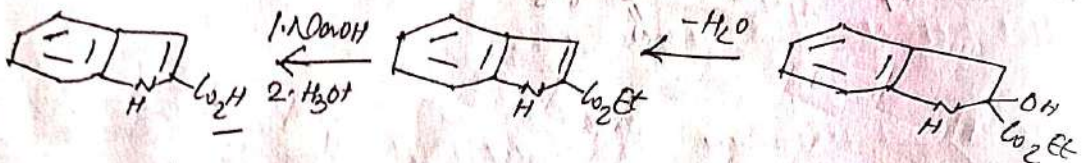
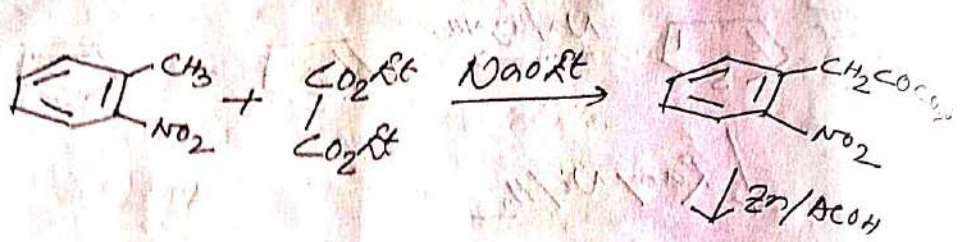


Indole

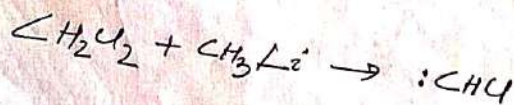
Fischer's indole synthesis is the most important method of preparing indole derivatives, and is carried out by heating phenyl hydrazone or substituted phenylhydrazone of an appropriate aldehyde, ketone or ketonic acid with ZnCl₂, poly phosphoric acid, H₂SO₄ in EtOH.

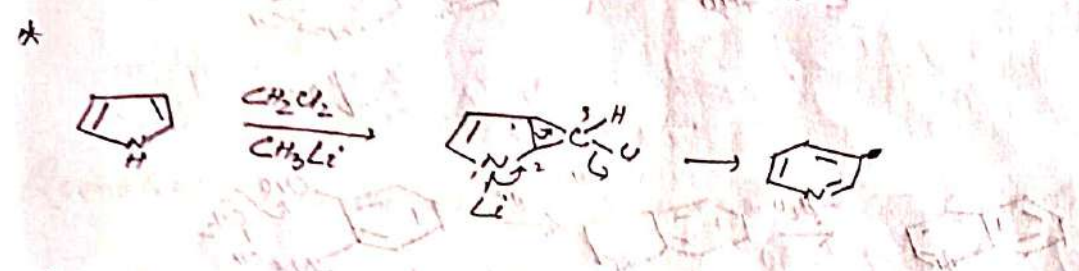
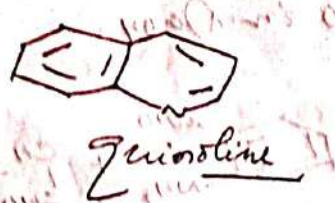
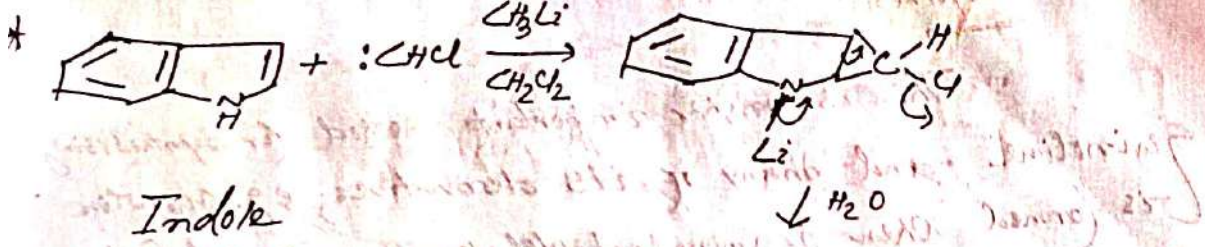


Preparation of Indole-2-acetic acid:



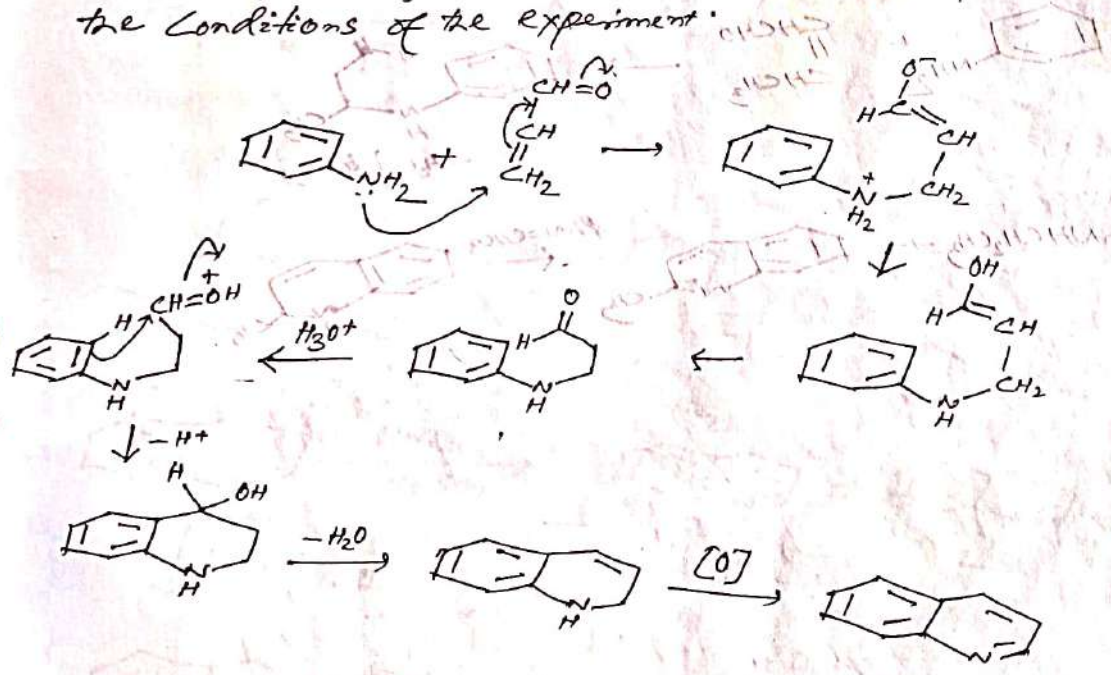
* When methyl-lithium is added to indole in methylene dichloride solution, geranioline is produced by ring expansion via the addition of chloromethylene.





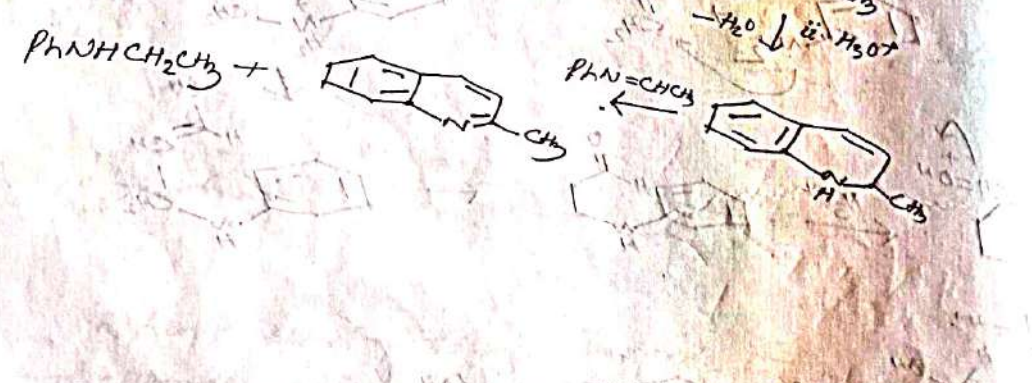
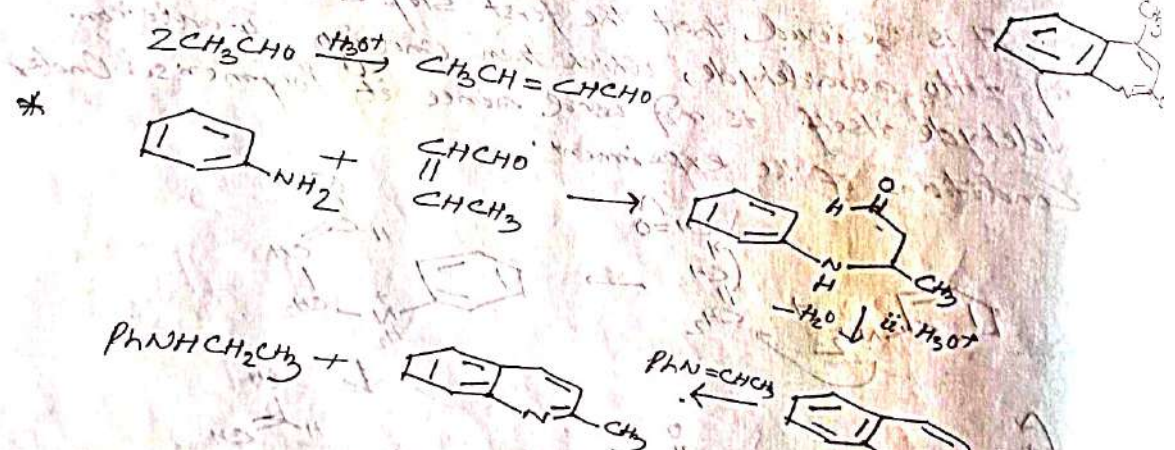
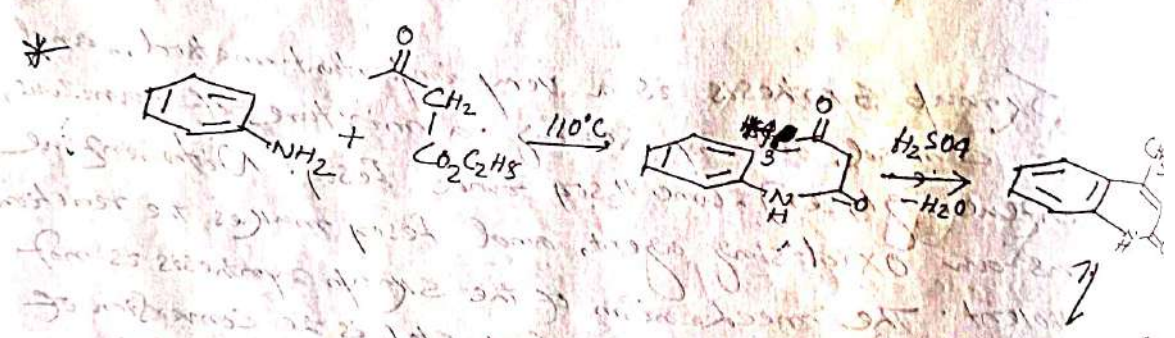
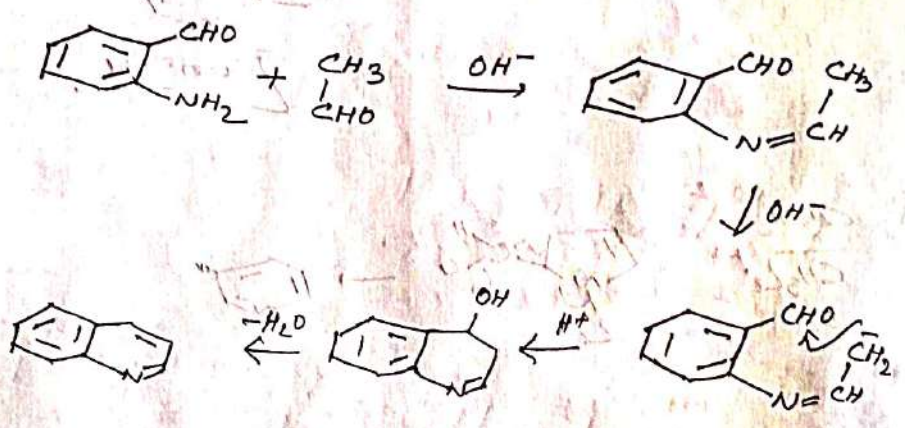
Quinoline

Skraup synthesis is a very important method, and may be carried out by heating a mixture of aniline, nitrobenzene, glycerol, conc. H_2SO_4 and FeSO_4 . Nitrobenzene acts as an oxidising agent, and FeSO_4 makes the reaction less violent. The mechanism of the Skraup synthesis is not certain. It is believed that the first step is the conversion of glycerol into acrolein, which then undergo 1,4-addition. Acrolein itself is not used since it polymerises under the conditions of the experiment.

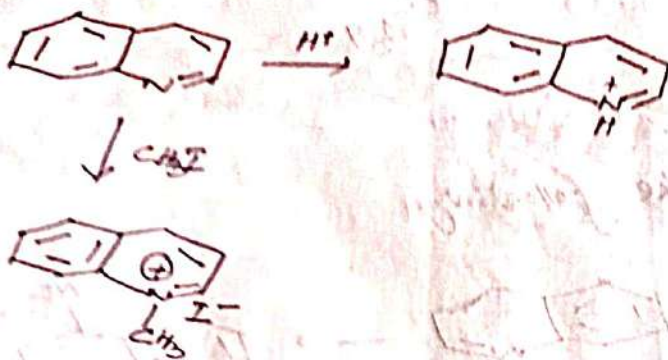


Friedlander's Synthesis:

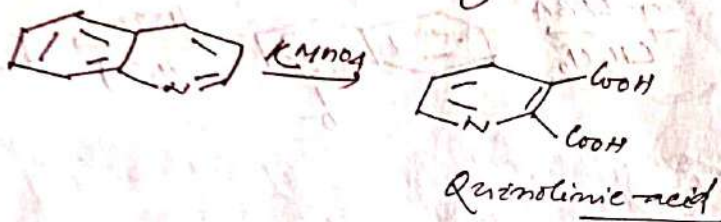
This is another important method for synthesizing quinoline and many of its derivatives; e.g. Quinoline is formed when o-amino benzaldehyde is condensed with CH_3CHO in NaOH .



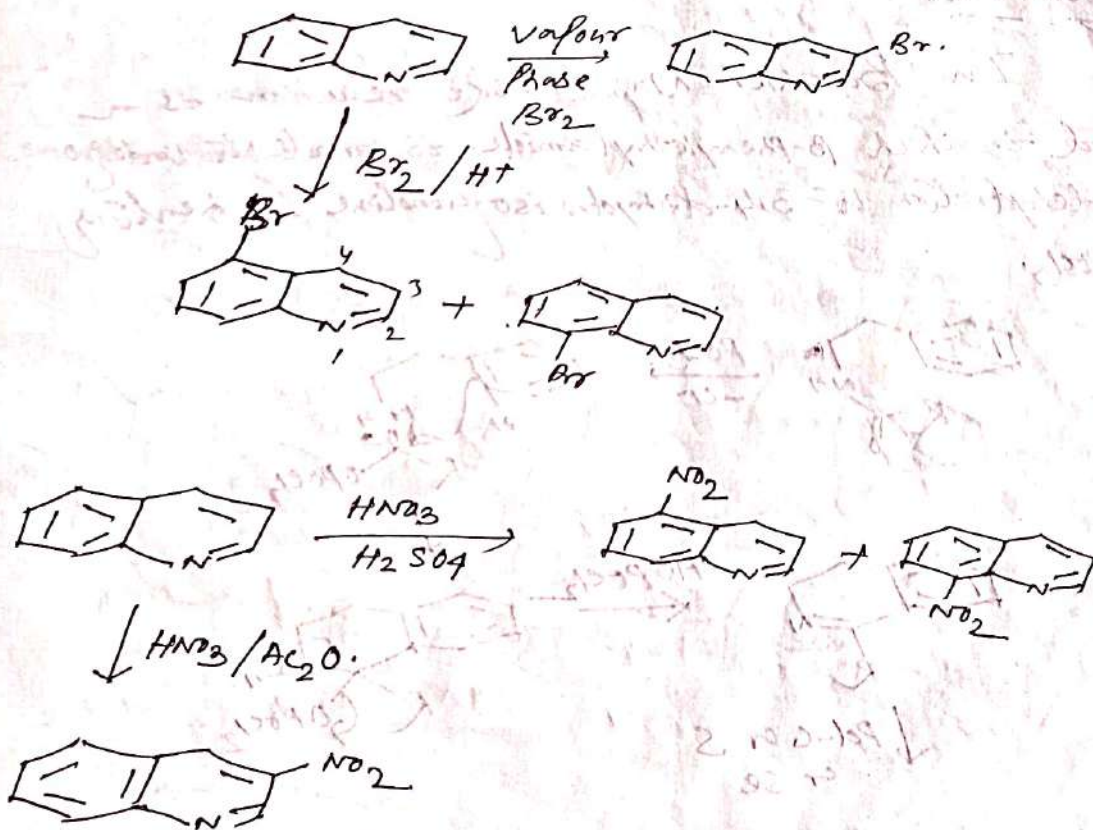
Quinoline is a tertiary base and forms salt with inorganic acid; with alkyl halides it forms quinuclidinium salts.

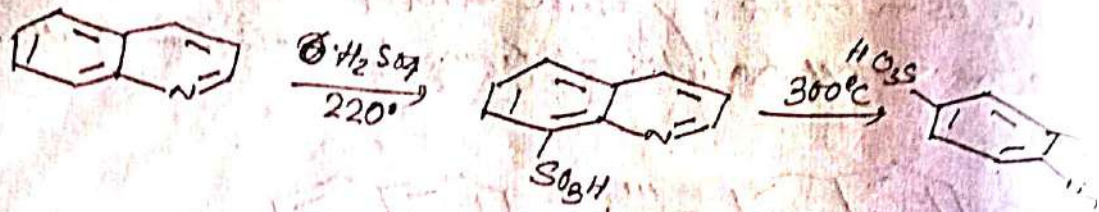


Quinoline is oxidised by permanganate to Quinolinic acid.

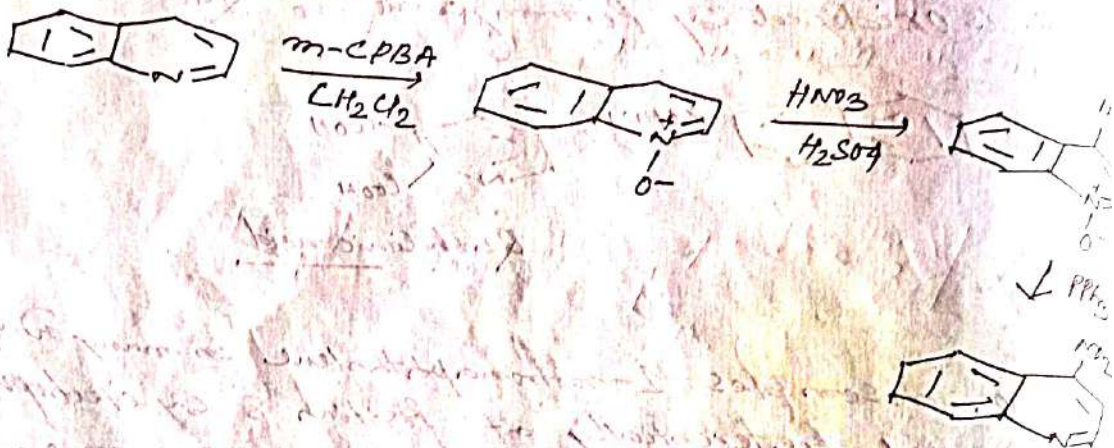


Quinoline resembles 1-nitronaphthalene in many ways. It is attacked preferentially at position '8' by electrophilic reagents, and position 2 and 4 by nucleophilic reagents.



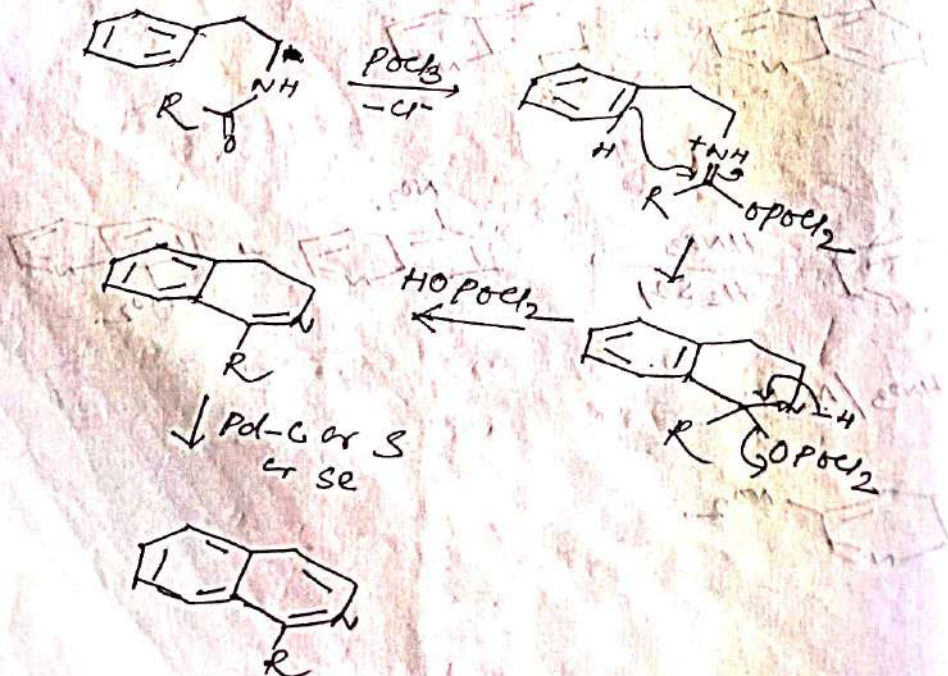


Convert the following

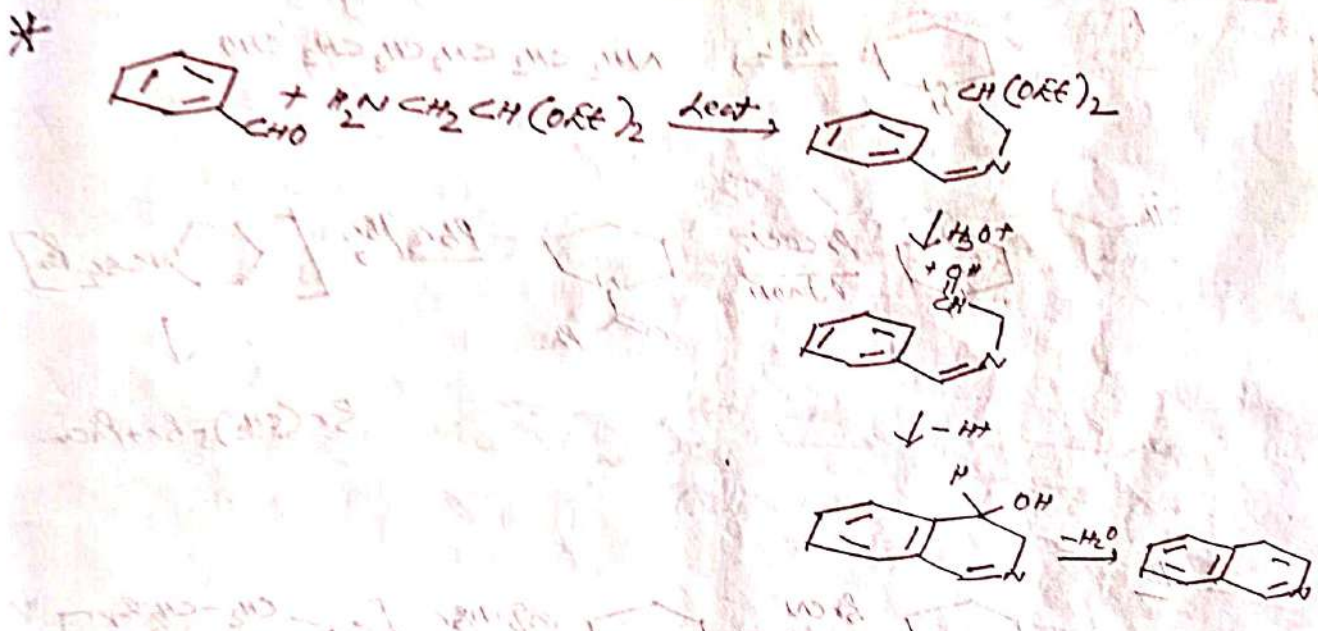
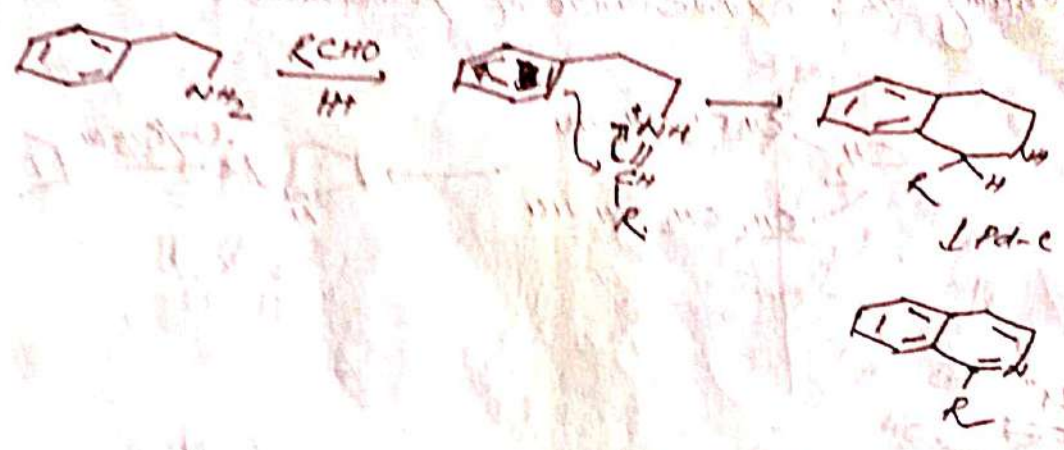


Isoquinoline:

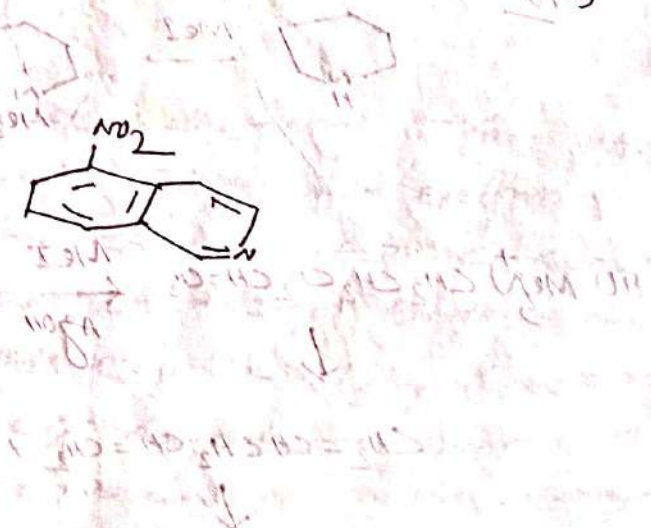
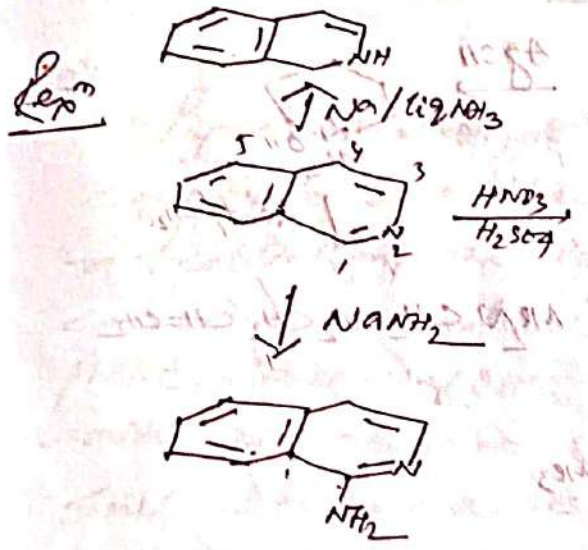
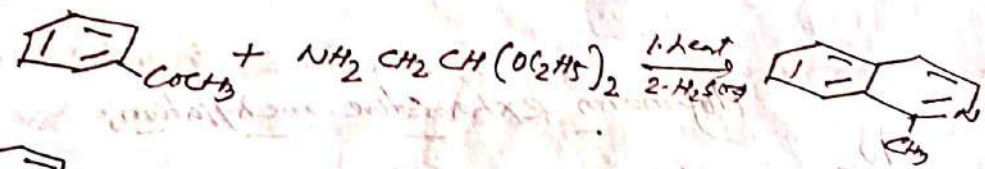
In Bischler-Napierowski reaction is a method in which β -phenylethylamide is made to undergo cyclodehydration to 3,4-dihydroisoquinoline by heating with POCl_3 .



* Condensation between α -arylethylamine and an aldehyde in the presence of a large excess of HCl at 100°C produces a 1,2,3,4-tetrahydroisoquinoline.



If an aromatic ketone is used instead of the aldehyde, then the product is a 1-substituted isoquinoline.

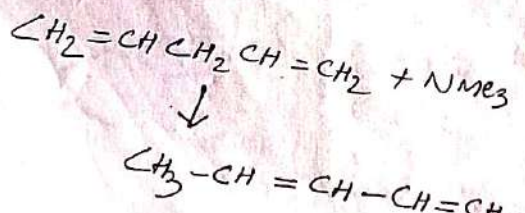
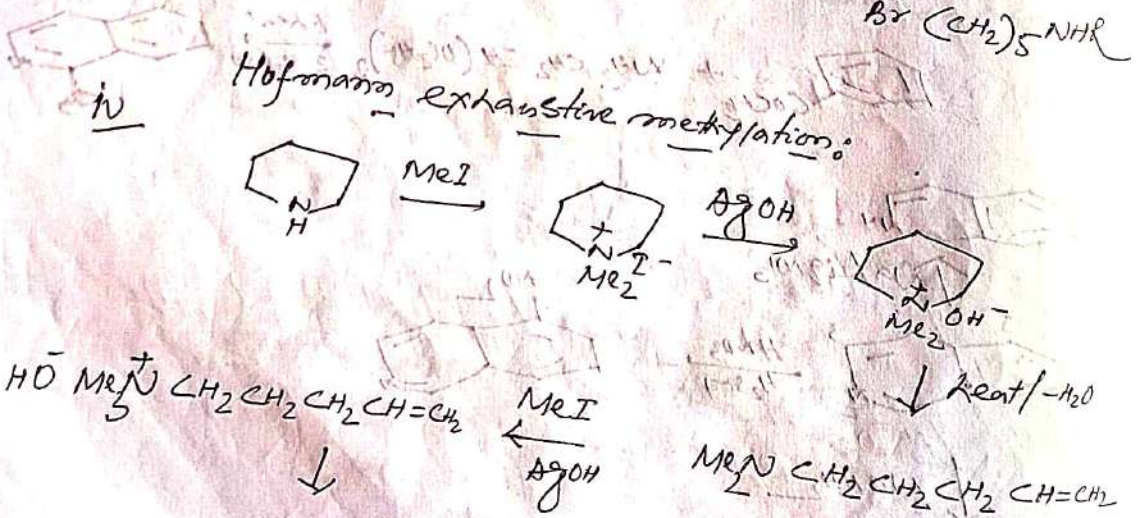
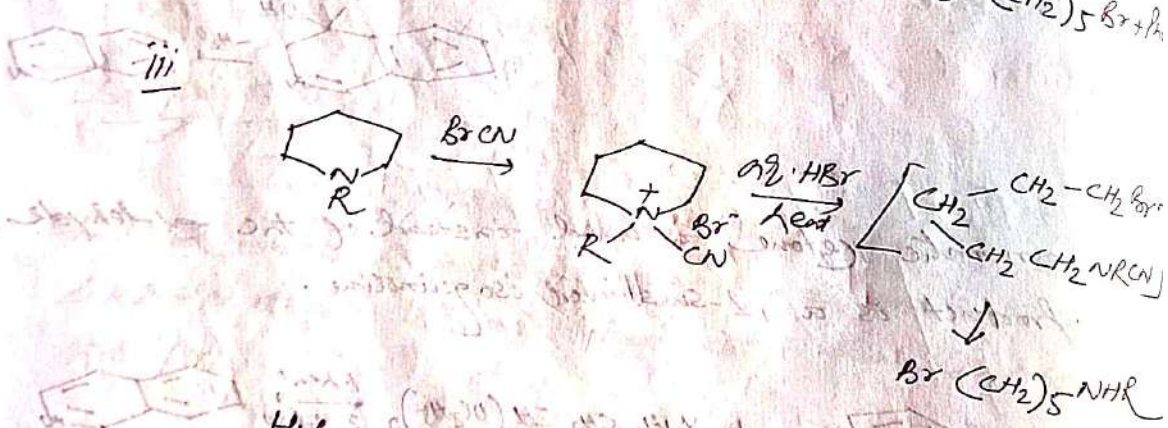
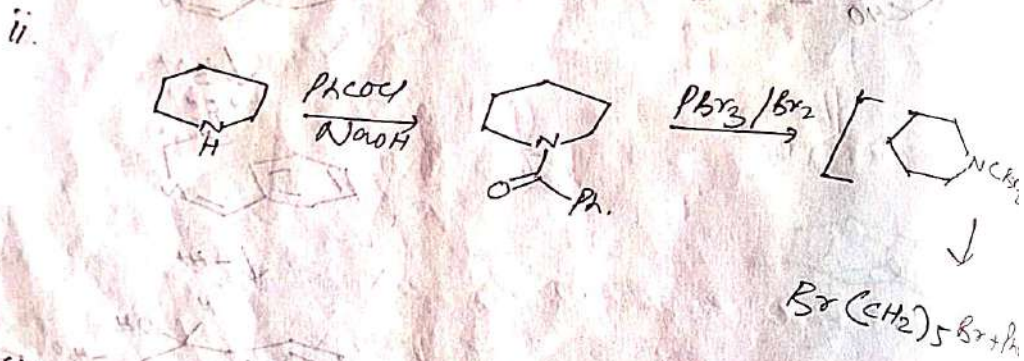
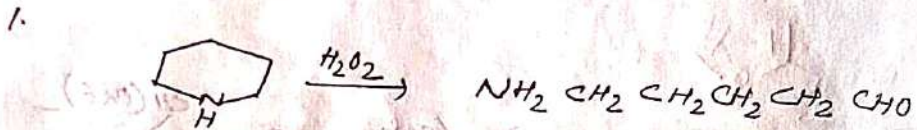


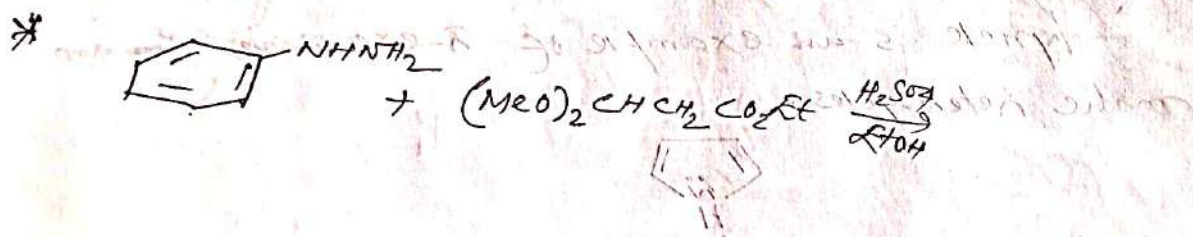
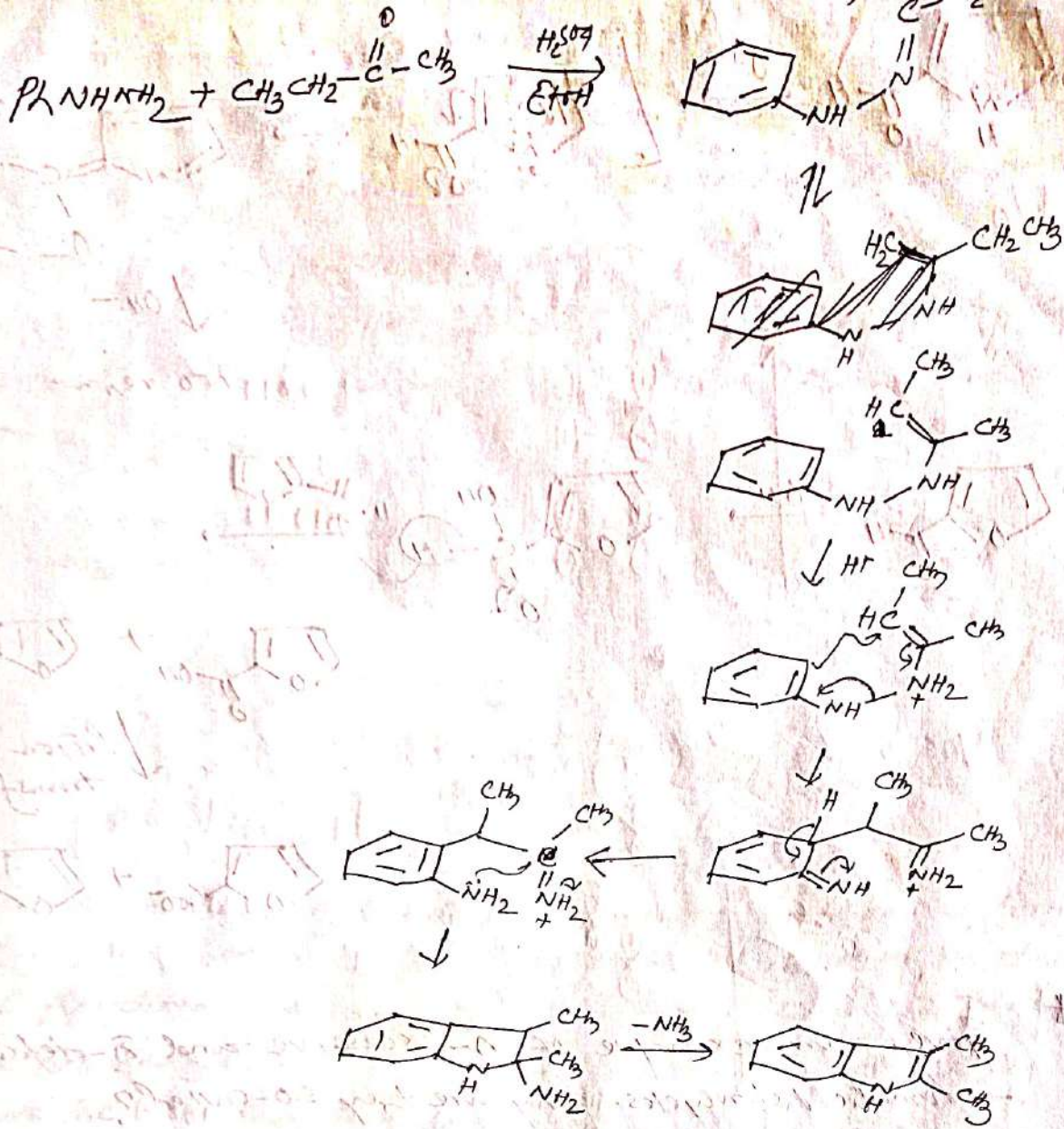
Piperidine:

It may be prepared by reducing Pyridine or heating the hydrochloride of pentamethylenediamine



Reactions

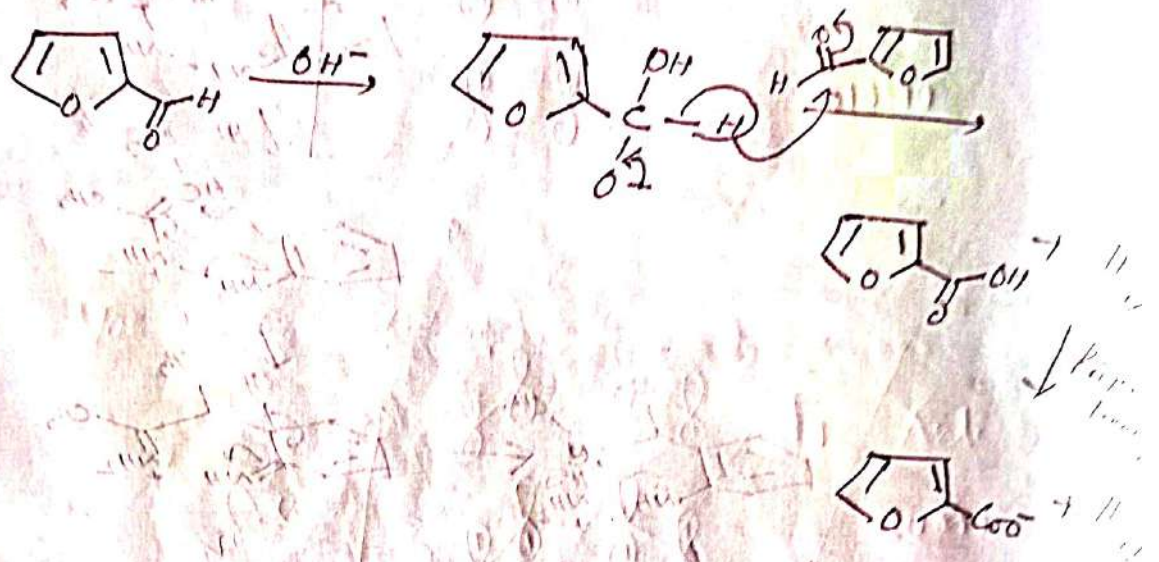
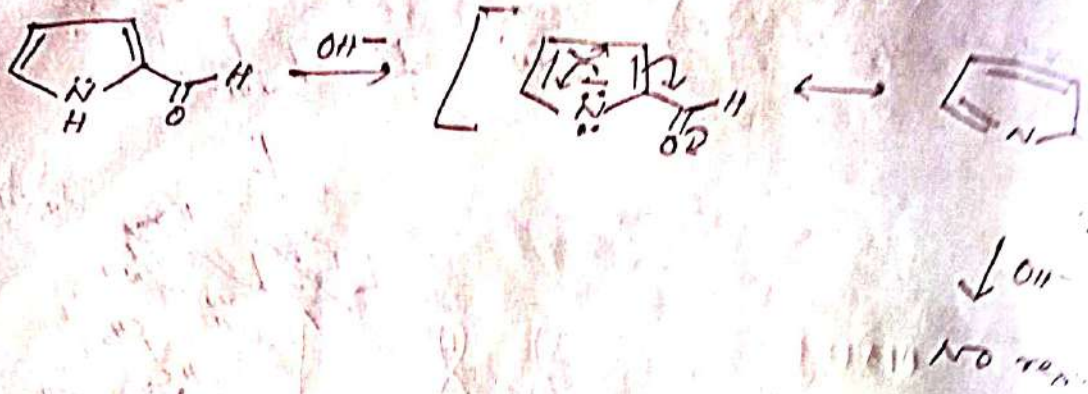




* Furan-2-aldehyde Undergoes Cannizzaro reaction but Pyrrole-2-aldehyde does not. Explain.

Ans:

Pyrrole-2-aldehyde reacts with alkali to form its conjugate base. Because of significant electron delocalization, the positive character of the carbonyl carbon is so reduced that it does not undergo nucleophilic attack by OH^- . This explains why pyrrole-2-aldehyde does not undergo Cannizzaro reaction. No such situation arises in the case of furan-2-aldehyde and so, it undergoes normal Cannizzaro reaction.



* Give an example of π -excessive and π -deficient aromatic heterocycles. Why are they so-called?

Ans. Pyrrole is an example of π -excessive aromatic heterocycles.

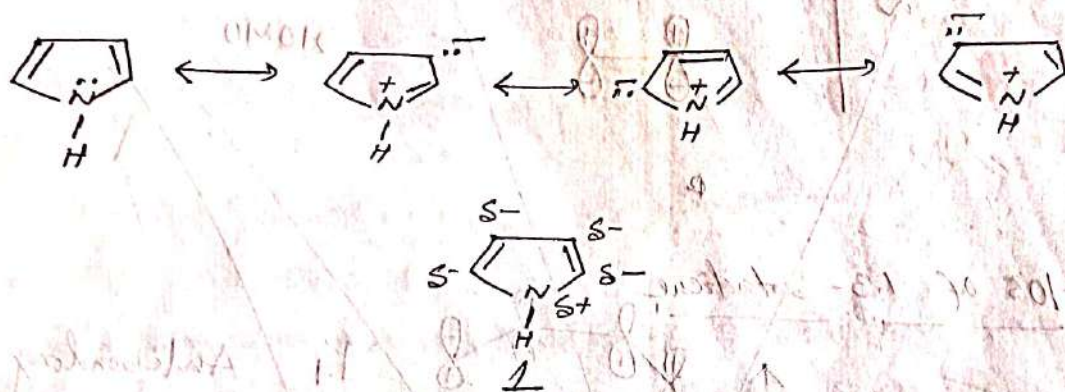


Pyridine is an example of π -deficient aromatic heterocycles.

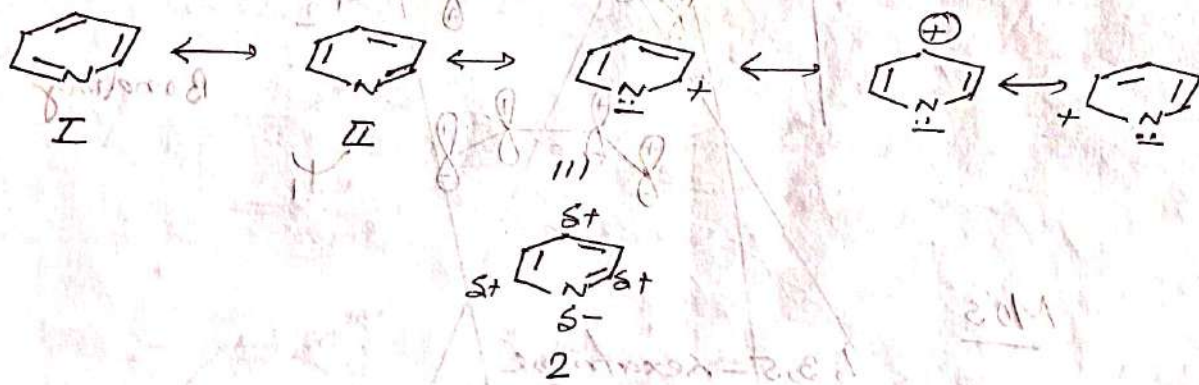


Pyrrole has a structure that is isoelectronic with the cyclopentadienyl anion, but is electrically neutral having a nitrogen atom with a pair of electrons, is part of the aromatic sextet, and its resonance hybrid can be represented as resonance combination

of main forms I-V, one without charge, and the others with charge separation. As a combination of all forms structure 1 indicates how the heteroatom bears a partial positive charge, while the carbon positions show an increase in electronic density, compared with typical aromatic system benzene. Thus pyrrole is an π -excessive aromatic system.



In the case of pyridine the main canonical forms (I-V) that contribute to the resonance hybrid of the structure of pyridine. Obviously, not all of them contribute equally. The two Kekulé form I and II, which are not charged are the more stable.



Thus the combination of main forms can be represented as structure '2', in which nitrogen bears a partial negative charge, and positions 2, 4 and 6 are electron deficient, thus pyridine is π -deficient aromatic heterocycles.