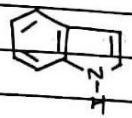
Unit - IV :

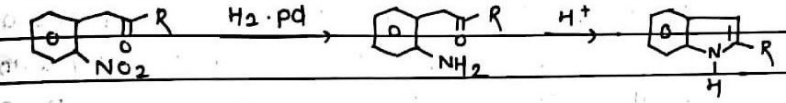
Synthesis, reactivity of Indole :-

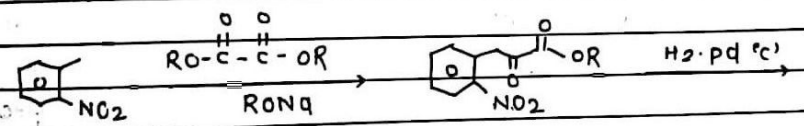
1. Indole -

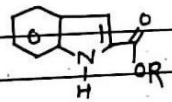


2) Synthesis -

The reductive cyclization of ortho nitro benzyl carbonyl comp. gives Indole.

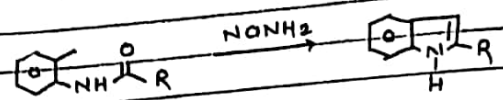
a) 

b) 

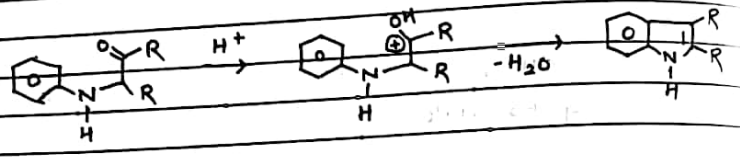


In this method, ortho nitro phenyl pyruvic acid obtained by Cleson condensation of ortho nitro toluene with oxalic ester. is subjected to catalytic hydrogenation in the presence of $H_2 \cdot pd$ (c) reduction of nitro group to an amino grp is followed by cyclo dehydration to give indole 2- carboxylic ester.

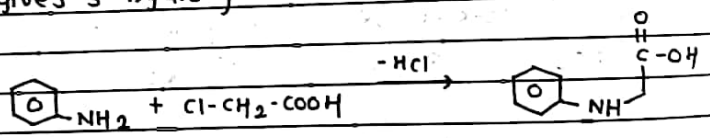
ii) The cyclodehydration of n-acyl ortho-toluidines is effected by sodamide to give 2-alkyl indole

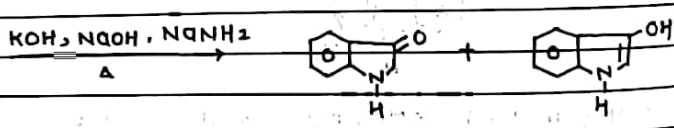


iii) α-aryl amino ketones undergo an intramolecular electrophilic substitution reactn under acid catalysis followed by elimination of H_2O mol gives indoles.



iv) Aniline & chloroacetic acid yields phenyl amino acetic acid & this amino acetic acid on melting with KOH, NaOH, $NaNH_2$ to gives indoxyl & it is on enolisation gives 3-hydroxy indole.

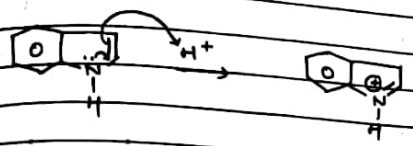




* Reactivity :

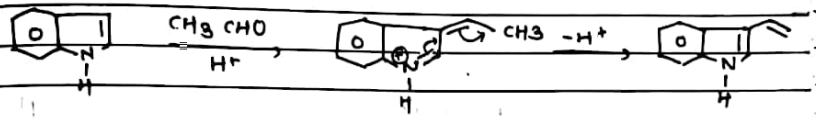
1. Acid-Base reactions :-

In indole protonation occurs mainly on C3 carbon with the formation of 3-H indolium ion.



Indole posses N-H acidity similar to that of pyrrole : Indole reacts with sodamide in liq. NH_3 with sodium hydroxide in organic solvent with grignard reagent & with butyl lithium gives 1- metallated indoles.

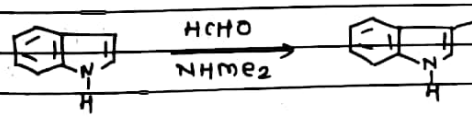
8. Electrophilic substitution reactions :-



In indole attack of electrophiles on the 3 position leads to the formation of low energy imminium structure of σ - complex.

Attack of electrophile on the 2 - position results in high energy ortho · quinoid imminium structure

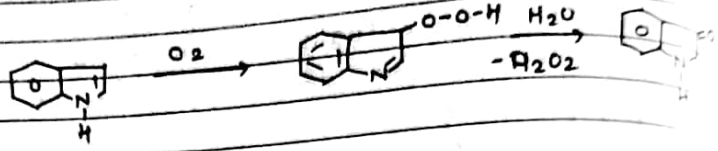
ii)



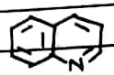
8. Addition reactions :-

catalytic hydrogenation of indoles under pressure & at elivated temp. leads to the formation of 2,3 - dihydro indoles.

Indoles like pyrroles are easily oxidised during auto oxidation. The 3-position is attacked by oxygen leading to a hydroperoxide which gives rise to indoxyl.

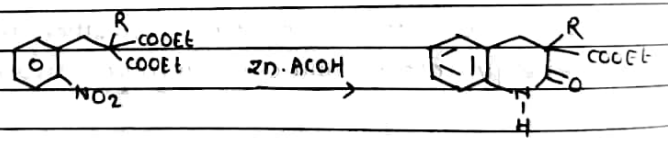


2. Quinoline :



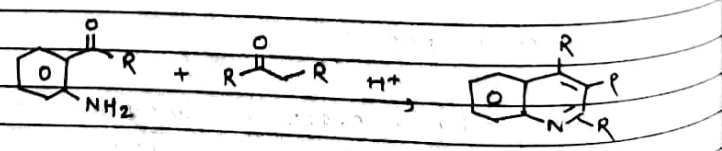
1) Synthesis -

i. Reductive cyclization of ortho nitro phenyl propane derivative for e.g ortho-nitro benzyl malonic ester gives 3,4-dihydro 2-quinolones.

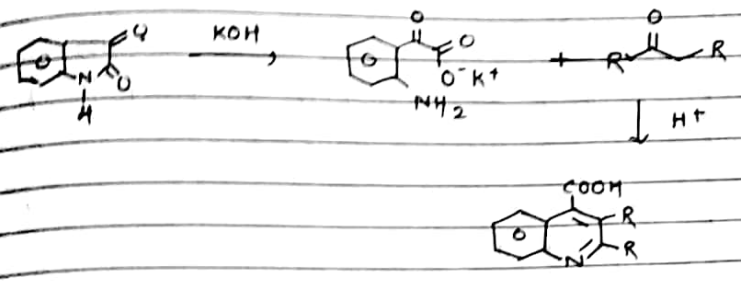


ii) cyclocondensation of ortho amino aryl ketones or aldehydes with ketones possessing an α-CH2 grp involves the formation of quinoline.

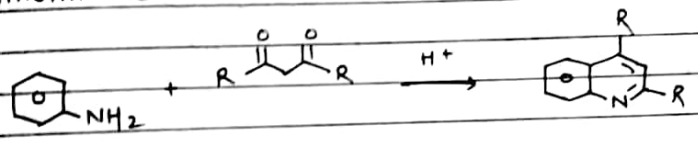
Friedlander Synthesis.



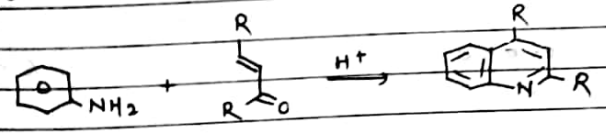
3) The reactn of methylene ketone with Isatin in an alkaline medium results in the formation of quinoline 4- carboxylic acid.



4) 1° aromatic amine with a free ortho possition can be made to undergo cyclocondensation with β-diketone or with β-keto acid in strongly acidic medium gives quinoline (combes synthesis)



5) In skrab synthesis of Quinoline 1° aromatic amine reacts with α,β- unsaturated carbony compin an acidic medium in the presence of an oxidising agent nitro arene.

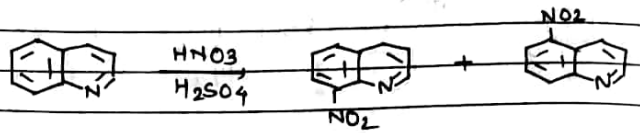


* Reactivity :-

Electrophilic substitution reactn :

1. Nitration :-

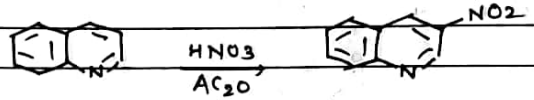
- Nitration takes place with nitrating mix under mild condn leading to the formatn of a mix of 5 & 8 - nitro quinoline.



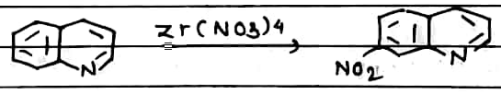
- Nitration of quinoline with nitric acid in acetic anhydride gives 3 - nitro quinoline. A transition metal can exert special effects for e.g zirconium nitrates gives a nitration reactn with quinoline as 7 - nitro quinoline.

Imp MCQ's

i)



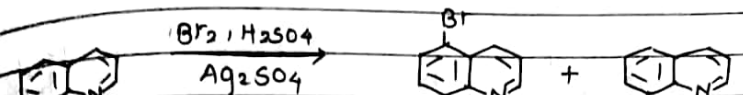
ii)

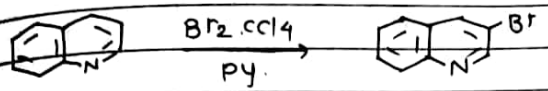


7. Halogenation :-

- Quinoline when brominated with Br2 in H_2SO_4 the in the presence of Ag_2SO_4 gives a mix of 5 & 8 bromo quinoline.

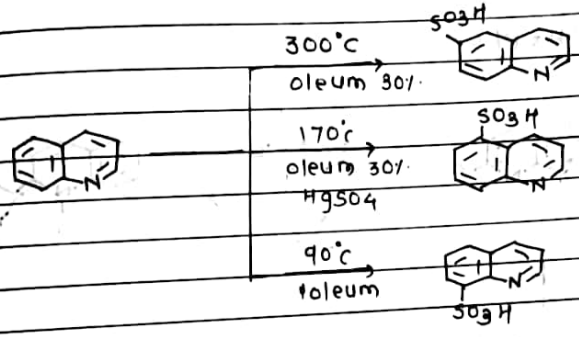
- Bromine is made to reacts with quinoline in the presence of pyridine in CCl_4 results in the formation of 3 - bromo quinoline





* Sulphonation :

imp MCQ's

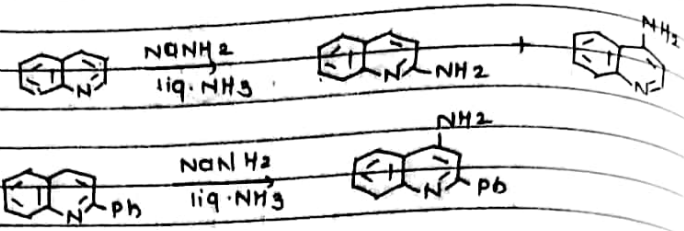


Sulphonatn of quinoline produces diff. product depending on reactn temp & at 90° the 8-sulphonic acid quinoline raising the temp at 170°C in the presence of $HgSO_4$ gives only 5-sulphonic acid. At 300°C quinoline 6-sulphonic acid is the sole product.

predo-minately

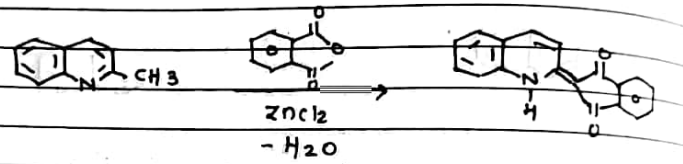
* Nucleophilic substitution reaction :

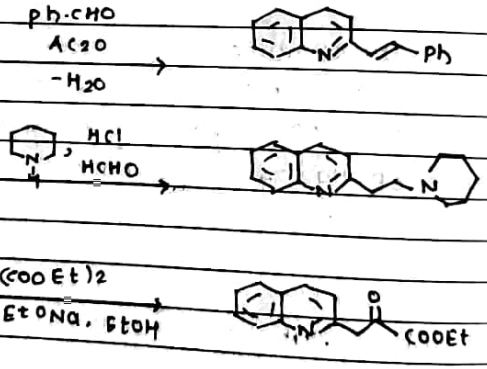
Chichibabin aminatn predo proceeds with alkali amide in liq. NH_3 in this reactn quinoline gives a mix of 2 & 4 amino quinoline.



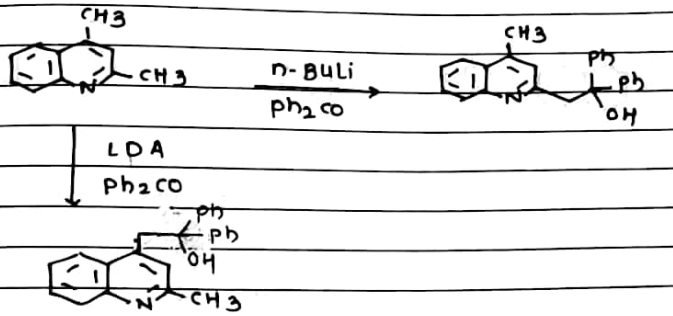
Where as 2-phenyl quinoline gives only 4-amino 2-phenyl quinoline.

* Reactivity of side chain :-





- CH_3 grp attach to the hetero moity of quinoline posses CH acidity thus 2-methyl quinoline undergo base or acid catalyzed C-C forming condensation reaction.

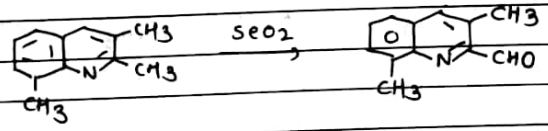


n-butyl lithium coordinates to quinoline nitrogen & preferentially deprotonate the CH_3 grp at 2-position where as LDA deprotonate the more acidic $-CH_3$ protons at 4-position.

* Oxidation :-

i)

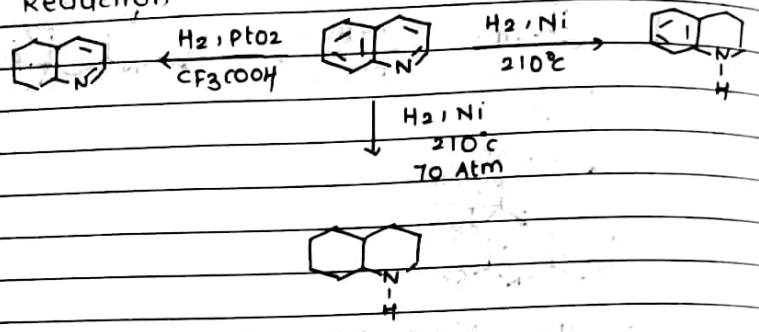
ii)



Alkaline permagnet causes oxidative cleavage of benzene ring in quinoline & 2-substituted quinoline to give 2,3-dicarboxylic acid. In contrast to acidic permagnet oxidises the pyridin anthralinic acid ring with the formation of N-acyl anthralinic acid.

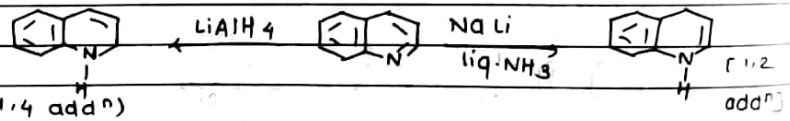
SeO_2 oxidises to an 2 & 4-methyl grp in quinoline to give formyl grp.

Reduction :



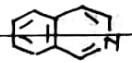
quinoline is reduced at high temp & pressure by Raney nickel as a catalyst to give decahydro system. At atmospheric pressure only in the presence of Raney nickel at 210°C temp gives 1,2,3,4 - tetrahydro quinoline. Selective hydrogenation of the benzene ring gives 5,6,7,8 - tetrahydro quinoline occurs in CF_3COOH with PtO_2 as a catalyst.

2)



quinoline is reduced by $LiAlH_4$ with n- coordination & hydride transfer to the 2 - position gives 1,2 - dihydroquinoline where as lithium or sod. in liq. NH_3 gives 1,4 - dihydro quinoline.

2. Isoquinoline :



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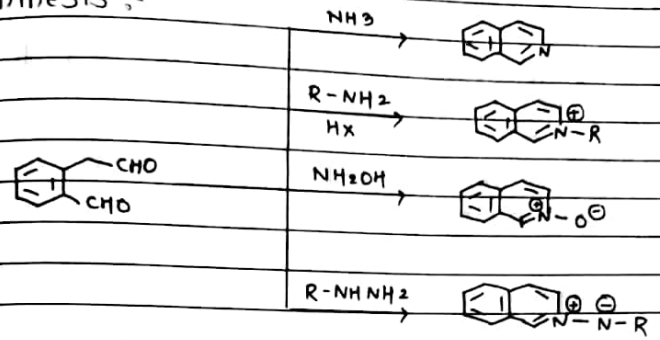
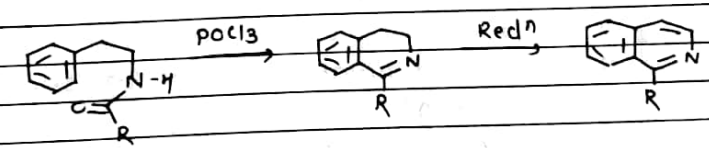
1. synthesis :-



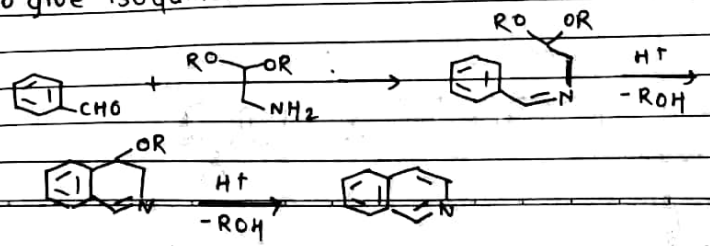
A dicarbonyl comp undergo cyclization with NH3 gives isoquinoline, with 1° amines gives N-substituted isoquinolium ions, with hydroxyl amines yields isoquinoline n-oxides & with hydrazines produced isoquinolinium n-betane.

2. On treatment with strong protic acid like H_2SO_4, PPA or lewis acid or $POCl_3$ to 2-aryl ethylamine cyclize giving 1-substituted 3,4-dihydro isoquinolines which on reduction gives isoquinolines (Bischler-Napieralski synthesis)

i)



3. Aryl aldehydes react with amino acetaldehyde acetals to give isoquinolines.



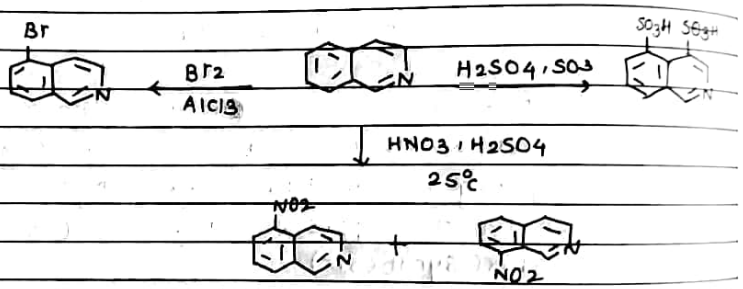
4.

The acid catalyzed cyclocondensation of 2-aryl ethyl amine with aldehyde is the most imp preparation method for 1,2,3,4-tetra hydro isoquinoline.

2. Reactivity :-

* Electrophilic substitution reactn :-

1.



Aromatic electrophilic sub. reactn occurs preferentially in the 5 & 8-position of isoquinoline.

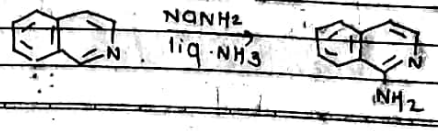
Nitration with nitrating acid at R.T affords 5 & 8 nitro compound.

Bromination in the presence of strong protic acid or $AlCl_3$ leads to the 5-broma compound

Sulphonation with oleum gives 5-sulphonic acid

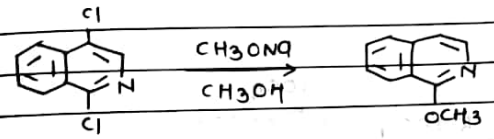
* Nucleophilic substitution reaction :-

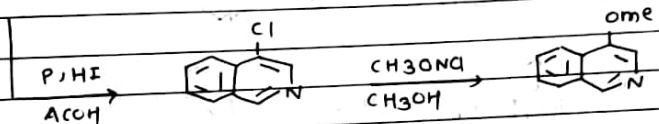
2.



Nucleophilic reactn takes place on hetero ring of Isoquinoline preferably on 1- position for e.g chichibabin amination with liq NH_3 gives 1-amino isoquinoline.

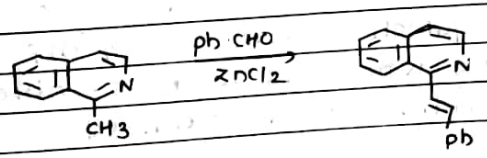
3.





* Reactivity of side chain :-

1.



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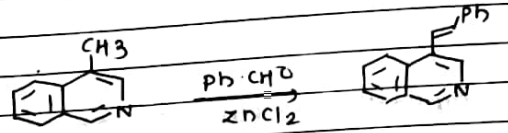
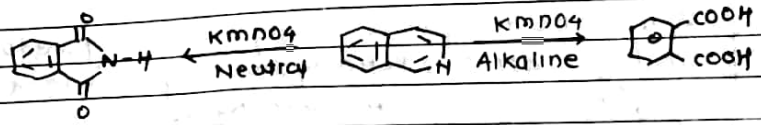
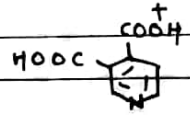
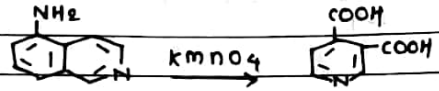


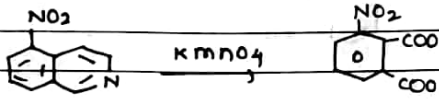
* Oxidation :-





- Oxidatn of Isoquinoline with alkaline $KMnO_4$ gives mix of pthalic acid & pyridine 3,4-dicarboxylic acid while $KMnO_4$ in neutral medium does not affect the benzene ring affording pthalimide as oxidatn product.

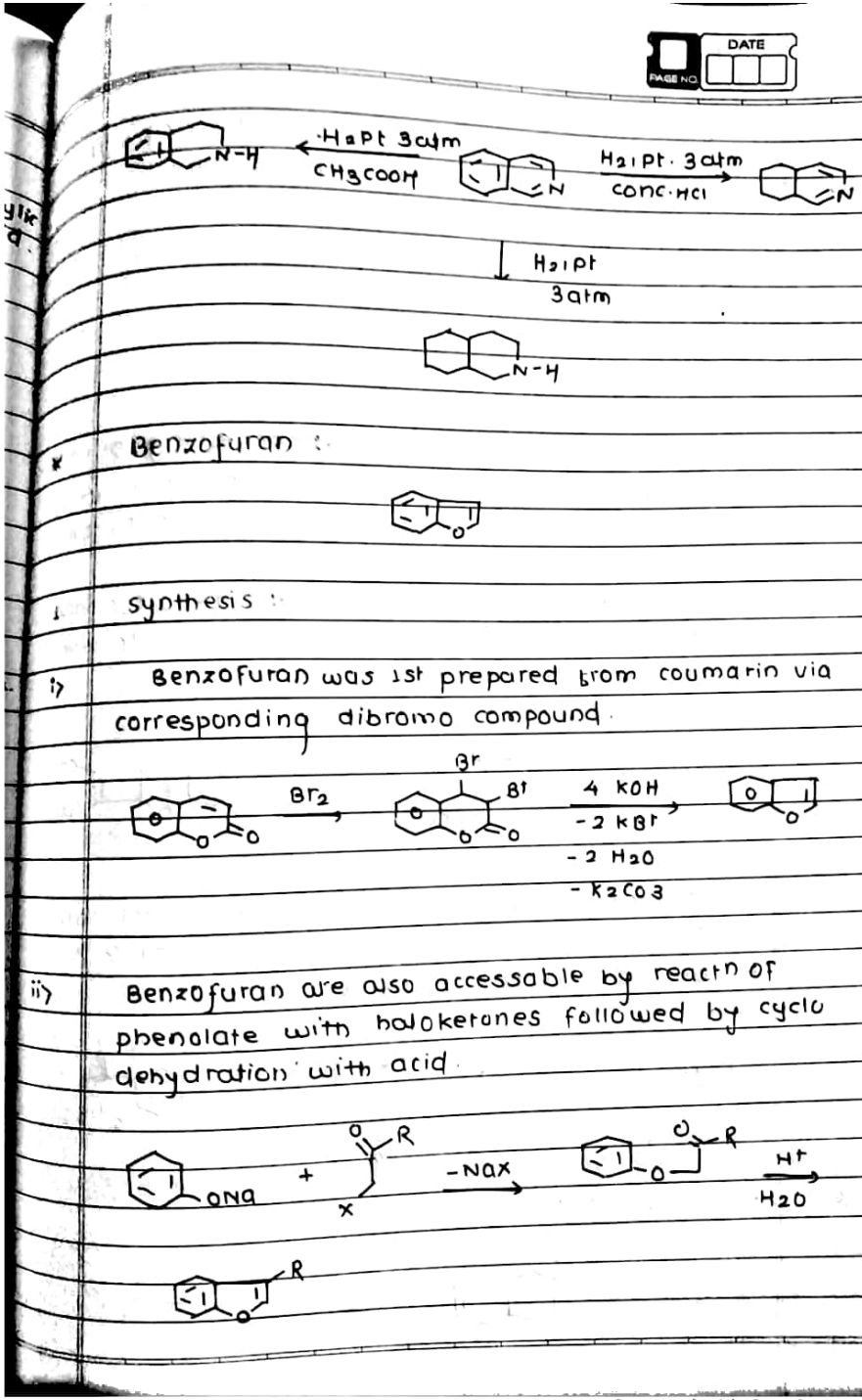




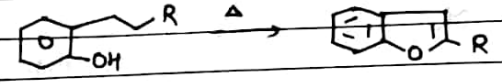
Oxidation of Isoquinoline in presence of substituent affects the oxidation product for e.g oxidatn of 5-amino isoquinoline with $KMnO_4$ affects only benzene ring where as with 5-nitro isoquinoline only pyridine ring is oxidised.

* Reduction :-

Reductn of Isoquinoline is carried out by catalytic hydrogenation, by hydride reagents or by metals. Selective reductn of the pyridine ring to 1,2,3,4-tetrahydro isoquinoline occurs in acetic acid. Where as in conc.HCl benzene ring selectively reduce to afford 5,6,7,8-tetrahydro isoquinoline & further hydrogenation leads to deca-hydro isoquincline.

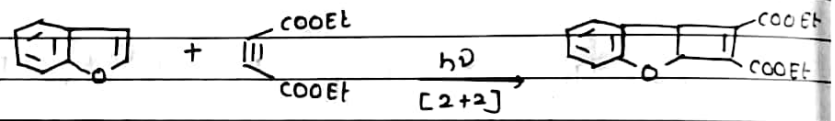


In contrast thermal cyclodehydration of 2-alkyl furans leads to 2-alkyl benzo furans.

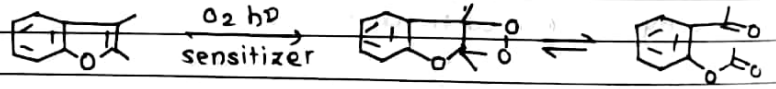


2. Reactivity :

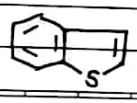
- In contrast to furan the benzene ring in benzofuran is dominant to such an extend that [4+2] cycloaddn are not possible b'coz of it's large resonance energy.
- on the other hand photochemically [2+2] cycloaddn occurs with acetylene dicarboxylic ester to give cyclobutene derivative.



2) photooxygenation of 2,3-dimethyl benzofuran produces dioxeta which isomerise at R.T to give 2-acetoxy acetophenone.

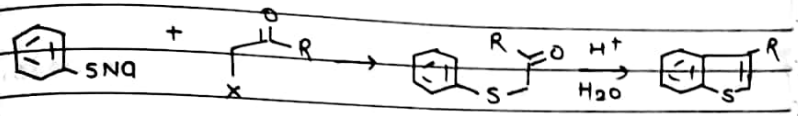


* Benzothiophene :

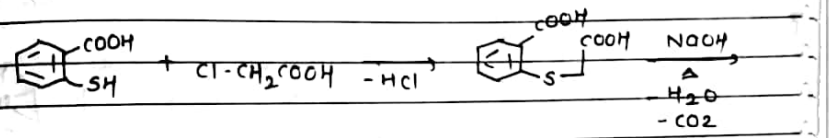


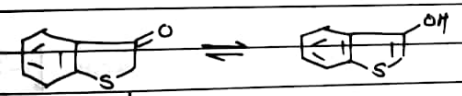
Synthesis :

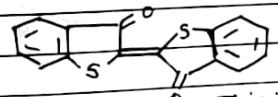
By anology with benzofurans benzothiophene can be obtain from thiophenolate & α-haloketone.



several comp. which are known as thioindigodies are derived from benzo thiophene.
Thioindigo itself is made from thiosalicylic acid via thioindoxyl.



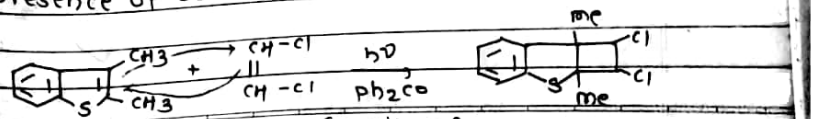




Thioindigodies

Reactivity -

Benzothiophenes undergo photochemical [2+2] cycloaddn for instance with 1,2-dichloroethene in the presence of benzophenone as sensitizer

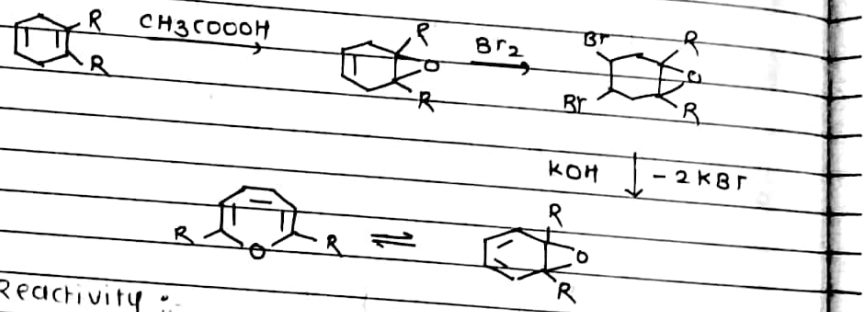


(sensitizer)

* Oxipines :

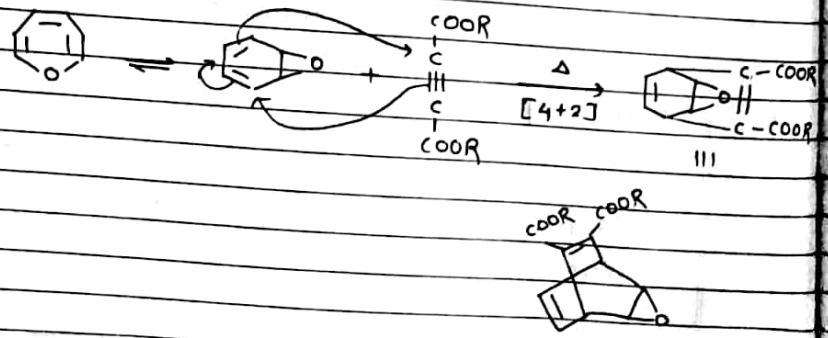
1) Synthesis :

i) The synthesis of monocyclic oxipine starts from 3,4-dibromo seve 7-oxa bicyclo [4.1.0] heptanes which are readily accessable from cyclohexa 1,4-dienes by monoepoxidation followed by bromine addn to the remaining double bond. A double dehydro bromination with a base KOH or methoxide yields benzeneoxide / be· oxipine.



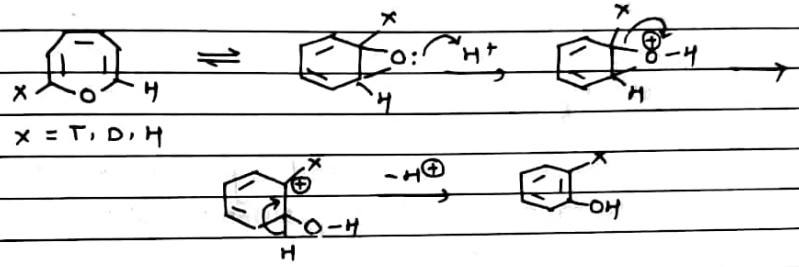
2) Reactivity :

ii)

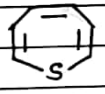


The possibility of valence isomerization also affects the reactn of oxipines for instance cyclo-addn involve the benzene oxide by Diels Alder reactn with activated alkynes gives epoxibarrie-lene.

iii) Acid catalyzed conversion into phenols is acheived by Deuterium & tritium labling experiments.

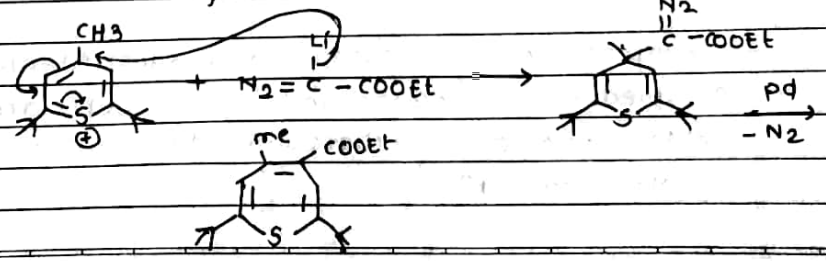


* Thiepines :

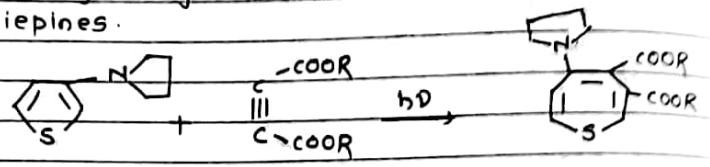


↓ synthesis :

The stable ~~thiepi~~ thiepines are obtained by interactn of thiopyrilium salt & ~~thi~~ lithio-diazo acetic ester via C_4 addn to the thiopyrilium salt & ring expansion of the carbene intermediate



ii) The parent comp. has not yet been synthesized however substituted thiepines are stable & accessable by various roots.
For instance 3-amino sub. thiepénes & activated alkynes undero [2+2] cycloaddn followed by electrocyclic cyclobutene fission to give respective thieplnes.



* Reactivity:

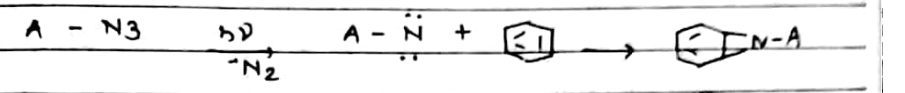
i) Thiepines are converted by valence isomerisn into thiiranes which on desulphurisation & ring contraction gives arenes.

* Azepines:

i) Synthesis:-

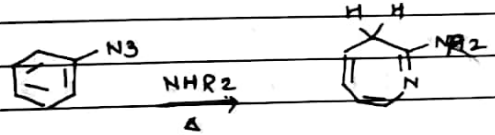
- Azepines with e⊖ accepting & substituents are obtained by a photoinduced reactn betn arenes & azides with e⊖ withdrawing substitutent leading to N_2 eliminatn

1. In the 1st step photolysis of azide giving nitrene intermediate which forms azepines by reactn wd [1+2] cycloaddn with arenes



A = e⊖ withdrawing grp

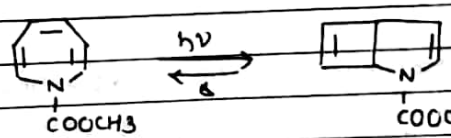
2. Thermolysis of aryl azide with 2° amine leads to 2 amino 3-H azepines.



3. Reactivity:-

1-H azepines with e⊖ accepting n-substituents are converted photochemically to 2-azabicyclo [3.2.0] heptadienes.

- The bicyclic compounds undergo thermal ring opening of cyclobutene ring thereby reversing electro cyclization reforming azepines.



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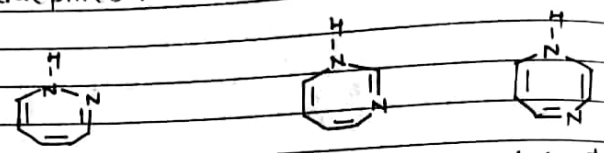
* synthesis & rearrangement of :-

1. Diazepines :



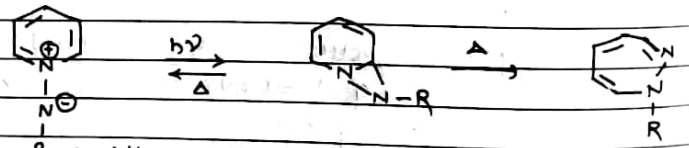
1,2 - diazepine 1,3 1,4 - diazepine

- synthesis of diazepines are carried out by various roots.

:> synthesis -

a) photochemically induced isomerisation of pyridine N-ylides gives 1H 1,2-diazepines with eℓ withdrawing N-substituent on nitrogen.

- The initial products of the photoreactn are 1,7-diaziridines which yield the product in thermal condition. The diaziridines can be thermally reconverted into pyridine N-ylides.

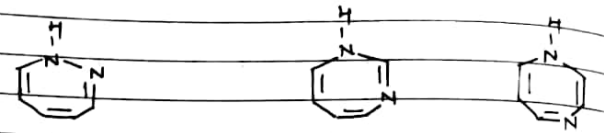


R pyridine N-ylide

b) on 1,7-electrocyclisation of diazo penta 2,4-dienes followed by a 1,5 hydrogen shift leads to 3H-1,2 diazepines.

* synthesis & rearrangement of :-

1. Diazepines :



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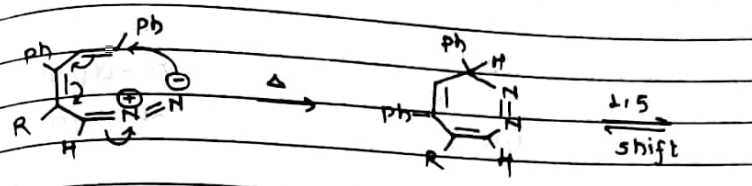
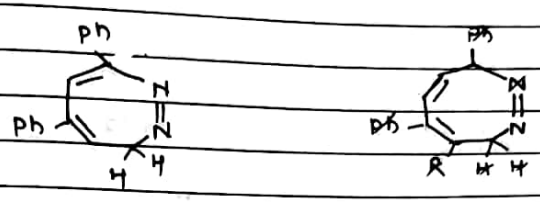
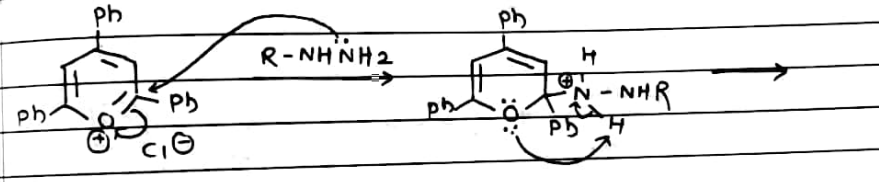
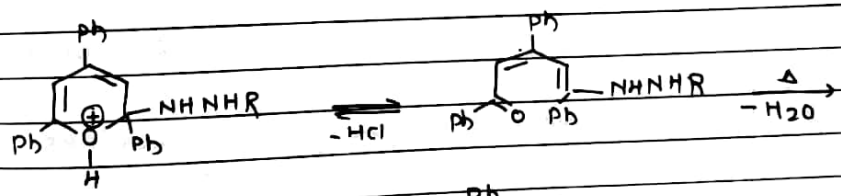
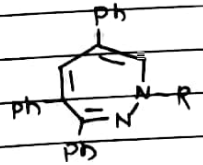




on reactn with hydrazine or alkyl hydrazine pyrilium or thiopyrilium salt produced. Diazepines via a sequence of ring opening & ring closing.



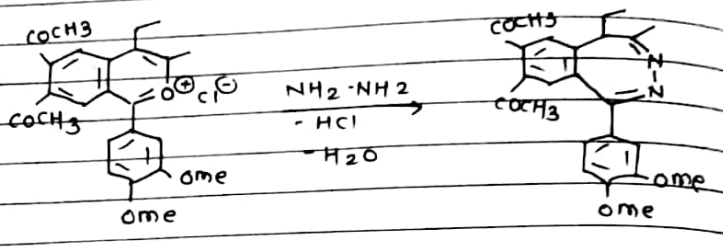




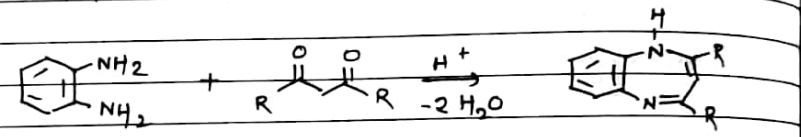
synthesis of :-

Benzodiazepine :-

1. The tranquilizer 5-H 2,3-benzodiazepine (Grandaxin) was commercially preapared from benzo pyrilium salt on reactn with hydrazine

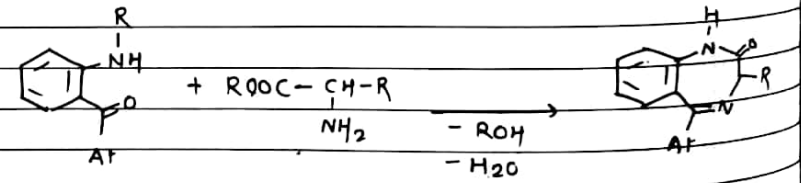


2. 1,5-benzodiazepines are obtain by a cyclocondensation of 1,2-diamino arenes with 1,3-diketones in the presence of acid.



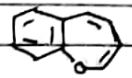
1,5 benzodiazepine

3. 2,3-dihydro 1-H 1,4-benzodiazepines-2-one are obtain from ortho-amino benzophenone by cyclocondensation with amino esters under basic conditions.



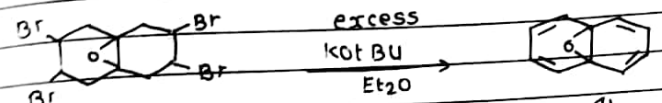
1,4-benzo diazepine.

Benzooxepines:

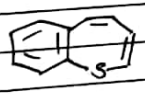


Synthesis:

Tetra bromo decaline epoxide on reactn with a base KotBu in diethyl ether solvent gives benzo oxepines by a way of 9,10 epoxy naphthalene.

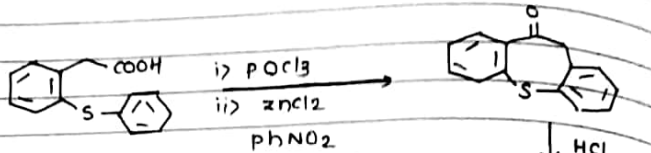


Benzothiepines:

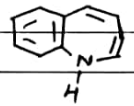


Synthesis:

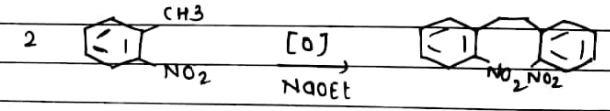
Benzothiepines are obtained by cyclisation of ortho phenyl thio phenyl acetic acid with pocl3. The reactn involves an intramolecular ~~free~~ friedal crafts acylation followed by halogenatn of the intermediate dihydrothio quinone probably via it's enol form.

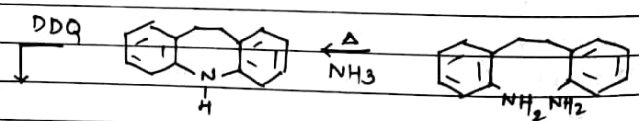


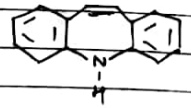
4) Benzoazepines :



oxidative self condensation of ortho nitro toluene giving dinitro-bi-benzyl & this on reduction with H_2-Pd/C & cyclisation under thermal condition follow by aromatisation with DDQ gives benzoazepines.

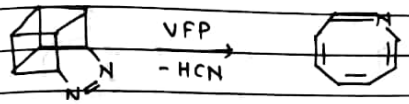




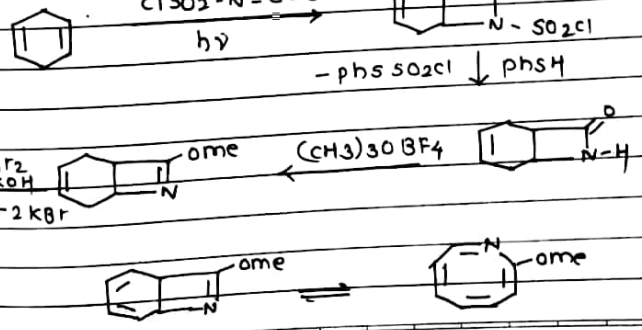


Azocine :

Azocine is the aza analogue of cyclo octa tetra ene. It obtain by vaccum flash pyrolysis (VFP) by Diaza pasketing & removal of HCN.

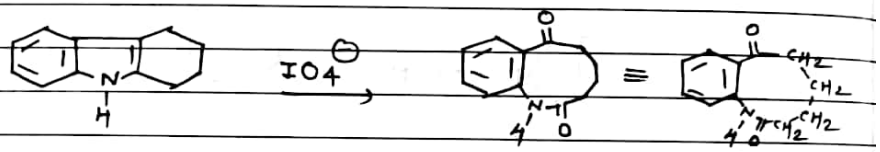


2-methoxy azocine is synthsize by [2+2] cycloaddn of chlorosulphonyl isocynate to 1,4-cyclohexadiene. The chlorosulphonyl grp in the adduct is removed by treatment with thiophenol & gives β-lactam this β-lactum is converted into imidic ester by alkylation with trimethyl oxonium tetrafluro borate.
A double allylic bromination with a brominating agent followed by dehydrobalogenation with base afford aza-bicyclo octatriene, which on rearrangement gives 2-methoxy azocine.



67 Azonines :

The periodate oxidation of 1,2,3,4 - tetrahydro carbazole afforded 3,4,5,6 - tetrahydro 1,H benzo. azonine 2,7 - dione.



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