SYLLABUS

Semester-III

17CHU303 ORGANIC CHEMISTRY III: 4H 4C

Nitrogen Containing Functional Groups, Heterocyclic chemistry and natural products

Instruction Hours/week:L: 4 T:0 P:0 Marks: Internal: 40 External: 60 Total:100

Scope

The course deals with the preparation and properties of nitrogen containing functional groups, alkaloids, heterocyclic compounds and terpenes.

Objectives

1. To provide the preparation and properties of amines, diaonium salts and polynuclear hydrocarbons.
2. To provide knowledge about the preparation and reactions of alkaloids along with the mechanism
3. To provide the preparation and reactions of nitrogen containing heterocyclic compounds.
4. To provide a knowledge about the terpenes.

Methodology

Blackboard teaching, Power point presentation and group discussion.

UNIT I

Nitrogen Containing Functional Groups

Preparation and important reactions of nitro compounds, nitriles and isonitriles.

Amines: Preparation and properties: Effect of substituent and solvent on basicity; Gabriel phthalimide synthesis, Carbylamine reaction, Mannich reaction, Hoffmann's exhaustive methylation, Hofmann-elimination reaction; Distinction between 1°, 2° and 3° amines with Hinsberg reagent and nitrous acid.

UNIT II

Diazonium Salts: Preparation and their synthetic applications.

Polynuclear Hydrocarbons

Aromaticity of polynuclear hydrocarbons, structure elucidation of naphthalene; Preparation and properties of naphthalene, phenanthrene and anthracene.

UNIT III

Heterocyclic Compounds

Classification and nomenclature, Structure, aromaticity in 5-numbered and 6-membered rings containing one heteroatom; Synthesis, reactions and mechanism of substitution reactions of:

Furan, Pyrrole (Paal-Knorr synthesis, Knorr pyrrole synthesis, Hantzsch synthesis), Thiophene, Pyridine (Hantzsch synthesis),

UNIT IV

Indole(Fischer indole synthesis and Madelung synthesis), Quinoline and isoquinoline, (Skraup synthesis, Friedlander's synthesis, Knorr quinoline synthesis, Doebner- Miller synthesis, Bischler-Napieralski reaction, Pictet-Spengler reaction, Pomeranz-Fritsch reaction)

UNIT V

Alkaloids

Natural occurrence, General structural features, Isolation and their physiological action, Hoffmann's exhaustive methylation, Emde's modification; Structure elucidation and synthesis of Nicotine. Medicinal importance of Nicotine, Hygrine, Quinine, Morphine, Cocaine, and Reserpine.

Terpenes

Occurrence, classification, isoprene rule; Elucidation of stucture and synthesis of Citral.

Suggested Readings

Text Books:

1. Morrison, R. T. & Boyd, R. N.(1992). *Organic Chemistry*. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).
2. Finar, I. L. (2002). *Organic Chemistry*. Volume 1. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

Reference Books

1. Finar, I. L.(2002). *Organic Chemistry*: *Stereochemistry and the Chemistry of Natural Products*. Volume 2. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).
2. Acheson, R.M. (1976). *Introduction to the Chemistry of Heterocyclic compounds*. John Welly& Sons.
3. Graham Solomons, T.W.(2012). *Organic Chemistry*. John Wiley & Sons, Inc.
4. Kalsi, P. S.(2009). *Textbook of Organic Chemistry*. 1st Ed. New Age International (P) Ltd. Pub.
5. Clayden, J., Greeves, N., Warren, S. & Wothers, P.(2012). *Organic Chemistry*. Oxford University Press.
6. Singh, J.; Ali, S.M. & Singh, J. (2010). *Natural Product Chemistry*. PrajatiParakashan.

KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed to be University Established Under Section 3 of UGC Act 1956)

Coimbatore – 641 021.

LECTURE PLAN

DEPARTMENT OF CHEMISTRY

STAFF NAME: B.Prabha & R.Kumar **SUB.CODE**:17CHU303

SUBJECT NAME: ORGANIC CHEMISTRY-III (Nitrogen containing functional groups, Natural Products & Heterocyclic Chemistry)

SEMESTER: III **CLASS**: II B.Sc., CHEMISTRY

S.No	Lecture hour	Topics	Support material
		Unit - I	
1	1	Introduction, Preparation and important reactions of nitro compounds.	T2: 711,719
2	1	Important reactions of nitriles and isonitriles	T1:702, T3:355
3	1	*Amines:* Preparation and properties	T2: 678, T3:367
4	1	Effect of substituent and solvent on basicity	T2: 679
5	1	Gabriel phthalimide synthesis, Carbylamine reaction	T2:680,1012, T3:193,370
6	1	Mannich reaction, Hoffmann's exhaustive methylation	T2:1102,T1:724,T3: 375,379
7	1	Hofmann-elimination reaction	T1:724, T3:379-381
8	1	Distinction between 1°, 2° and 3° amines with Hinsberg reagent and nitrous acid	T1:746, 734
9	1	Revision and discussion of important questions	
	Total No of Hours Planned For Unit 1= 9		
	Unit – II		
1.	1	Diazonium Salts: Preparation and their synthetic applications.	T1:736-737, T3:826,781

2.	1	Aromaticity of polynuclear hydrocarbons	T2:1162, T3:781-783
3.	1	structure elucidation of naphthalene	T2:1163, T3:793
4.		Preparation and properties of naphthalene	T2:1163, T3:793
5.	1	Preparation and properties of phenanthrene	T2:1196, T3:817
6.	1	Preparation and properties of anthracene.	T2:1187, T3:811
7.	1	structure elucidation of phenanthrene	T2:1188, 1197, T3:817,811
8.	1	structure elucidation of anthracene	T2:1188, 1197, T3:817,811
9.	1	Revision and discussion of important questions	
	Total No of Hours Planned For Unit 2 =9		
		Unit - III	
1.	1	HeterocyclicCompounds: Introduction, Classification and nomenclature	T2:1201, T3:826
2.	1	Structure, aromaticity in 5-numbered rings containing one heteroatom	T2:1202 T3:828
3.	1	Structure, aromaticity in 6-numbered rings containing one heteroatom	T2: 1229 T3: 848
4.	1	Synthesis, reactions and mechanism of substitution reactions of:Furan,Pyrrole(Knorr pyrrole synthesis	T2:1203, 1209 T3:828, 837
5.	1	Paal-Knorr synthesis	T3:837
6.	1	Hantzsch synthesis	T3:837
7.	1	Thiophene	T2:1219, T3:834
8.	1	Pyridine (Hantzsch synthesis)	T2:1229, T3:838
9.	1	Revision and discussion of important questions	
	Total No of Hours Planned For Unit 3 =9		
		Unit - IV	
1.	1	Indole (Fischer indole synthesis and Madelung synthesis)	T2: 791
2.	1	Quinoline and isoquinoline	T2: 785,788, R1: 838, 877
3.	1	Skraup synthesis	T2: 785,788, R1: 838, 877
4.	1	Friedlander's synthesis	T2: 785-788
5.	1	Knorr quinoline synthesis	T2: 786-788, R1: 900-901
6.	1	Doebner- Miller synthesis	T2: 785, 900
7.	1	Bischler-Napieralski reaction, Pictet-Spengler reaction	T2: 789-792, R1: 761-780

8.	1	Pomeranz-Fritsch reaction	T2: 789-791
9.	1	Revision and discussion of important questions	
	Total No of Hours Planned For Unit 4 =9		
		Unit - V	
1.	1	Alkaloids: Natural occurrence, General structural features	R1: 710
2.	1	Isolation and their physiologicalaction, Hoffmann's exhaustive methylation	R1: 711, 712
3.	1	Emde's modification	R1: 713
4.	1	Structure elucidation of Nicotine	R1: 731
5.	1	Synthesis and Medicinal importance of Nicotine	R1: 731-733
6.		Medicinal importance of Hygrine, Quinine, Morphine.	R1: 722, 752, 762, 743
7.	1	Medicinal importance of Cocaine, and Reserpine.	R1: 722, 752, 762, 743
8.	1	Terpenes: Occurrence, classification, isoprene rule	R1: 368, 369
9.	1	Elucidation of stucture and synthesis of Citral	R1: 370
10	1	Revision and discussion of important questions	
11	1	Discussion of previous year ESE question paper	
12	1	Discussion of previous year ESE question paper	
	Total No of Hours Planned For Unit 5 =12		
Total Hours Planned		**48**	

Text Books:

T1: Morrison, R. T. & Boyd, R. N.(1992). *Organic Chemistry*. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

T2: Arun Bahl(2005). Advanced organic chemistry, S.Chand & Company Pvt.Ltd. Ramnagar, New Delhi.

T3: Finar, I. L. (2002). *Organic Chemistry*. Volume 1. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

Reference Books

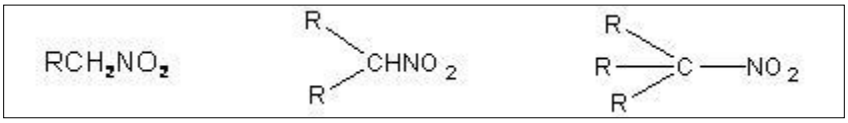
R1: Finar, I. L. (2002). *Organic Chemistry*: *Stereochemistry and the Chemistry of Natural Products*. Volume 2. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

UNIT I
SYLLABUS

Preparation and important reactions of nitro compounds, nitriles and isonitriles. *Amines:* Preparation and properties: Effect of substituent and solvent on basicity; Gabrielphthalimide synthesis, Carbylamine reaction, Mannich reaction, Hoffmann's exhaustivemethylation, Hofmann-elimination reaction; Distinction between 1°, 2° and 3° amines withHinsberg reagent and nitrous acid.

Nitro compounds

Nitro alkanes are derivatives of alkanes. They are isomeric to nitrites (esters) classified as primary, secondary and tertiary depending on the nature of carbon atom to which nitro group is linked.

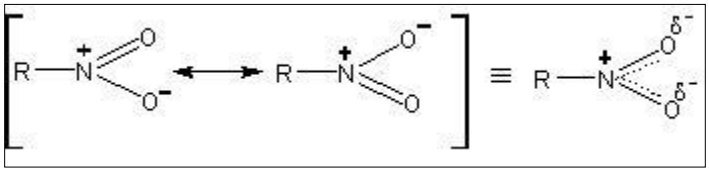


Primary nitro alkane Secondary Nitro alkane Tertiary nitro alkane

—NO_2 group is an ambident group. If it attacks through nitrogen. It is called nitro and if it attacks through oxygen atom, it is called nitrite. Hence nitrites and nitro compounds are isomers.

What are ambident nucleophiles?

Nucleophiles which can attack from two sites such as CN^-, NO_2^- are called ambident nucleophiles. Evidences show that nitrogen is attached to one of the oxygen atoms by a double bond and to the other by a dative bond. The resonance hybrid is shown as under which confirms the spectroscopic evidence that both nitrogen – oxygen bonds have same bond length.



Resonating forms Hyrbid structure

Out of three hybrid orbitals of nitrogen one overlaps with alkyl group and two with oxygens while the unhybridized p orbital of N – atom containing a pair of electrons and lying perpendicular to the plane of hybrid orbitals overlaps sideway with half filled 2 p – orbitals of two oxygen atoms. This

forms π-bond above and below the plane of molecule.

Preparation of Nitro Compounds

(i) From alkyl halides:

Alkyl halides react with silver nitrite in ethanolic solution to give nitro compounds. Alkyl nitrite is formed in minor quantity. This reaction is used to prepare 1^o nitro compounds primarily while $2^o$and 3^o halides give major proportion of alkenes due to β – elimination. Contrary to this alkali nitrites give alkyl nitrites as major product. This is due to ionic nature of alkali nitrite.

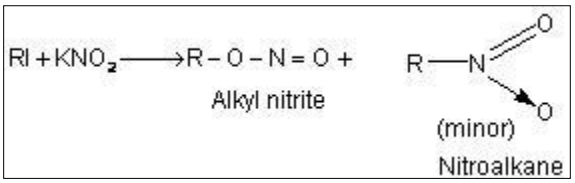
But if the reaction is carried out in solvents like DMF or DMSO, then even $NaNO_2$ or KNO_2 give good yield (about 60%) of nitro compound.

Reactions:

$$R—I + AgNO_2 \longrightarrow RNO_2 + AgI$$

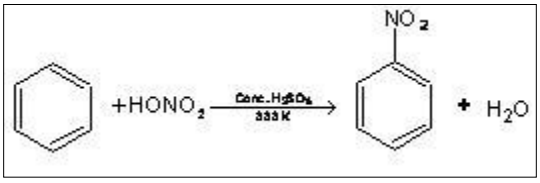
$$C_2H_5I + AgNO_2 \longrightarrow C_2H_5NO_2 + AgI$$

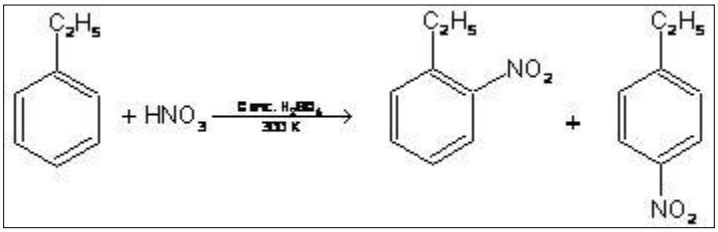
Nitroethane



(ii) Nitration:

Nitro derivatives of aromatic compounds like nitrobenzene are produced when benzene is allowed to react with nitrating mixture.(conc. HNO_3/conc.H_2SO_4).

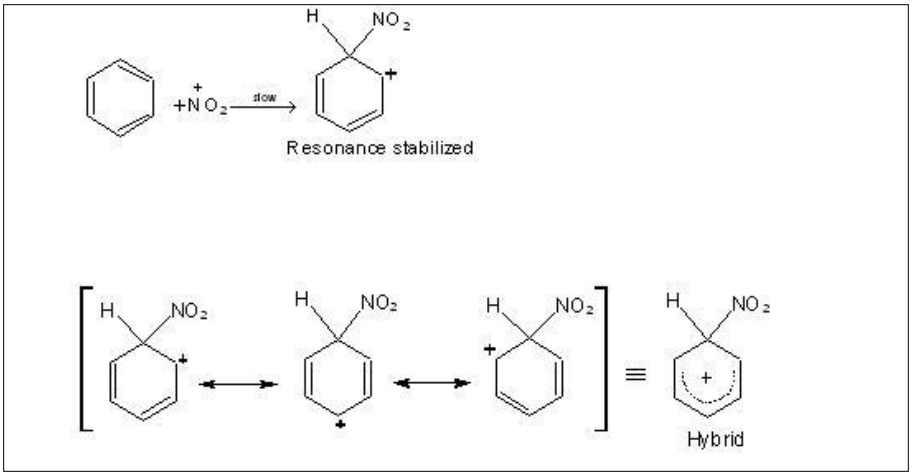




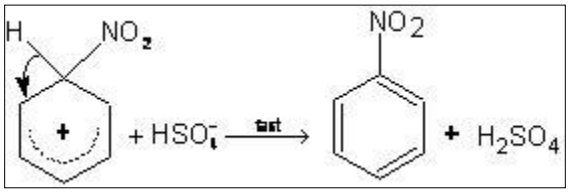
Mechanism:

Generation of nitronium ion

Attack of the nitronium ion NO_2^+ on benzene molecule



Loss of proton:



Nitrobenzene

Direct nitration of alkane involves vapour phase nitration at high temperature.

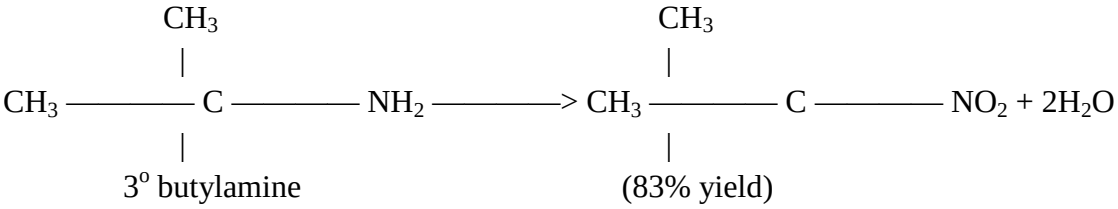
$$R — H + HONO_2 \xrightarrow[675\ K]{} R — NO_2 + H_2O$$
low yield

Problem faced in the method is that at such high temperature, a mixture of nitro alkanes is formed due to C – C cleavage.

e.g. $CH_3CH_2CH_3 + HNO_3 \longrightarrow CH_3CH_2CH_2NO_2 + CH_3CH_2NO_2 + CH_3NH_2$ + other products

(iii) From amines:

3^o nitroalkanes can be produced as follows:



3^o butylamine (83% yield)

Distinguish test between nitroalkanes and alkyl nitrites

1. Nitroalkane on reduction with H_2/Ni produce 1^o amines while alkyl nitrites produce alcohols and NH_3

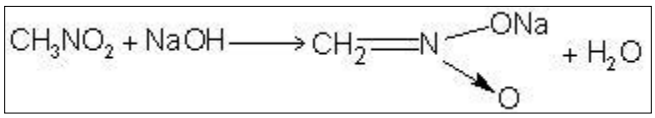
$$CH_3CH_2NO_2 \xrightarrow{[6H]} CH_3CH_2NH_2 + H_2O$$

1^o amine

$$CH_3CH_2 — O — N = O \xrightarrow{[6H]} CH_3CH_2OH_2 + NH_3 + H_2O$$

Ethyl nitrite

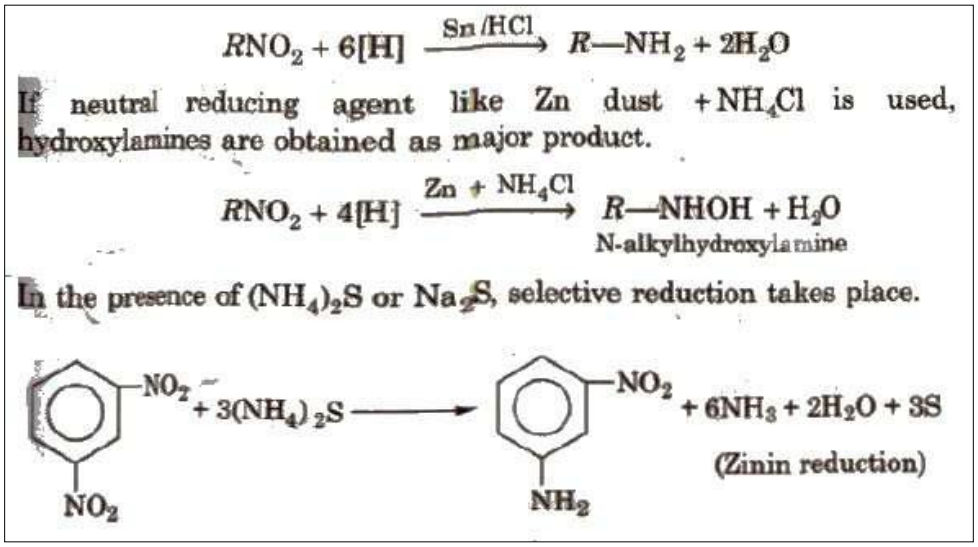
2.Nitroalkanes do not get hydrolysed in basic conditions while nitrites produce alcohols



CH_3 O – N = O + NaOH ——> CH_3OH + $NaNO_2$

Reduction

With Sn/HCl or catalytic hydrogenation, nitroalkanes are reduced to amines.



Nitrobenzene gives different products with different reagents and in different mediums.

Medium	Reagent	Product
Acid	Sn/HCl	aniline
Neutral	Zn/NH_4Cl	N-phenyl hydroxylamine
	$Na_3AsO_3/NaOH$	azoxybenzene ($C_6H_5N{=}\overset{\uparrow}{N}C_6H_5$, O)
Alkaline	$Zn/NaOH, CH_3OH$	azobenzene
	$Zn/NaOH, C_2H_5OH$	hydrazobenzene
Metallic hydride	$LiAlH_4$	aniline
Electrolytic	dil H_2SO_4	*p*-aminophenol

(ii) Action of HNO_2

1° nitroalkane gives nitrolic acid which gives red colour with NaOH.

$$RCH_2NH_2 \xrightarrow[-H_2O]{HNO_2} \underset{\text{nitrolic acid}}{RC(NO_2){=}NOH} \xrightarrow{NaOH} \underset{\text{(red)}}{RC(NO_2){=}NONa}$$

2° nitroalkanes give pseudonitrol with HNO_2.

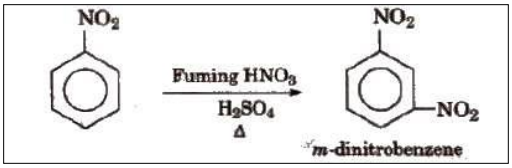
$$R_2CH(NO_2) \xrightarrow[-H_2O]{HNO_2} \underset{\text{pseudonitrol}}{R_2C(NO_2)-NO} \xrightarrow{NaOH} \text{Blue}$$

3° nitroalkanes does not react with HNO_2

(iii) Nef carbonyl synthesis Na or K salt of 1° or 2° nitroalkanes give carbonyl compounds on acidification with 50% H2SO4 at room temperature. This reaction is called Nef carbonyl synthesis.

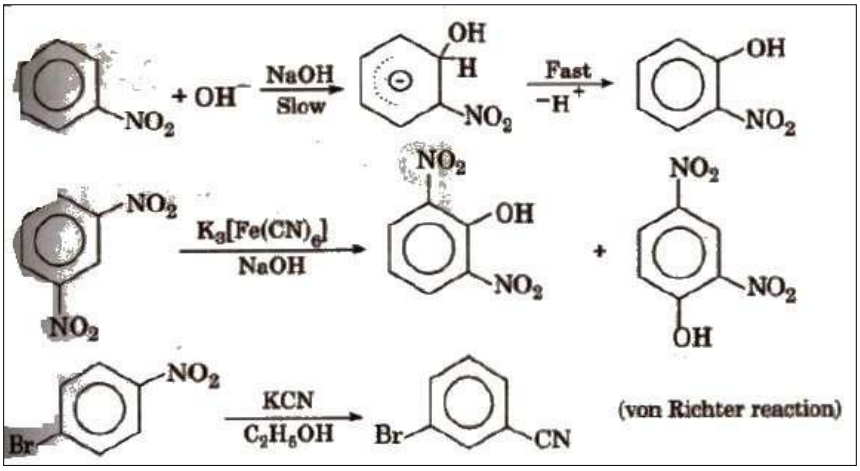
$$R{-}CH_2NO_2 \xrightarrow{NaOH} R{-}CH{=}\overset{+}{N}\begin{matrix}O^-Na^+\\O^-\end{matrix} \xrightarrow{50\%\ H_2SO_4} \underset{\text{aldehyde}}{R{-}CH{=}O}$$

(iv) Electrophilic substitution on nitration, nitrobenzene gives m-dinitrobenzene (as $-NO_2$ is a m-directing group and strongly deactivating).



It does not give Friedel-Craft's alkylation.

(v) Nucleophilic substitution reaction -NO_2 group activates the ring towards nucleophilic substitution.

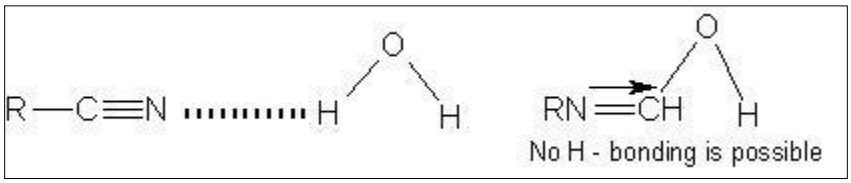


Cyanides and Isocyanides

Both alkyl cyanides (RCN) and alkyl isocyanides (RNC) are organic derivatives of hydrocyanic acid HCN. Alkali cyanides are ionic $\left(:C\equiv\bar{N}:\right)$ and cyanide ion is ambident in nature (can form covalent bond either from carbon or nitrogen).AgC = N is covalent, hence lone pair on nitrogen is mainly available for covalent bond formation, resulting in predominant formation of isocyanides.

Illustration . How would you account for the fact that alkyl cyanides are soluble in water but alkyl isocyanides are insoluble in water?

Solution: Alkyl cyanides possess the tendency to form H – bonding with water which is absent with isocyanides



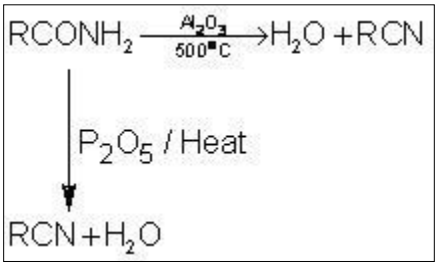
Alkyl Cyanides'

These compound have formula RCN. These are the derivatives of RCN.
According to IUPAC system, cyanides are named as 'alkane nitrile', e.g.,

C_3H_7CN	C_6H_5CN
Butanenitrile	benzenenitrile

Methods of preparation of Cyanides

1.Dehydration of Amides:



High molecular weight acid amides are dehydrated to the corresponding cyanide by heat alone.

$$CH_3(CH_3)_6\ OCNH_2 \xrightarrow{Heat} CH_3(CH_2)_6\ CN$$

2. From RX:

$$RX + KCN \longrightarrow RCN + KX$$

This method is satisfactory only if R is 1^o or 2^o group. If it is 3^o group, then it is converted into alkene.

$$CH_3CH_2Cl + KCN \rightarrow CH_3CH_2CN + KCl$$

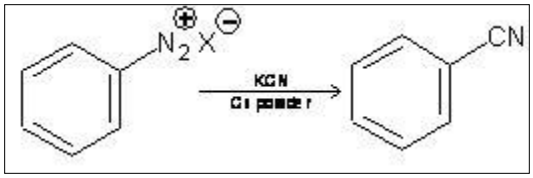
3. By Grignard's reagent and Cyanogen chloride reaction:

$$RMgCl + CICIN \rightarrow RCN + MgCl_2$$

This is best method for preparing 3^o alkyl cyanides.

$$(CH_3)_3CMgCl + CICN \rightarrow (CH_3)_3\ CCN + MgCl_2$$

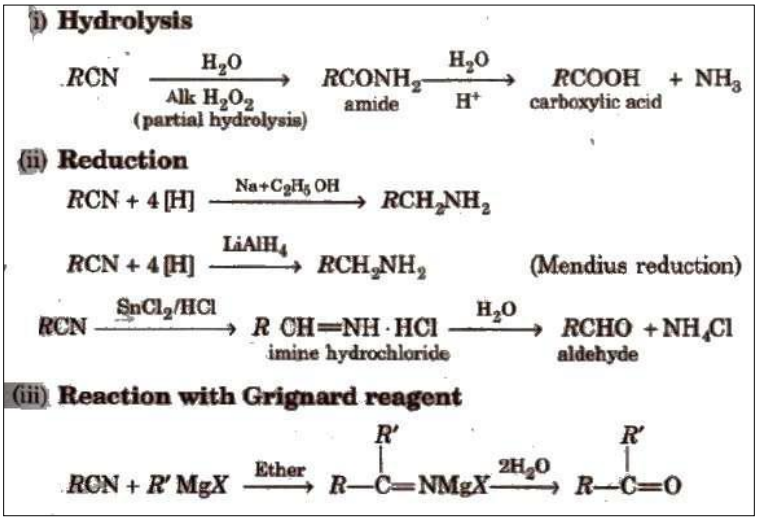
4. From Diazonium salt



Physical properties

1. These are neutral compound with pleasent odour, similar to bitter almonds.
2. These are soluble in water as well as organic solvents.
3. These are poisonous but less than HCN.

Chemical Properties



Alkyl iscoyanides (RNC)

Accordinlg to IUPAC system, these are named as 'alkane isonitrile'

e.g., CH_3NC methyl isonitrile

C_6H_5NC benzene isonitrile

Methods of Preparation of Isocyanides

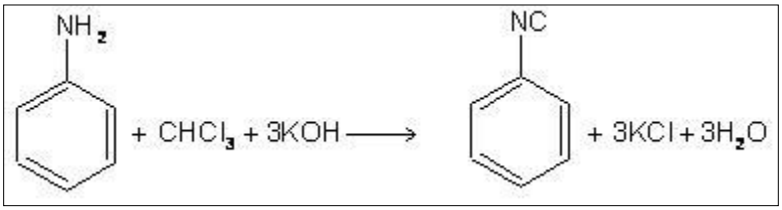
1. By heating an alkyl iodide with AgCN in aqueous ethanolic solution

$$Rl + AgCN \rightarrow RNC + AgI$$
$$C_2H_5l + AgCN \rightarrow C_2H_5NC + AgI$$
Ethylisocyanide

2. By carbylamine reaction

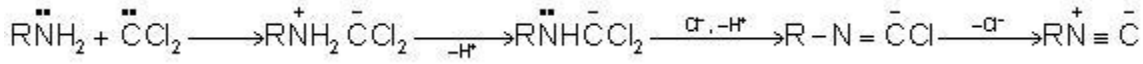
Heating a mixture of 1^o amine and chloroform with ethanolic potassium hydroxide

$$RNH_2 + CHCl_2 + 4KOH \longrightarrow RNC + 3KCl + 3H_2O$$



Mechanism proceeds via intermediate formation of dichloromethylene or, dichloro carbene produced from chloroform in alkaline solution. (Via a-elimination)

$$CHCl_3 + KOH \longrightarrow KCl + H_2O + :CCl_2$$



Properties of Isocyanides

1. Alkyl isocyanides are poisonous, unpleasant smelling, with lower boiling points than isomeric cyanides.
2. RNC are not very soluble in water, nitrogen atom not having a lone pair of electrons available for hydrogen bonding.

Reactions:

1. Hydrolysis:

$$RNC + 2H_2O \xrightarrow{Acid} RNH_2 + HCO_2H$$

$$CH_3NC + 2H_2O \xrightarrow{Acid} CH_3NH_2 + HCO_2H$$

RNC are not hydrolysed by alkalis.

2. Reduction:

$$RNC \xrightarrow{H_2/Pt} R\ NHCH_3$$

2^o amine

$$CH_3NC \xrightarrow{H_2/Pt} CH_3NHCH_3$$

Methyl isocyanide Dimethyl amine

3. When alkyl isocyanides are heated for a long time, they arrange to form cyanide

$$RNC \rightarrow R\ CN$$

$$CH_3CH_2NC \rightarrow CH_3CH_2CN$$

4. With non metals:

(i) $RNC + X_2 \longrightarrow RNCX_2$

$CH_3NC + Cl_2 \longrightarrow CH_3NCCl_2$

(ii) $RNC + S \longrightarrow RNCS$

Alkyl isothiocyanates

$CH_3NC + S \longrightarrow CH_3NCS$

5. Oxidation with HgO:

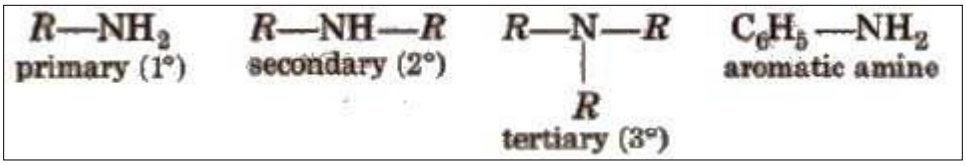
$RNC + HgO \rightarrow RNCO + Hg$

Akyl isocyanates

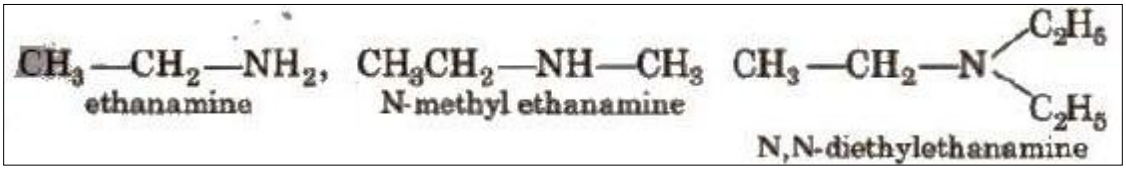
$CH_3NC + HgO \rightarrow CH_3NCO + Hg$

Amines

Amines constitute an important class of organic compounds derived by replacing one or more hydrogen atoms ofNH_3 molecule by alkyl/aryl group(s).

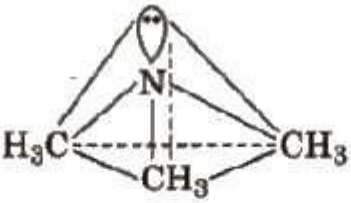


In the IUPAC system, the amines are regarded as alkanamines, e.g.,

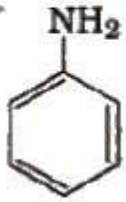


Structure

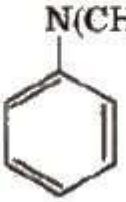
The nitrogen atom in amine is spa-hybridised. The three hybrid orbitals are involved in bond formation and one hybrid atomic orbital contains the lone pair of electrons, giving the pyramidal geometry of amines.



In arylamines, $-NH_2$ group is directly attached to the benzene ring.



aniline
(benzenamine)



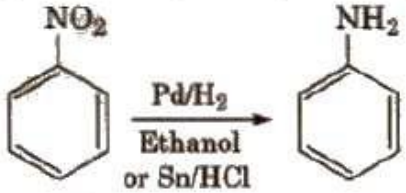
(N,N-dimethylbenzenamine)

Methods of Preparation of Amines

(i) Reduction of nitro compounds

$$R{-}NO_2 \xrightarrow[\text{Reduction}]{} R{-}NH_2 + 2H_2O$$

Reduction can takes place by Sn/HCl, Ni/H_2, Zn/NaOH, Pd/H_2.



The reduction of nitroalkane or nitrobenzene in neutral medium gives hydroxyl amines.

(ii) Ammonolysis of alkyl halides

$$\ddot{N}H_3 + R{-}X \longrightarrow \underset{\text{substituted ammonium salt}}{R{-}\overset{+}{N}H_3X^-}$$

$$R{-}\overset{+}{N}H_3\bar{X} + NaOH \longrightarrow R{-}NH_2 + H_2O + Na^+X^-$$

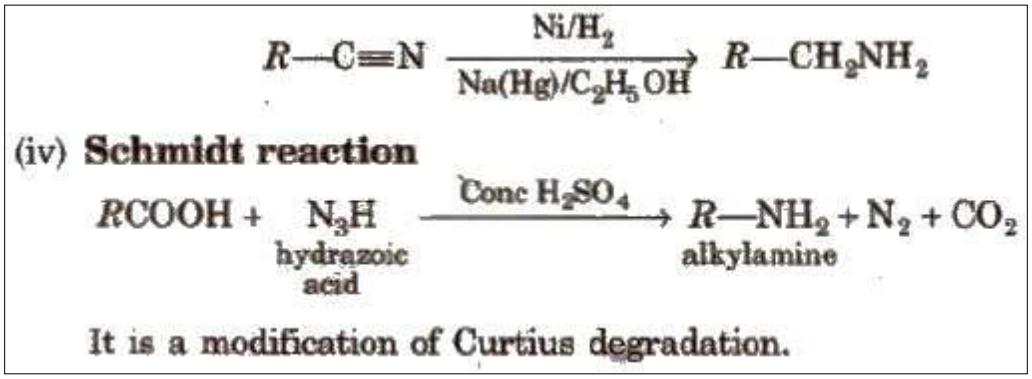
$$\underset{(1^\circ)}{RNH_2} \xrightarrow[RX]{} \underset{(2^\circ)}{R_2NH} \xrightarrow{RX} \underset{(3^\circ)}{R_3N} \xrightarrow{RX} \underset{\text{quaternary ammonium salt}}{R_4N^+X^-}$$

Ammonolysis has the disadvantage of yielding a mixture of primary, secondary and tertiary amines and also a quaternary ammonium salt. However, primary amine is obtained as a major product by taking large excess of NH_3.

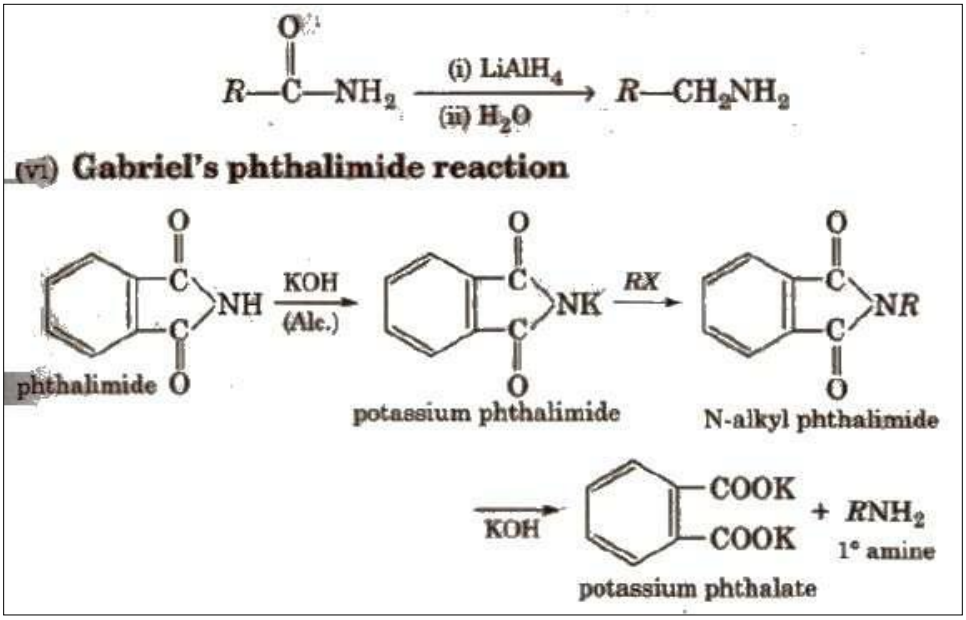
Order of reactivity of halides 'with amines is RI > RBr > RCI.

Aromatic amines could not be prepared since aryl halides are much less reactive towards nucleophilic substitution reactions.

(iii) Reduction of nitriles or cyanides



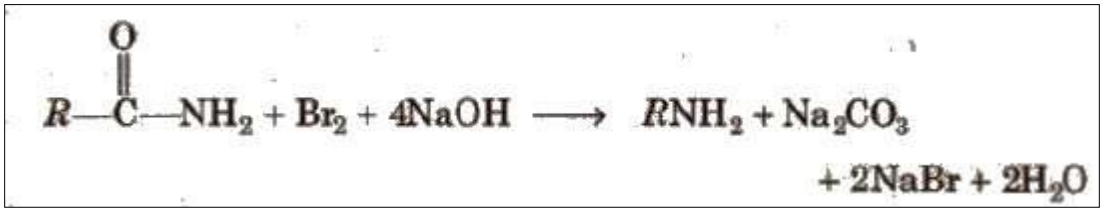
(v) Reduction of amides



It only produces 1 0 amines. This method is not suitable for 1° arylamine because aryl halide

does not give nucleophilic substitution reaction.

(viii) Hofmann bromamide degradation reaction



In Hofmann degradation reaction, the amine formed has one carbon less than the parent amide. To obtain primary amine with same number of carbon atoms from primary amide, reduction is done with $LiAlH_4$/ether.

Physical Properties of Amines

1. The lower aliphatic amines are gases with fishy smell.

2. Primary amines witb three or more carbon atoms are liquid and higher members are all solids.

3. Lower aliphatic amines are water suluble because they can form hydrogen bonds with water molecules, however the solubility decreases with increase in hydrophobic alkyl group.

4. Boiling points order primary > secondary > tertiary

5. Tertiary amines does not have intermolecular association due to the absence of hydrogen atom available for hydrogen bond formation.

Basic Strength of Amines

Amines act as Lewis bases due to the presence of lone pair of electrons on the nitrogen atom. More the Kb (dissociation constant of base), higher is the basicity of amines. Lesser the pKb‘ higher is the basicity of amines.

Aliphatic amines (CH_3NH_2) are stronger bases than NH_3 due to the electron releasing +/ effect of the alkyl group.

Among aliphatic methyl amines, the order of basic strength in aqueous solution is as follows

$$(C_2H_5NH > (C_2H_5)_3N > C_2H_5NH_2 > NH_3$$

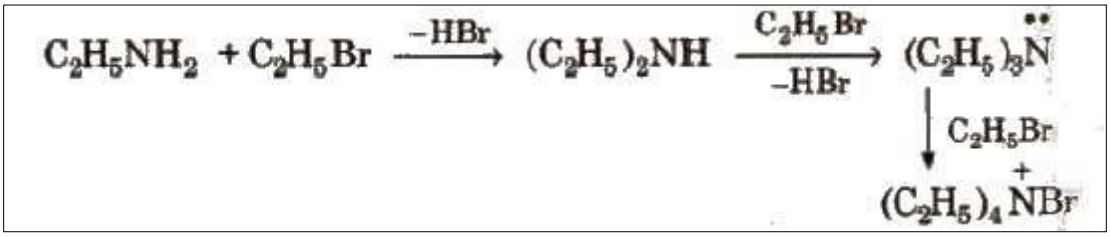
$(CH_3)_2NH > CH_3NH_2 > (CH_3)_3N > NH_3$

Aromatic amines are weaker basesthan aliphatic amlnes and NH3,due to the fact that the electron pair on the nitrogen atom is involved in resonance with the π-electron pairs of the ring. Electron releasing groups (e.g.,-CH_3,-OCH_3,-NH_2 etc.) increase the basic strength of aromatic amines while electron withdrawing groups (like – NO_2, -X,-CN etc.) tend to decrease the same. o-substituted aromaticamines are usually weaker basesthan aniline irrespective of the nature of substituent whether electron releasing or electron withdrawing. This is called ortho effect and is probably due to sterk and electronic factors.

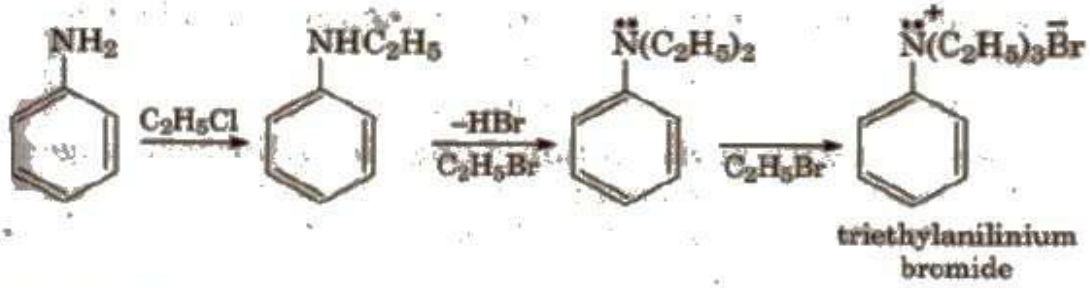
Chemical Properties of Amines

(i) Alkylation

All the three types of amines react with alkyl halides to form quaternary ammonium salt as the final product provided alkyl halide is present in excess.



Aromatic amines also undergo alkylation as given below.



triethylanilinium bromide

(ii) Acylation

$$C_2H_5—NH_2 + CH_3COCl \xrightarrow{Base} C_2H_5—\underset{H}{N}—\underset{O}{C}—CH_3 + HCl$$

$$C_2H_5—NH_2 + CH_3—\underset{O}{C}—O—\underset{O}{C}—CH_3 \longrightarrow$$

$$C_2H_5—\underset{H}{N}—\underset{O}{C}—CH_3 + CH_3COOH$$

acetanilide

(iii) Benzoylation

$$CH_3NH_2 + C_6H_5COCl \xrightarrow{Pyridine} CH_3NHCOC_6H_5 + HCl$$

Benzoylation of aniline is known as **Schotten Baumann reaction.**

(vii) Carbylamine reaction [only by 1° amines]

$$R—NH_2 + CHCl_3 + 3KOH \xrightarrow{Heat} R—N \rightleftharpoons C + 3KCl + 3H_2O$$

isocyanide
(a bad smelling compound)

MIC or methyl isocyanate gas ($CH_3—N=C=O$) was responsible for Bhopal gas tragedy in December 1984.

(v) Reaction with nitrous acid

$$RNH_2 + HNO_2 \xrightarrow{NaNO_2 + HCl} [RN_2^+Cl] \xrightarrow{H_2O} ROH + N_2 + HCl$$

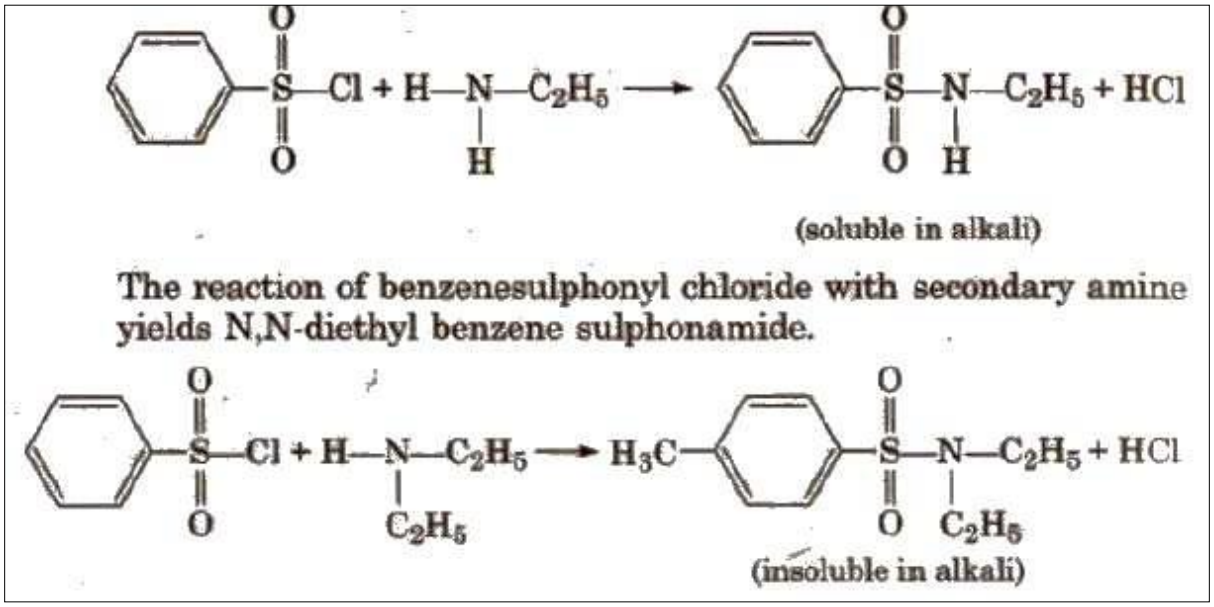
Quantitative evolution of nitrogen is used in estimation of amino acids and proteins.

$$\underset{\text{aniline}}{C_6H_5—NH_2} \xrightarrow[273-278\ K]{NaNO_2 + 2HCl} \underset{\text{benzene diazonium chloride}}{C_6H_5N_2^+Cl^-} + NaCl + 2H_2O$$

But secondary and _tertiary amines react with nitrous acid in different manner.
Methyl amine give dimethyl ether with HNO_2.

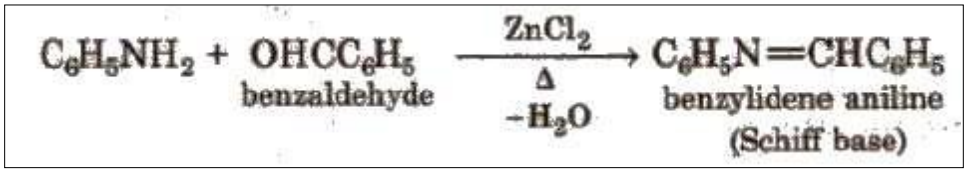
(vi) Reaction with aryl sulphonyl chloride [Hinsberg reagent]

The reaction of benzenesulphonyl chloride with primary amine yield N-ethyl benzene sulphonyl amide.

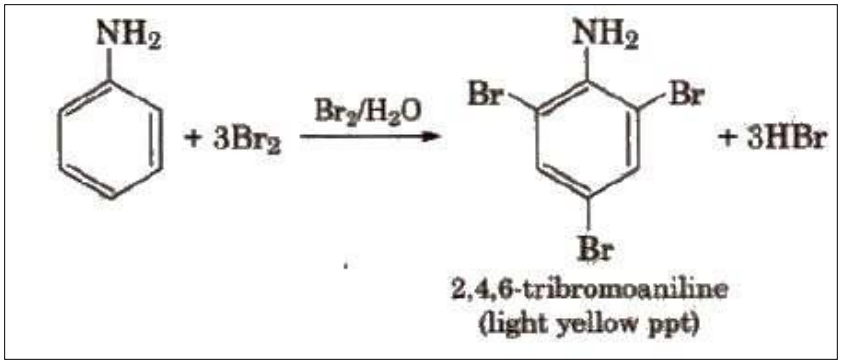


Tertiary amines does not react with benzenesulphonyl chloride.

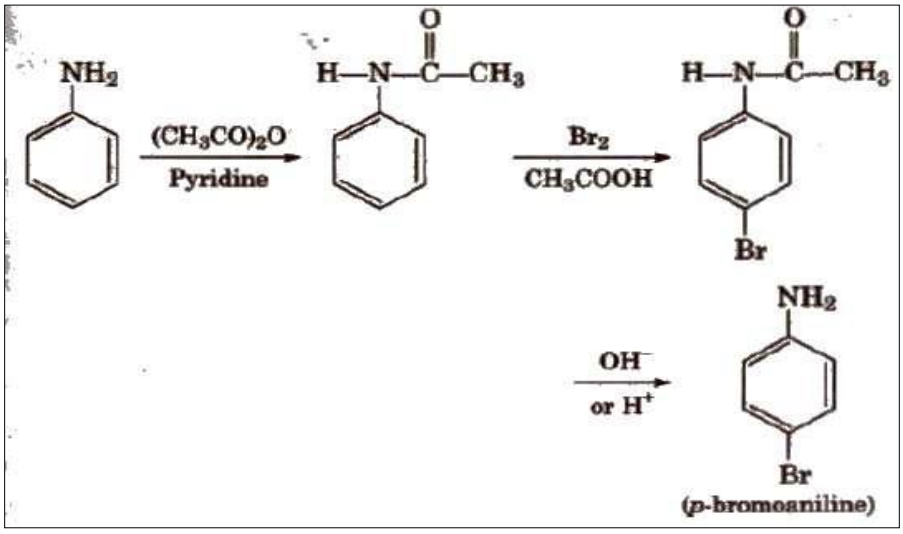
(vii) Reaction with aldehydes Schiff base is obtained.



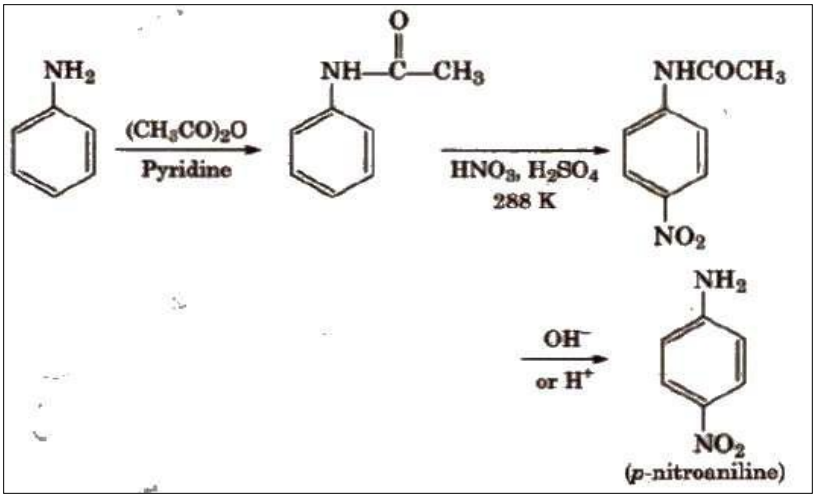
(viii) Electrophihc substitution reactions Aniline is ortho and para directing towards electrophilic substitution reaction due to high electron density at ortho and para-positions.



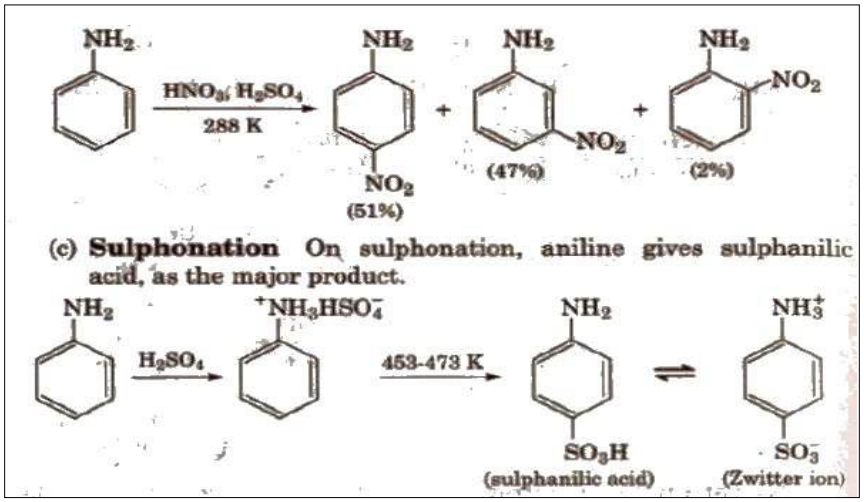
To prepare monosubstituted derivative, activating effect of $-NH_2$ group must be controlled. It can be done by protecting the $-NH_2$ group by acetylation with acetic anhydride.



(b) Nitration Direct nitration of aniline is not possible as it is susceptible to oxidation, thus amino group is first protected by acetylation.



In strongly acidic medium, aniline is protonated as anilinium ion which is meta directing so it gives meta product also.



(c) **Sulphonation** On sulphonation, aniline gives sulphanilic acid, as the major product.

Aniline does not undergo Friedel-Crafts reaction due to salt formation with aluminium chloride, the Lewis acid, which is used as a catalyst. Due to this, nitrogen of aniline acquires positive charge and hence behaves like a strong deactivating group for further chemical reaction.

(ix) Oxidation Use of diffrent oxidising agents gives different products.e.g.,

Oxidising agent	Product
Accidified $KMnO_4$ (or $Na_2Cr_2O_7 + CuSO_4$ + dil acid)	Aniline black (a dye)
Chromic acid ($Na_2Cr_2O_7$ + Conc H_2SO_4)	*p*-benzoquinone
Caro's acid (H_2SO_5)	nitrobenzene and nitrosobenzene
Conc. nitric acid	decomposes

Separation of Mixture of Amines (1°, 2° and 3°)

(a) **Fractional distillation:**

This method is based on the boiling points of amines and is used satisfactorily in Industry.

(b) **Hofmann's method:**

Diethyloxalate is called Hofmann's reagent with which mixture of amines is treated.

- 1° amine forms solid dialkyl oxamide $(CONHR)_2$
- 2° amine forms liquid dialkyl oxamlc ester($CONR_2$-$COOC_2H_5$)
- 3° amines do not react

(c) **Hinsberg's method:**

Amines serve as nucleophiles in attacking the sulfonyl chloride electrophile, displacing chloride. The sulfonamides resulting from primary and secondary amines are poorly soluble and precipitate as solids from solution:

$$PhSO_2Cl + 2\ RR'NH \rightarrow PhSO_2NRR' + [RR'NH_2]Cl$$

For primary amines (R' = H), the initially formed sulfonamide is deprotonated by base to give water-soluble sulfonamide salt ($Na[PhSO_2NR]$):

$$PhSO_2N(H)R + NaOH \rightarrow Na^+[PhSO_2NR^-] + H_2O$$

Tertiary amines promote hydrolysis of the sulfonyl chloride functional group, which affords water-soluble sulfonate salts.

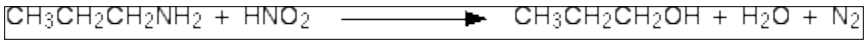
$$PhSO_2Cl+R_3N+H_2O\rightarrow R_3NH^+[PhSO^-_3]$$

(d) **Nitrous acid method:**

Primary amines and nitrous acid

The main observation is a burst of colourless, odourless gas. Nitrogen is given off.

Amongst the products you get an alcohol where the $-NH_2$ group has been replaced by OH. (taking 1-aminopropane as an example for single step explanation):



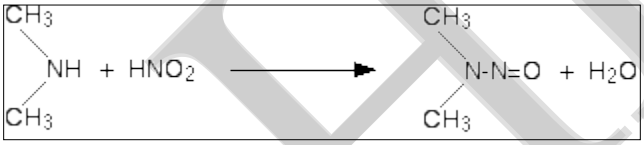
but the propan-1-ol will be only one product among many - including propan-2-ol, propene, 1-chloropropane, 2-chloropropane and others.

The nitrogen, however, is given off in quantities exactly as suggested by the equation. By measuring the amount of nitrogen produced, you could use this reaction to work out the amount of amine present in the solution.

Secondary amines and nitrous acid

This time there isn't any gas produced. Instead, you get a yellow oil called a nitrosamine. These compounds are powerful carcinogens.

For example:



Tertiary amines and nitrous acid

Again, a quite different result is occurrence of colourless solution.

All that has happened is that the amine has formed an ion by reacting with the acid present. With trimethylamine, for example, you would get a trimethylammonium ion, $(CH_3)_3NH^+$.

SUGGESTED MATERIALS:

Text books:

T1: Morrison, R. T. & Boyd, R. N.(1992). *Organic Chemistry*. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).
T2: Arun Bahl(2005). Advanced organic chemistry, S.Chand & Company Pvt.Ltd. Ramnagar, New Delhi.
T3: Finar, I. L. (2002). *Organic Chemistry*. Volume 1. Dorling Kindersley (India) Pvt. Ltd., (Pearson Education).

Reference Books

R1: Finar, I. L. (2002). *Organic Chemistry*: *Stereochemistry and the Chemistry of Natural Products*. Volume 2. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

POSSIBLE QUESTIONS:

Part-A (1 Mark)

(Online Examination for Q.No.1 to 20)

Part-B (2 Marks)

1. How nitrobenzene is prepared
2. Explain the Tautomerism present in aliphatic nitro compounds
3. Show that aliphatic compounds are acidic in nature
4. What is meant by carbylamines reaction
5. Why ammonia is a stronger base than aniline
6. What is the relationship between ammonia and amines?
7. Why aliphatic amines are stronger base than aromatic amines?

Part-C (6Marks)

1. Distinguish primary, secondary and tertiary amines using p-toluene sulphonyl chloride Reagent.
2. Write notes on
   a. Hofmann exhaustive methylation b. Gabriel Phthalamide synthesis
3. Discuss the action nitrous acid on primary, secondary and tertiary amines
4. Write any three methods how nitro compounds are prepared
5. Explain the relative bascities of amines
6. Write any three methods how amines are prepared
7. Explain the reduction of an aromatic nitro compound in different conditions
8. Write notes on the preparation and properties of nitriles and isonitriles
9. Explain the reduction of aliphatic nitrocompounds in different conditions
10. Distinguish primary, secondary and tertiary amines using p-toluene sulphonyl chloride reagent

Karpagam Academy of Higher Education
Coimbatore-21

(For the candidate admitted on 2017 onwards)
Department of Chemistry
III- semester
ORGANIC CHEMISTRY-III

UNIT I- Objective Questions for online examination (Each carry 1 Marks)

Question	Option-A	Option-B	Option-C	Option-D	Answer
Nitroalkanes on reaction with Sn/HCl give	alcohol	Primary amine	Secondary amine	Tertiary amine	Primary amine
Nitroethane on reaction with Sn/HCl give	ethanol	ethylamine	Diethyl amine	triethylamine	ethylamine
Nitration of alkanes gives	Nitro compounds	Alkyl nitrites	Primary amines	Secondary amines	Nitro compounds
Nitration of propane gives	Propyl nitrite	Nitro propane	Propyl amine	Isopropyl amine	Nitro propane
On boiling an aqueous solution of sodium nitrite with an alpha halogen carboxylic acid, it gives	Nitro compound	Alkyl nitrites	alkyl amines	Chloro methyl amines	Nitro compound
On boiling an aqueous solution of sodium nitrite with an alpha chloro acetic acid, it gives	Nitromethane	Methyl nitrites	Methyl amines	Chloro methyl amines	Nitro methane
Catalytic reduction of nitrocompounds in presence of Hydrogen and nickel gives	Primary amine	Hydroxyl amines	Nitroso amines	hydroxylamine	Primary amine
Catalytic reduction of nitro methane in presence of Hydrogen and nickel gives	Methyl amine	Methyl hydroxyl amine	nitrosoamine	N-alkyl hydroxylamine	Methyl amine
In neutral reducing medium nitro compounds are reduced to	Primary amine	Hydroxyl amines	Nitroso amines	hydroxylamine	N-alkyl hydroxylamine
Primary nitro alkanes react with nitrous acid to form	acid	Nitrolic acid	Seudo nitrole	amine	Nitrolic acid
Nitro methane react with nitrous acid to form	Acetic acid	Nitrolic acid	pseudo nitrole	amine	Nitrolic acid
Nitro alkanes can be obtained by	Oxidation of oximes	Oxidation of aldehydes	Nitration of ketones	Nitration of oximes	Oxidation of oximes

Nitro alkanes can be obtained by	Reduction of oximes	Hydrolysis of alpha nitro alkenes	Action of potassium nitrate on alkyl halides	Oxidation of aldehydes	Hydrolysis of alpha nitro alkenes
Nitro alkanes can be obtained by	Reduction of oximes	Hydrogenation of alpha nitro alkenes	Silver nitrite on alkyl halides	Oxidation of aldehydes	Action of Silver nitrite on alkyl halides
Nitro methane can be obtained by	Reduction of oximes	Hydrogenation of alpha nitro alkenes	Silver nitrite on methyl bromide	Oxidation of aldehydes	Action of Silver nitrite on methyl bromide
Nitrolic acid dissolves in sodium hydroxide to give	Blue colour solution	Red colour solution	Colour less precipitate	turbid solution	Red colour solution
Nitration of phenol with dil nitric acid gives	o-nitro phenol	m-nitrophenol	A mixture of m- and o-nitrophenol	A mixture of m- and p-nitro phenol	o-nitro phenol
Nitration of phenol with dil nitric acid gives	A mixture of o- and p-nitro phenol	m-nitrophenol	A mixture of m- and o-nitrophenol	A mixture of m- and p-nitro phenol	A mixture of o- and p-nitro phenol
The –OH group in phenol is a	Ortho directing group	Meta directing group	Para directing group	Ortho and para directing group	Ortho and para directing group
Organic derivatives of hydrocyanic acid are called	Alkyl cyanides	Formates	Acetates	acids	Alkyl cyanides
Organic derivatives of hydrocyanic acid are called	Alkyl iso cyanides	Formates	Acetates	Alkanoic acids	Alkyl cyanides
Which is soluble in water	Alkyl cyanides	Alkyl isocyanides	aldehydes	amines	Alkyl cyanides
Which is insoluble in water	Alkyl cyanides	Alkyl isocyanides	alcohol	acetone	Alkyl isocyanides
Dehydration of amides gives	Alkyl cyanides	Alkyl isocyanides	alcohol	acetone	Alkyl cyanides
Dehydration of acetamide gives	methyl cyanides	Methyl isocyanides	methanol	acetone	methyl cyanides

Reduction of nitrobenzene in acid medium gives	Phenyl hydroxylamine	Hydrazo benzene	Azo benzene	aniline	aniline
Reduction of nitrobenzene in neutral medium gives	Phenyl hydroxylamine	Hydrazo benzene	Azo benzene	aniline	Phenyl hydroxylamine
Electrolytic reduction of nitro benzene gives	Phenyl hydroxylamine	Hydrazo benzene	Azo benzene	para amino phenol	para amino phenol
Reduction of nitrobenzene in alkali medium(Zn/NaOH) gives	Phenyl hydroxylamine	Hydrazo benzene	Azo benzene	para amino phenol	Azo benzene
Reduction of nitrobenzene in alkali medium(Zn/NaOH, in methanol) gives	Phenyl hydroxylamine	Hydrazo benzene	Azo benzene	para amino phenol	Hydrazo benzene
Example for a primary amine	Methyl amine	Ethyl methyl amine	Trimethyl amine	Dimethyl amine	Methyl amine
One of the following is a secondary amine	Methyl amine	aniline	amine	amine	Dimethyl amine
Choose a tertiary amine	Methyl amine	aniline	amine	amine	Trimethyl amine
Example for an alkyl amine	Methyl amine	aniline	toludine	amine	Methyl amine
Choose an aromatic amine	Methyl amine	aniline	amine	amine	aniline
Suitable example for a mixed amine	Methyl amine	Ethyl methyl amine	Trimethyl amine	Dimethyl amine	Ethyl methyl amine
Amines have the	Pyramidal shape	Square planar shape	Trigonal shape	Octahedral shape	Pyramidal shape
Which is having a pyramidal shape	Amine	acetylene	alkenes	trifluoride	Amine
When the reduction is carried out using sodium and alcohol, it is called	Clemmensen reduction	Mendius reduction	Stephen's reduction	Wolf-kishner reduction	Mendius reduction
Gabriel synthesis is carried out for the preparation of	Aldehydes and ketones	alcohols	Primary amines	Carboxylic acids	Primary amines
Hinsberg method is used for the separation of a mixture of	Primary, secondary and tertiary alcohols	Primary, secondary and tertiary amines	Ortho, meta and para nitrophenols	Ortho, meta and para aminophenols	Primary, secondary and tertiary amines
On treatment with bromine and potassium hydroxide amides are converted into	Aldehydes and ketones	alcohols	Primary amines	Carboxylic acids	Primary amines

The reagents used in Hofmann's degradation of amides are	Sodium and alcohol	Ammonium hydrogen sulphide	Hydrogen in presence of nickel	bromine and potassium hydroxide	bromine and potassium hydroxide
Phthalimide is converted into primary amine in	Hofmann's degradation	Gabriel synthesis	Carbylamine reaction	Hofmann's elimination	Gabriel synthesis
Hinsberg's reagent is	p-toluenesulphonyl chloride and NaOH	bromine and potassium hydroxide	Sodium and alcohol	Hydrogen in presence of nickel	p-toluenesulphonyl chloride and NaOH
In Hinsberg's test for the separation of amines , primary amines form	Sodium salt of alkyl sulphonamide soluble in alkali	Dialkyl sulphonamide which is incoluble in alkali	Gets converted into secondary amine	Hydroxylamine hydrochloride	Sodium salt of alkyl sulphonamide soluble in alkali
In Hinsberg's test for the separation of amines , secondary amines form	Sodium salt of alkyl sulphonamide soluble in alkali	Dialkyl sulphonamide which is incoluble in alkali	Gets converted into secondary amine	Hydroxylamine hydrochloride	Dialkyl sulphonamide which is incoluble in alkali
In Hinsberg's test for the separation of amines , tertiary amines form	Sodium salt of alkyl sulphonamide soluble in alkali	Dialkyl sulphonamide which is incoluble in alkali	Gets converted into secondary amine	Does not react	Does not react
Aromatic primary amines react with nitrous acid to form	N-nitroso amines	Benzene diazonium chloride	Trialkyl ammonium nitrite	Nitrogen and alcohol	Benzene diazonium chloride
Aliphatic primary amines react with nitrous acid to form	N-nitroso amines	Benzene diazonium chloride	Trialkyl ammonium nitrite	Nitrogen and alcohol	Nitrogen and alcohol

Aliphatic secondary amines react with nitrous acid to form	Yellow colour N-nitroso amines	Benzene diazonium chloride	Trialkyl ammonium nitrite	Nitrogen and alcohol	Yellow colour N-nitroso amines
Tertiary amines react with nitrous acid to form	Yellow colour N-nitroso amines	Benzene diazonium chloride	Trialkyl ammonium nitrite	p-nitroso-N-dimethyl amine	Green colour p-nitroso-N-dimethyl amine
Carbylamine test is answered by	Primary amine	Secondary amine	Tertiary amine	Quarternary salt	Primary amine
A compound when heated with chloroform and alcoholic potassium hydroxide gives a strong offensive smell	Primary amine	Secondary amine	Tertiary amine	Quarternary salt	Primary amine
A compound when heated with chloroform and alcoholic potassium hydroxide gives a strong offensive smell	Methyl amine	Dimethyl amine	Trimethyl amine	Quarternary salt	Methyl amine
A primary amine when heated with chloroform and alcoholic potassium hydroxide gives	An offensive smell	Pleasant smell	A red precipitate	flourscence	An offensive smell
A primary amine when heated with chloroform and alcoholic potassium hydroxide gives	Isocyanides	Alkyl cyanides	Amino aldehydes	Amino ketones	Isocyanides
Which is more basic	Trimethyl amine	Dimethyl amine	methylamine	ammonia	Dimethyl amine
Which is more basic	P-toludine	m-toludine	o-toludine	aniline	P-toludine

UNIT II
SYLLABUS

Diazonium Salts: Preparation and their synthetic applications.

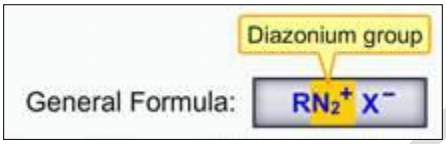
Polynuclear Hydrocarbons

Aromaticity of polynuclear hydrocarbons, structure elucidation of naphthalene; Preparation and properties of naphthalene, phenanthrene and anthracene.

Diazonium Salts

Benzene Diazonium Chloride ($C_6H_5N_2^+;Cl^-$)

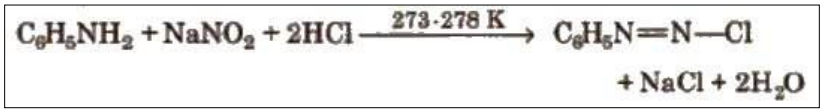
Diazonium salts have the general formula



Where X = Cl^-, Br^-, HSO^{4-}, BF^{4-}...etc

Preparation

Diazotisation reaction:



The excess acid in diazotisation reaction is necessary to maintain proper acidic medium for the reaction and to prevent combination of diazonium salt formed with the undiazotised amine. Diazonium salts are prepared and used in aqueous solutions because in solid state, they explode.

Properties

It is a colourless crystalline solid, soluble in water.
It has tendency to explode when dry.

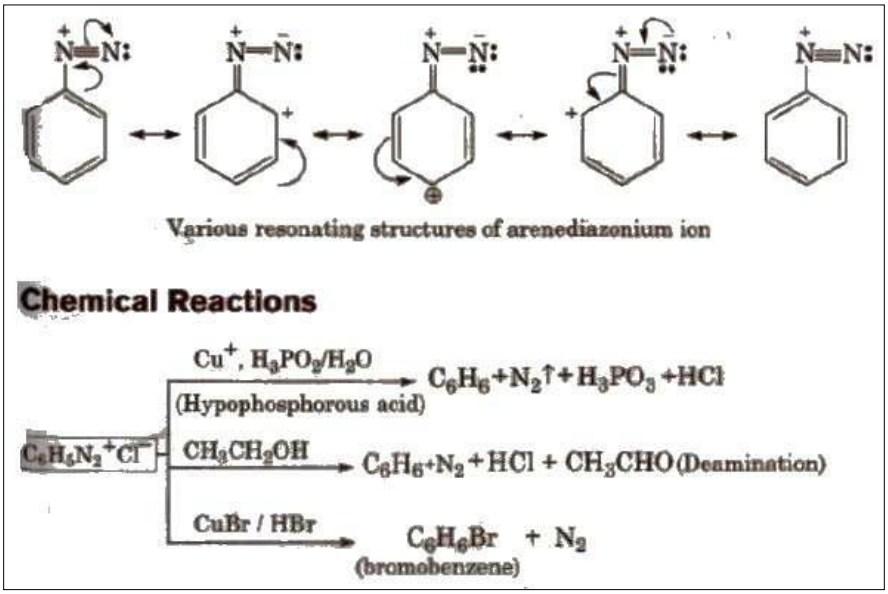
Reactions Benzene diazonium chloride undergoes two main types of reaction

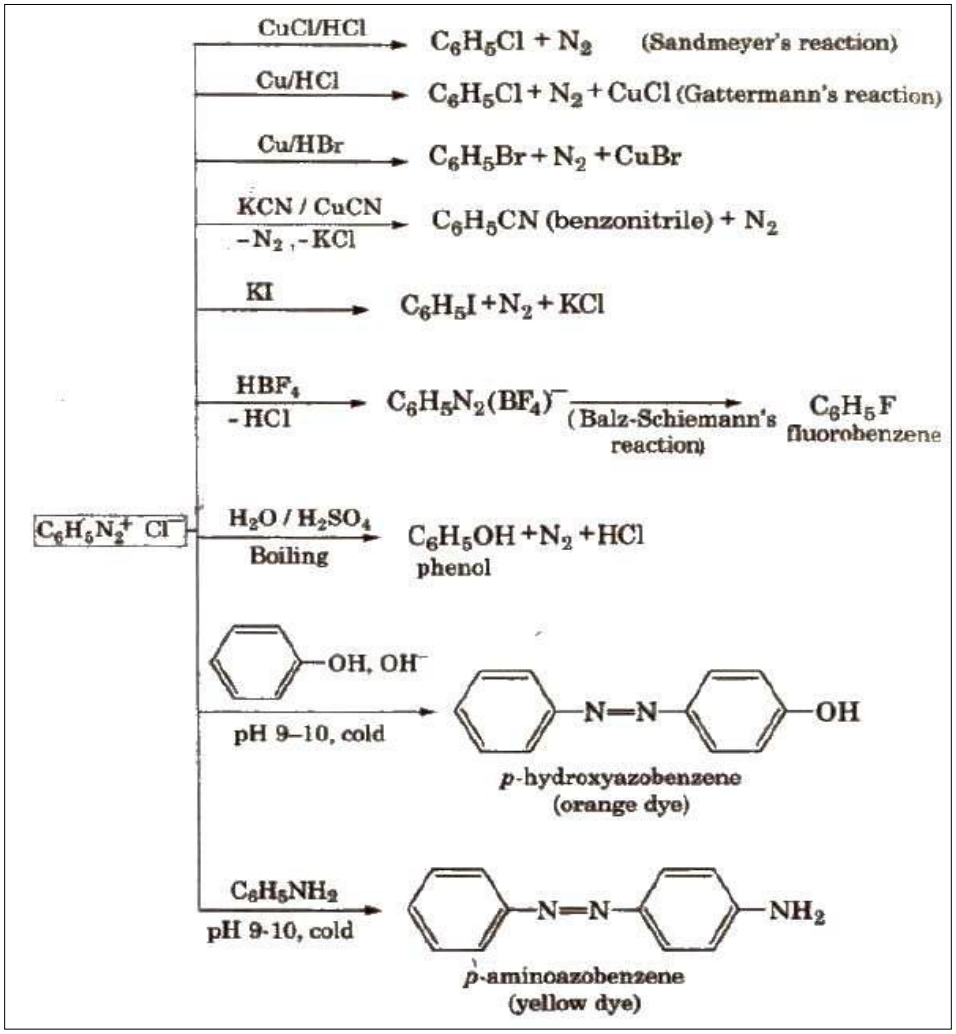
- **Substitution of the diazonium group** *nitrogen expelled*
- **Coupling reactions** *the nitrogen atoms are retained*

Aryl diazonium salts are used as intermediates to synthesise a wide variety of organic compounds. Primary alkyl diazonium ions are not very stable. They decompose easily and tend to be explosive when dry. Aryl diazonium salts are stable only for short times at low temperatures. Resonance structures help to stabilise the ion by delocalising the positive charge around the aromatic ring.

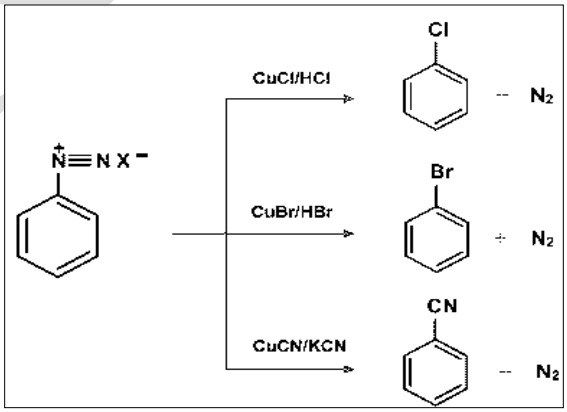
Stability of Arenediazonium salts

It is relatively more stable than the alkyldiazonium salt. The arene diazonium ion is resonance stabilised as is indicated by the following resonating structures:

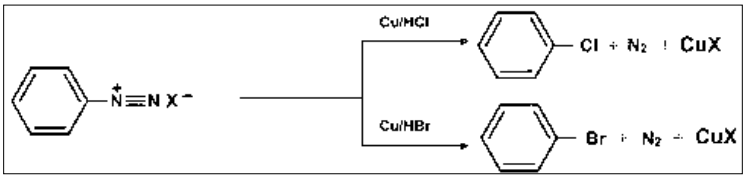




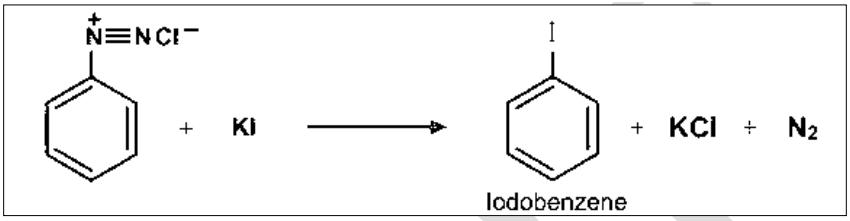
In the **Sandmeyer reactions**, diazonium groups are replaced by chloride, bromide or cyanide in the presence of copper (I) ions.



In the **Gatterman reactions**, diazonium groups are replaced with Chlorine (or) Bromine by treating the diazonium salt solution with haloacid in the presence of copper powder.

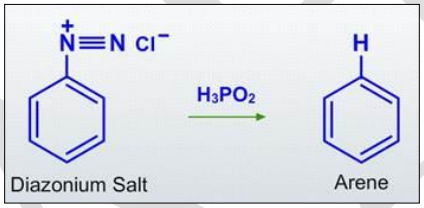


Diazonium group may be replaced by iodine by treatment with potassium iodide.

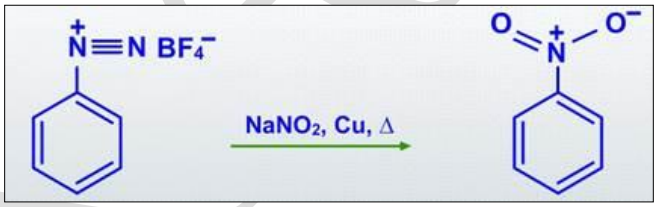


The **Schiemann reaction** is a method for the production of aryl fluorides.

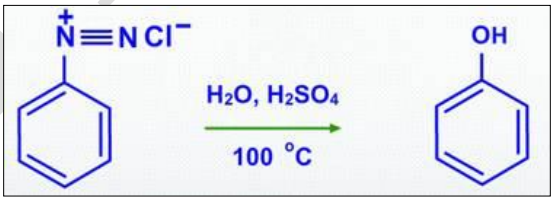
In reductive deamination, the diazonium group is replaced by hydrogen after treatment with mild reducing agents such as hypophosphorous acid (or) ethanol.



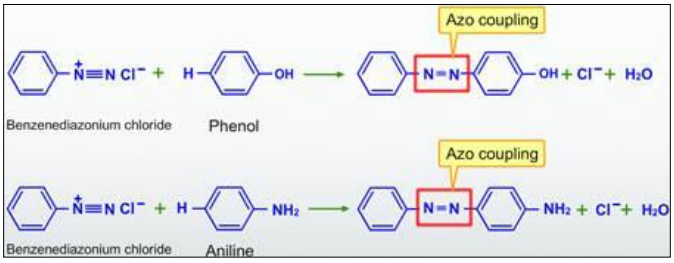
In nitration reactions, the diazonium group is replaced by an $-NO_2$ group.



Phenols can be prepared from diazonium salts by hydrolysing with dilute sulphuric acid and heating.



Azo coupling reactions occur when diazonium salts react with phenol (or) aniline.

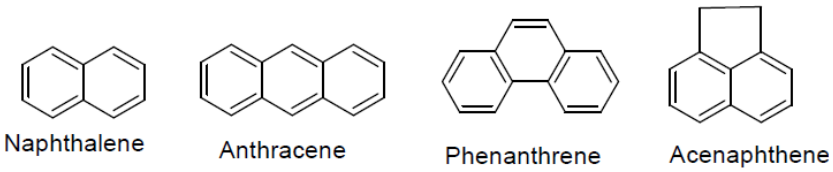


Polynuclear Hydrocarbons

Classification Polynuclear Hydrocarbons

Compounds with benzene nuclei linked through one or more carbon

2. Condensed polynuclear hydrocarbons: The compounds in which two or more rings are fused due to the sharing of two or more carbon atoms by two or more rings. They are known as fused or condensed polynuclear hydrocarbons, e.g.,



Condensed polynuclear hydrocarbons

The chemistry of isolated polynuclear compounds is similar to that of simple aromatic hydrocarbons. However, the condensed polynuclear hydrocarbons like naphthalene e, anthracene

Polynuclear Hydrocarbons may be divided into two groups,

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur (the most common heterocyclic elements), the permutations and combinations of such a replacement are numerous.

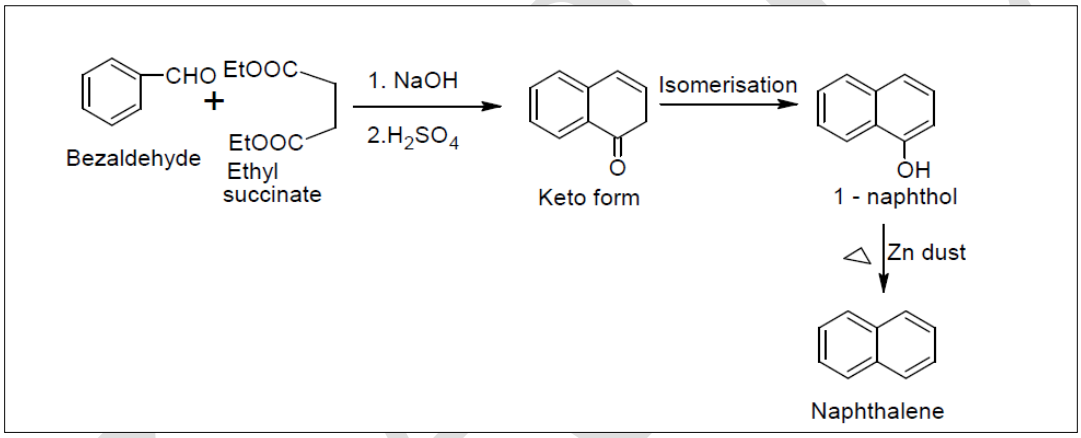
Naphthalene ($C_{10}H_8$)

Naphthalene is the simplest example of a polycyclic aromatic hydrocarbon containing the benzene rings fused in ortho positions.

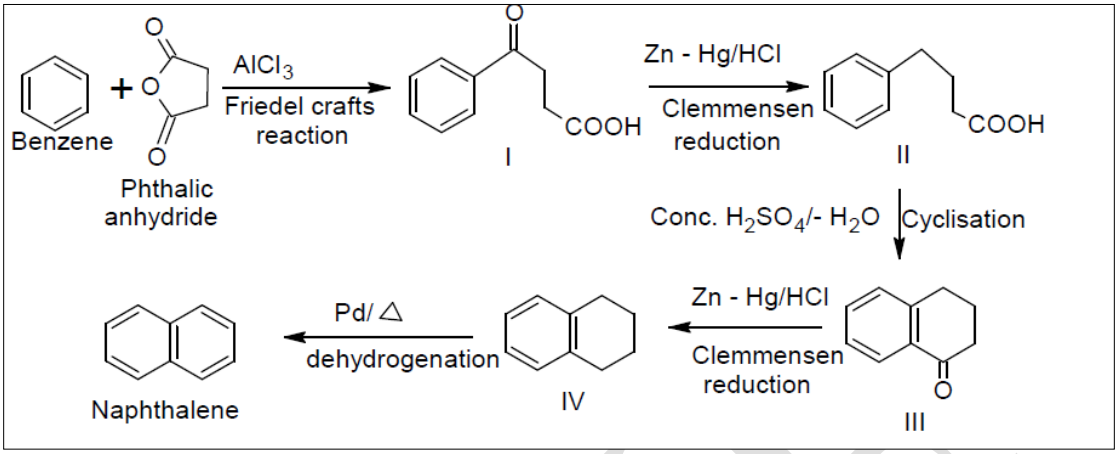
Source and its isolation: It is largest single compound present in coal-tar. It is obtained from 'middle or heavy oil' by chilling these fractions when naphthalene crystallizes out. The crude naphthalene is separated by pressing or centrifuging. The resultant solid mass is washed with hot water and aqueous alkali to remove traces of oils and phenols. It is then washed with dilute sulphuric acid to remove basic impurities. Finally it is purified by sublimation.

Method of preparation : It can be prepared by using following methods-

1. From benzaldehyde and ethyl succinate (Fitting and Erdmann Synthesis): The reaction of benzaldehyde and ethyl succinate in the presence of basic catalyst like sodium hydroxide or potassium tertiary butoxide followed by cyclisation and isomerisation gives α- naphthol which further on reduction with Zn dust afforded naphthalene.



Haworth synthesis (1932) : Friedel crafts reaction of succinic anhydride with benzene in presence of $AlCl_3$ gives a ketonic acid I which is reduced to II. This on cyclisation gives ketone III which on reduction yields tetralin IV. Dehydrogenation of tetralin gives naphthalene.



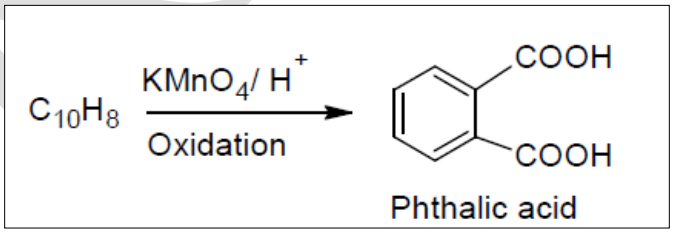
Constitution or Structure of Naphthalene:

Analytical evidence: The structure of naphthalene was arrived at by following analytical evidence.

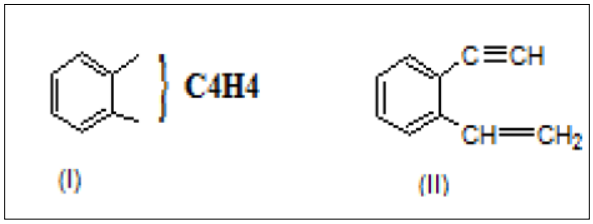
1. On the basis of analytical data its molecular formula is found to be $C_{10}H_8$.

2. Like benzene it is resistsnt to addition reactions though less than benzene. It resembles benzene in other chemical properties also and undergoes electrophilic substitution reactions like halogenation, nitration etc., more readily than benzene.

3. Its nuclear substituted hydroxy derivative are phenolic in nature and amino derivatives undergo diazotization and coupling reactions. This again shows it to be similar to benzene the structure**.**
Graebe in 1869 obtained phthalic acid (o-benzene dicarboxylic acid) on oxidation of naphthalene with acid permanganate . This showed that at least one benzene ring is present in naphthalene and there may be two side chains in ortho positions to each other.



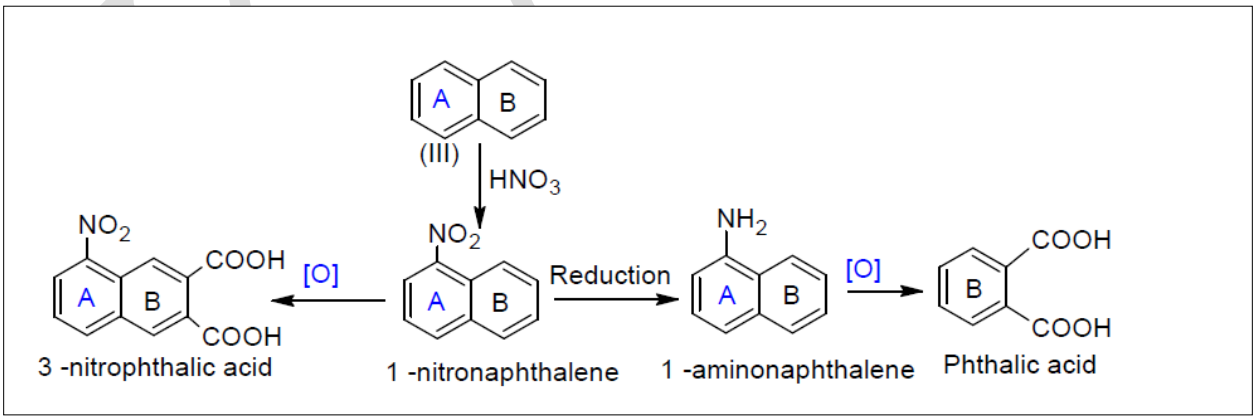
Hence the formula of the naphthalene may be written as (I).The two side chains on the basis of valency requirements must be highly unsaturated and formula (II) may be suggested for it.



However ,such structure would be in contrast to known aromatic character of naphthalene. Therefore, structure (II) and related structures for naphthalene are ruled out.

5. Graebe further proved that naphthalene consists of two benzene rings fused in o-positions. This was based on following experimental proof:

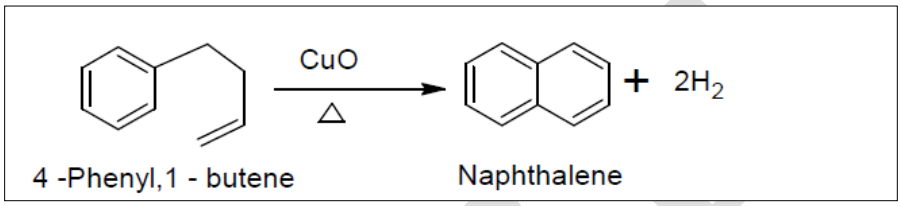
Naphthalene gave phthalic acid on oxidation**.** When naphthalene was nitrated it yielded nitrophthalene which oxidation gave 3-nitro phthalic acid. This showed that nitro group was present in the benzene ring and side chains were oxidized. But when nitro group of nitro naphthalene was reduced to amino group and the resulting aminonaphthalene oxidized, phthalic acid and not amino phthalic acid was obtained. An amino group attached to benzene ring is known to render the ring highly susceptible to oxidative degradation. The logical conclusion therefore could be that during the oxidation of aminonaphthalene – it was the benzene ring containing an amino group which was destroyed and the benzene ring present in oxidation product phthalic acid is other than that which had the nitro group. It was therefore concluded that two benzene rings were fused in ortho-position i.e. naphthalene contained two benzene rings. In oxidation of nitronaphthalene, nitro phthalic acid was obtained because nitro group attached to benzene ring made the ring resistant to oxidation.



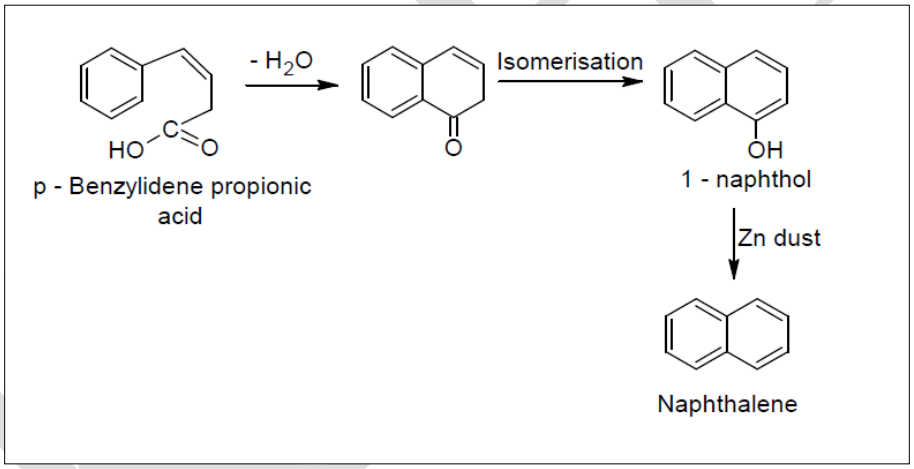
The above scheme clearly demonstrates the presence of two benzene rings fused in o-positions. The structure (III) was intuitively suggested by Erlenmeyer in 1866 and is known as Erlemeyer's structure of naphthalene.

Synthetic evidence: Synthetic evidence which support the Erlenmeyer's formula for naphthalene, some are given below:

a) If 4-phenylbutene-1 is passed over red hot calcium oxide, naphthalene is obtained.

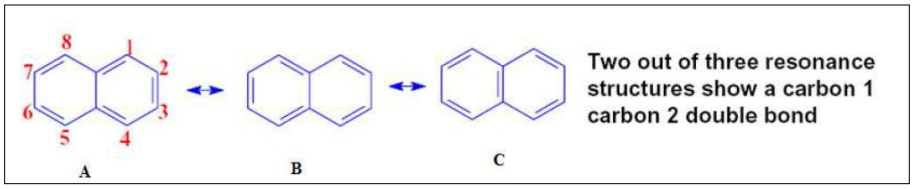


Fittig's synthesis: Cyclisation of p-benzylidene propionic acid gives α - naphthol which on distillation with zinc dust yields naphthalene.

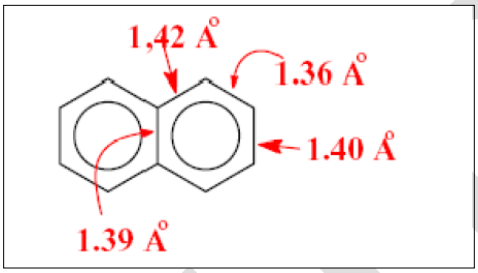


Modern views about structure of Naphthalene: Like benzene, the structure of naphthalene can be explained on the basis of following concepts.

i) Resonance concept: Naphthalene is considered to be the resonance hybrid of various contributing structures of which following three are important.



Naphthalene is planar molecule. X-ray studies have indicated that all carbon-carbon bonds in naphthalene are not equivalent. The C_1-C_2 bond is having relatively greater double bond character and is 1.36A_o as compare to C_2-C_3 bond having greater single bond character length 1.40A_o. This is obvious, if we see the contributing structures in which C_1-C_2 bond are double bond in structures B and C and single bond character in the structure A. Thus it has a two-third double bond character. On the other hand C_2-C_3 bond is a single bond in structures B and C and double bond in structure A. Thus it has two-third single bond character.



The resonance energy of naphthalene is 61 Kcals. Since the resonance energy of benzene is 36 Kcals, the additional energy due to second benzene ring is only 25 Kcals. This decreased resonance energy is in accordance with relatively greater reactivity of naphthalene.

II) Molecular orbital concept: All carbon atoms in naphthalene are in sp^2 hybridization state and lie at the corners of two fused hexagons. Each one of the carbon atom is attached to two other carbon atoms and one hydrogen by σ -bonds formed by the overlapping of trigonal sp^2 hybrid orbitals. The unhybridized *p* orbital at each carbon overlaps with the *p* orbitals on its side forming a π electron cloud above and below the plane of the ring containing all the carbon and hydrogen atoms. The π electron cloud has a shape of 8 and consists of two partially overlapping sextets-thus imparting aromatic character to naphthalene. However, since a pair of π electros is common to both the rings, it has less aromatic character than benzene.It must be noted that it contains 10 π electrons, a number for exhibiting aromatic character according to Huckel's rule.

The M.O,picture of naphthalene also explains the nature of substitution reactions. Since it has a π electron cloud on either side of the plane of the ring, it acts as a source of electrons and its important reactions are electrophilic substitution reactions.

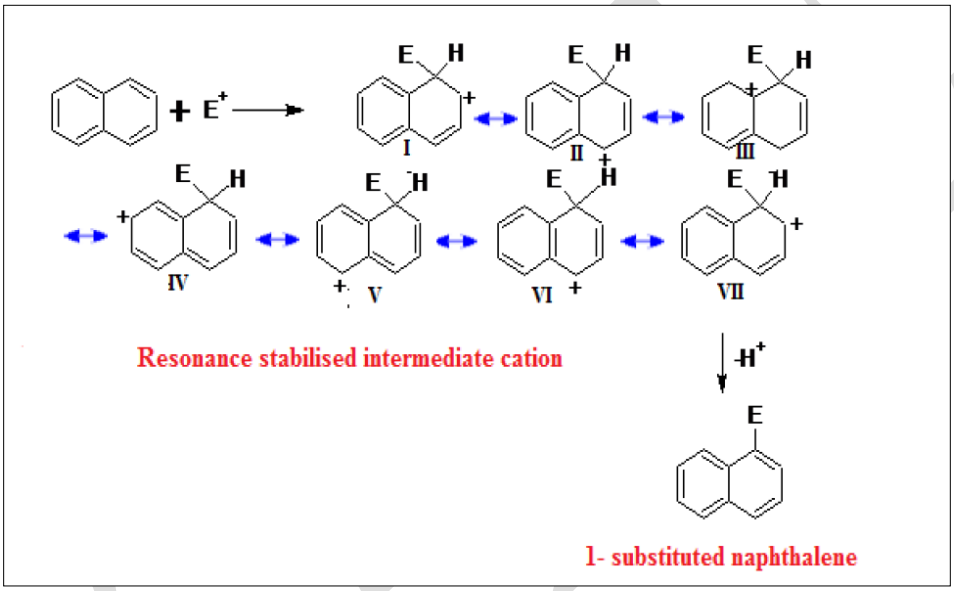
Physical properties: Naphthalene exist as a colourless lustrous plates, m.p. 353K, insoluble in water but soluble in alcohol, ether and benzene. It has strong characterstic odour. It is volatile and sublimes on heating.

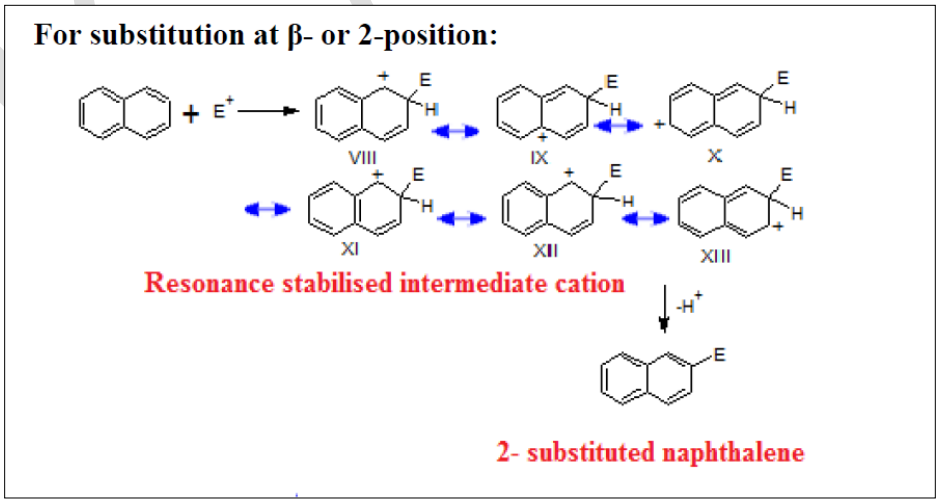
Chemical properties : It resembles benzene in its reactions. However, it is more reactive than benzene and forms the addition and substitution products much more readily. It is also more

susceptible to oxidation and reduction**.** Like benzene, it undergoes electrophilic substitution reactions and normally occurs more readily at α-position than β-position. Because, the carbonium ion intermediate formed by attack on β-position is less stabilized by resonance as the benzenoid structure of both rings is distributed in contributory structures.

Electrophilic substitution reaction: When electrophilic attack takes place at 1- or α-position and 2- or β-position.

For substitution at α- or 1- position:



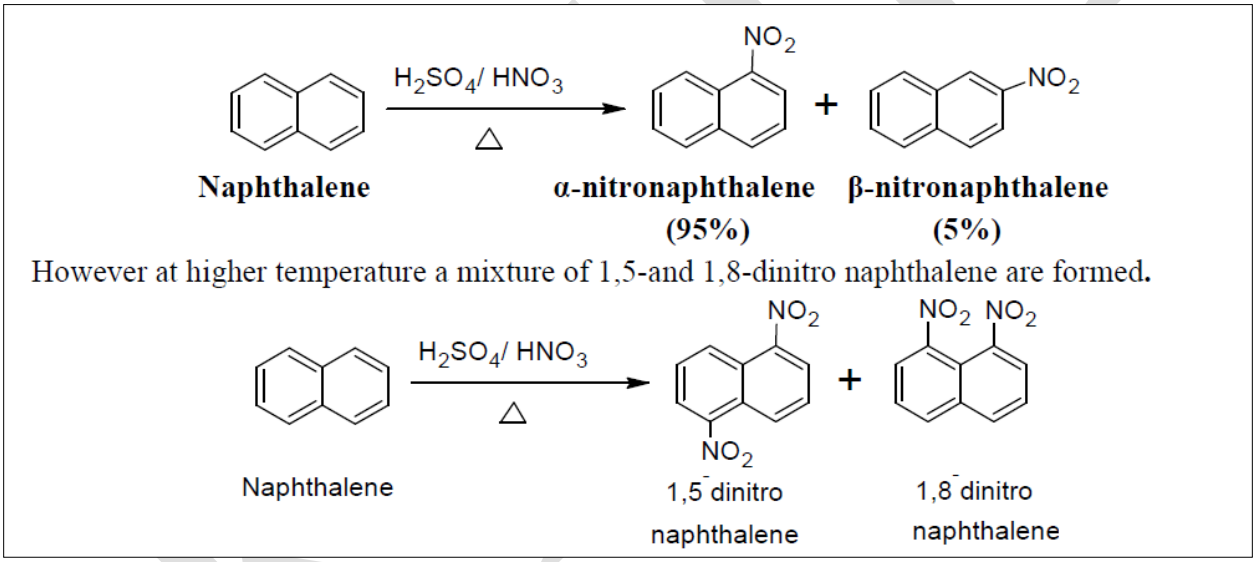


E^+ represents an electrophile and may be Cl - , Br - . I – in halogenation , NO_2^+ in nitration

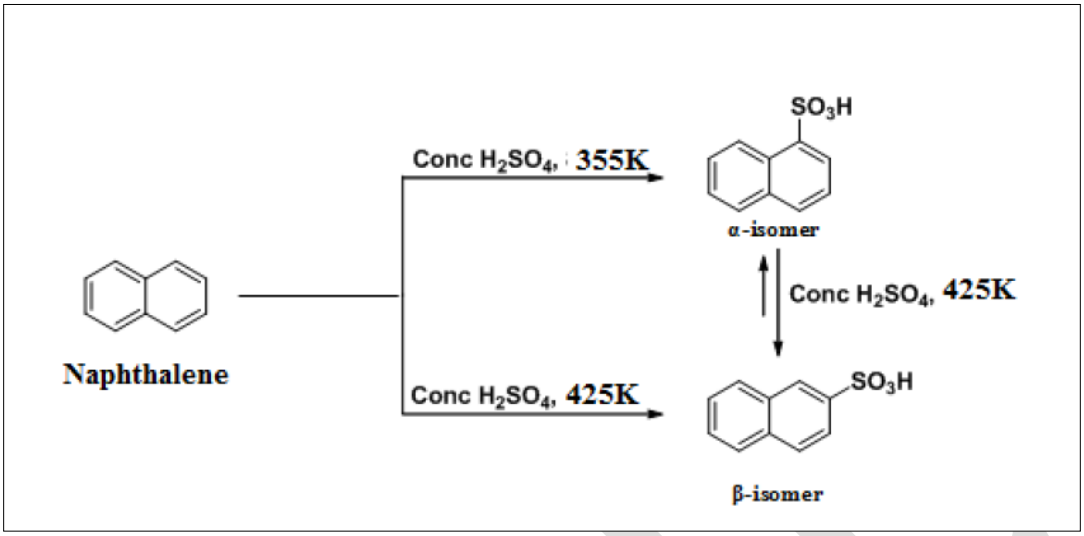
SO_3 in sulphonation, R^+ or RCO^+ in friedel –crafts reaction. From a comparative study of resonance stabilized intermediate carbocation of 1- and 2- substitution, it is obvious that structures I,II,VI,VII, VIII and XII are more stable because they contain at least one benzene ring intact (because benzene has a large resonance energy).

Out of these four i.e. I,II,VI and VII are involved during α-substitution while only two i.e. VIII and XII are involved during β-substitution. Consequently, the carbocation formed during the α-substitution and transition state leading to that ion is much more stable than the carbocation and the corresponding transition state formed during the β-substitution. Hence the α-substitution is the preferred orientation of substitution in naphthalene.

Nitration: Nitration of naphthalene with mixture of concentrated nitric acid and sulphuric acid yields predominantly the α-nitro naphthalene (95%) with minor amounts (5%) of β- Nitro naphthalene.

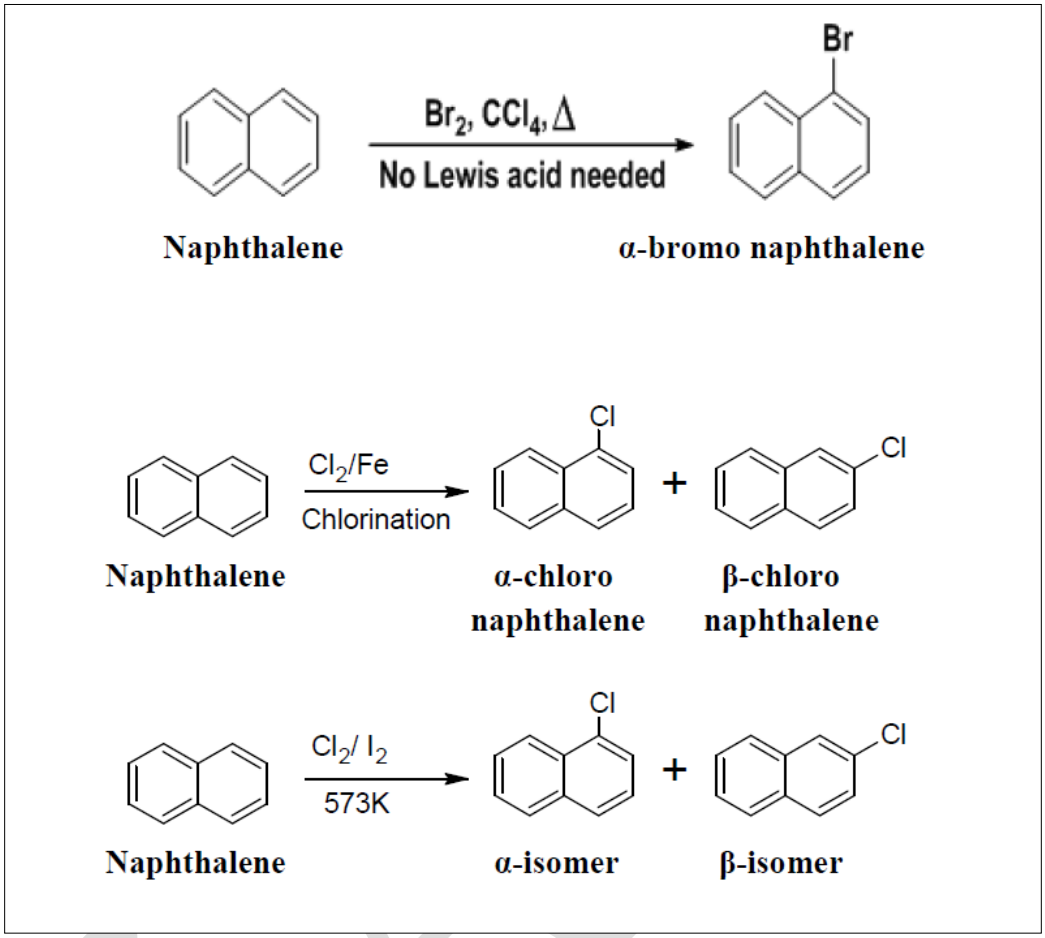


Sulphonation : Naphthalene can be sulphonated at 355K to yield mainly i-naphthalene sulphonic acid whereas if the reaction is carried out at 425K, 2-naphthalene sulphonic acid is the main product. This is reversible. It has been shown that when 1-naphthalene sulphonic acid is heated, it is highly converted in to the 2-isomer.



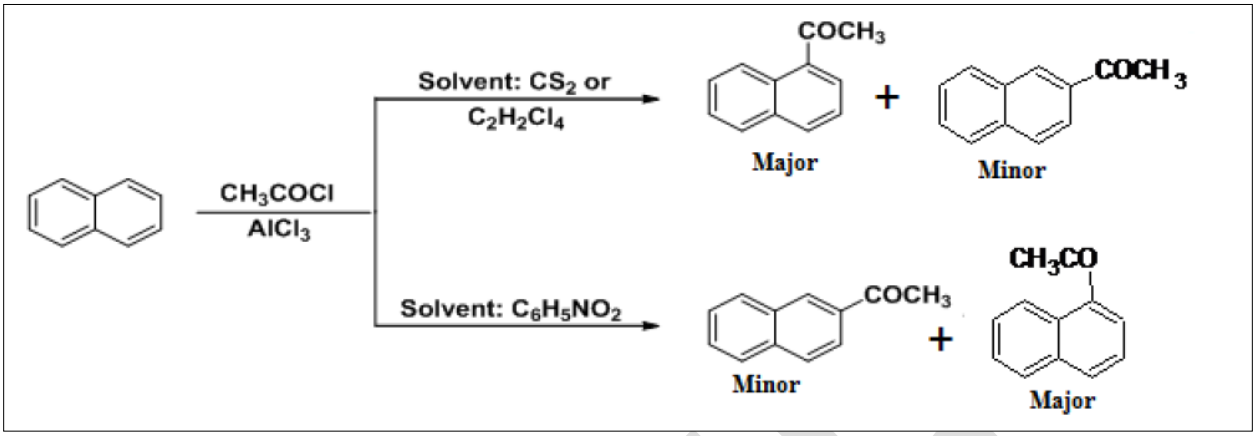
Halogenation:

Halogenation of naphthalene takes place very readily and no catalyst is needed for the purpose. The reaction takes place almost exclusively at 1- positions. When brominated in boiling carbon tetrachloride solution, naphthalene gives 1-bromo derivative in good yield. 1-Chloronaphthalene can be obtained either by reacting naphthalene with sulphuryl chloride (SO_2Cl_2) in presence of aluminium chloride at 298K or by chlorination in the presence of ferric chloride.

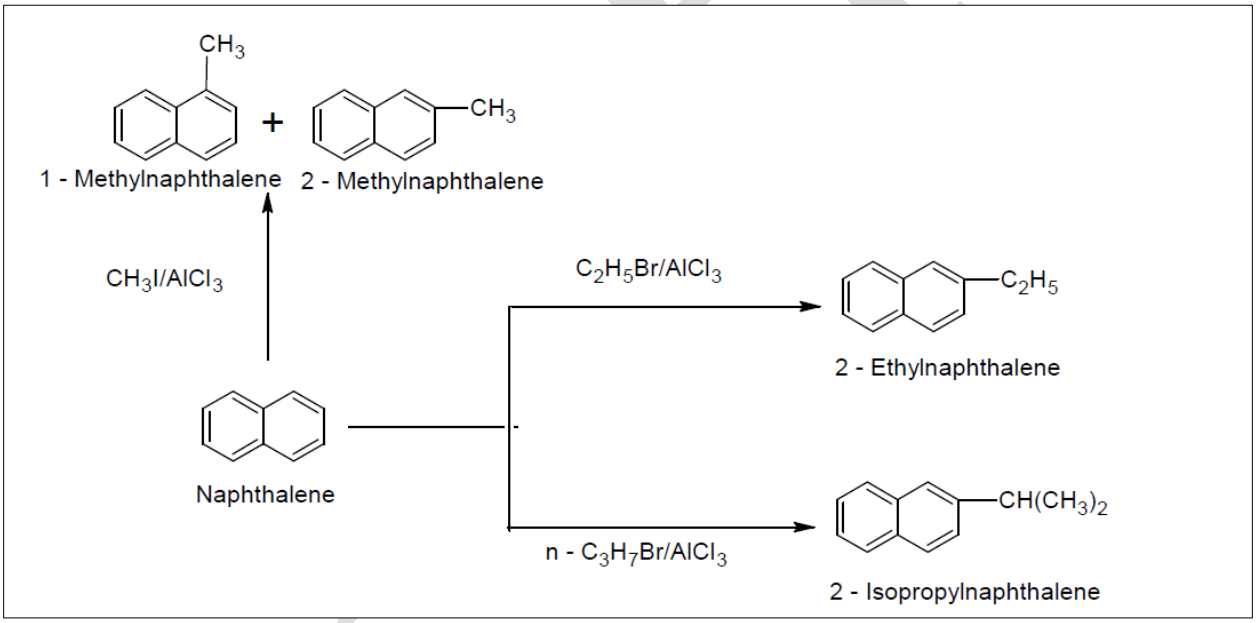


Friedel crafts Reaction: Naphthalene undergoes friedel crafts acylation and alkylation gives acylated and alkylated product.

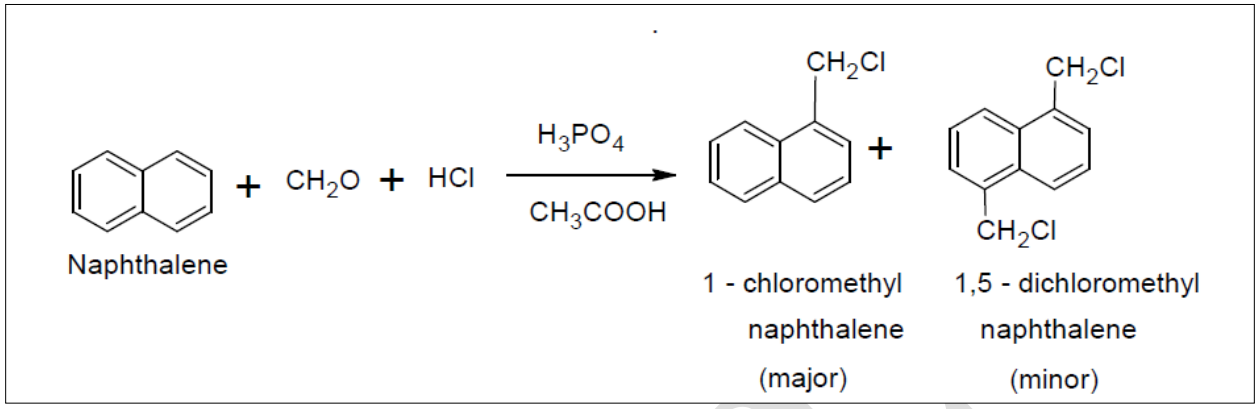
a) Friedel crafts acylation: Acylation of naphthalene gives 1- and 2- acyl naphthalene as a product but their proportion depends on the solvent used. For instant, acyl chloride in the presence of anhydrous aluminium chloride in carbon disulphide gives 1- and 2-acyl naphthalene in the ratio 3:1 where as in nitrobenzene as the solvent the ratio is 1:9.



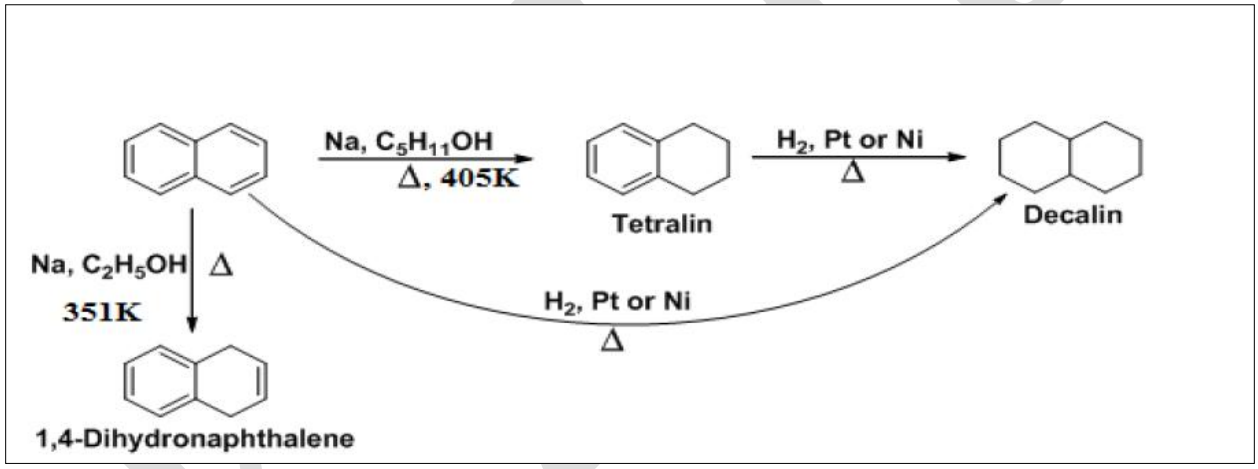
Friedel craft alkylation: Alkylation of naphthalene gives a mixture of α-and β-isomers is obtained, their relative proportions depending on the reaction conditions and the size of alkyl group to be introduced. Thus with CH3I a mixture α-and β-methyl naphthalenes is formed, while C2H5Br gives mainly β-ethylnaphthalene and n-C3H7Br forms only β-isopropyl naphthalene, with alcohols usually polyalkylated products are formed.



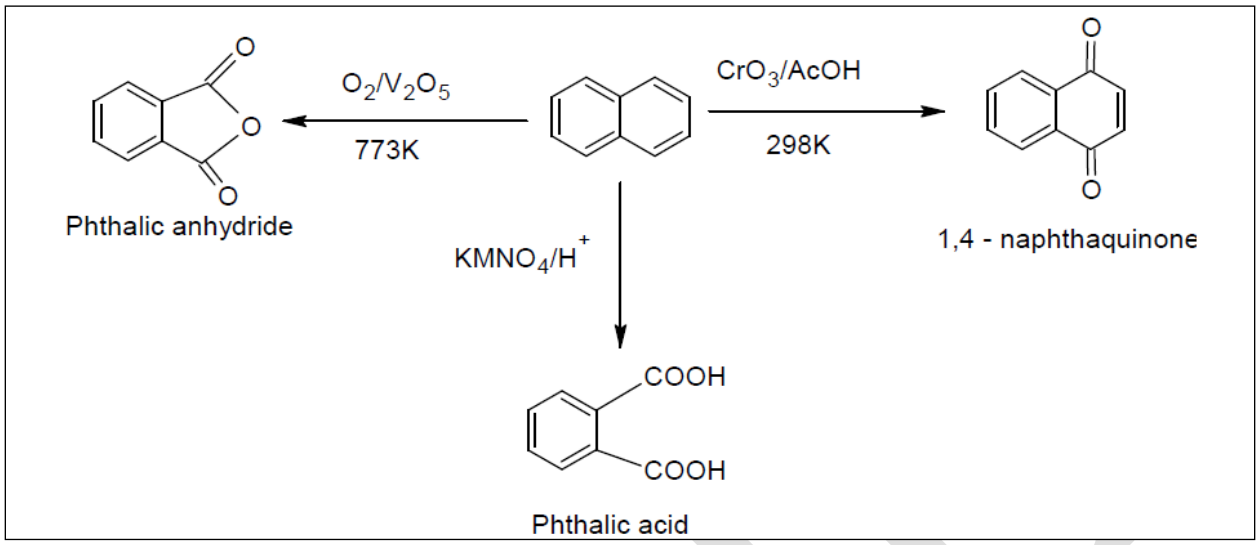
Chloromethylation: Naphthalene on reaction with paraformaldehyde , hydrochloric acid,glacial acidic acid and phosphoric acid gives α - chloromethyl naphthalene as the main product (56%) together with 1,5-bichloromethylnaphthalene.



Reduction: Unlike benzene, naphthalene on reduction forms number of products which depends on reducing agents used .Naphthalene on reduction with Na in C_2H_5OH (Birch reduction) gives 1,4-dihydronaphthalene, with sodium in amyl alcohol at 405K gives tetralin and with Pt/Ni gives decalin. Tetralin and decalin are widely used as solvents for vernishes, lacquers etc.

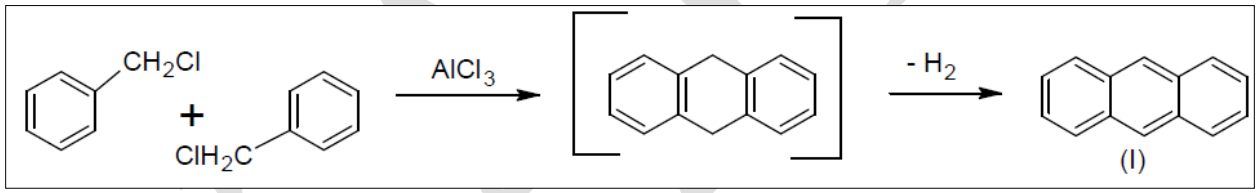


Oxidation: Naphthalene on oxidation with oxygen or air in the presence of vanadium pentoxide catalyst forms phthalic anhydride .In place of vanadium pentoxide, Conc. Sulphuric acid with mercuric sulphate can be used and in presence of potassium permanganate in acid it gives phthalic acid while with chromic acid in acetic acid gives 1,4-naphthaquinone

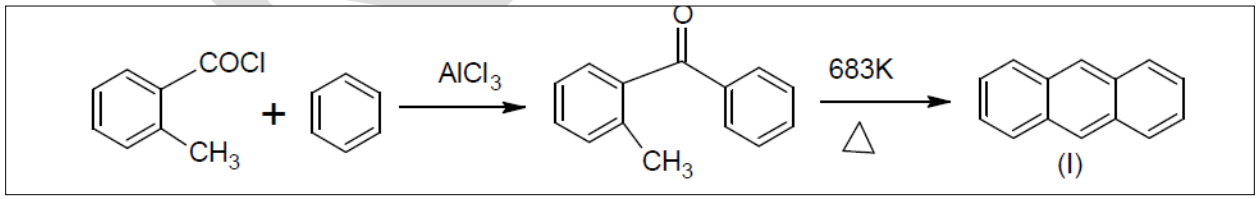


Anthracene , $C_{14}H_{10}$

Friedel crafts alkylation between two molecules of benzyl chloride gives 9.10-dihydroanthracene which is oxidized readily under the reaction conditions yielding anthracene.

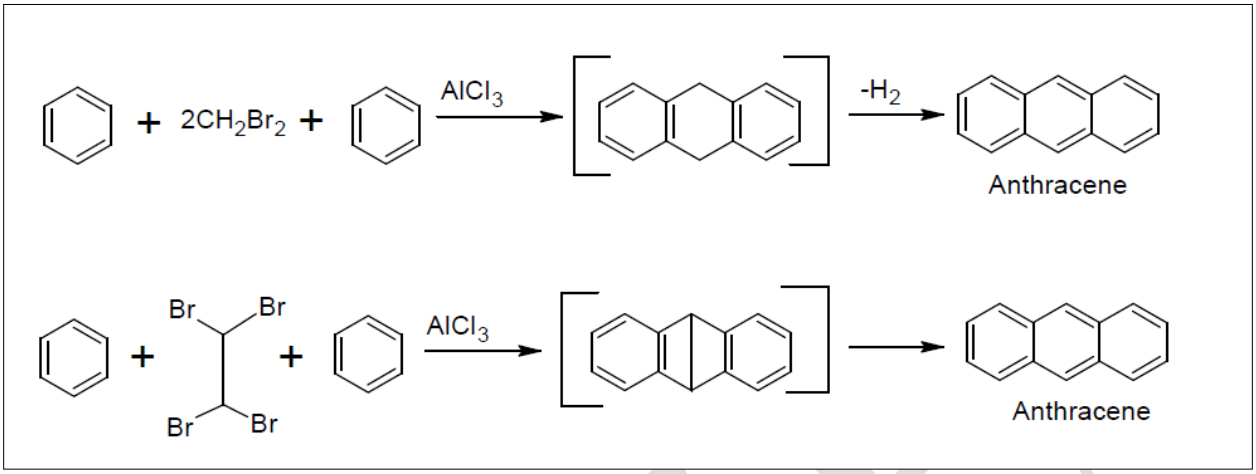


2. This method is based on Elbs reaction in which a polynuclear aromatic hydrocarbon having an anthracene moiety is formed by pyrolysis of a diaryl ketone containing a methyl or methylene group ortho to the carbonyl group.

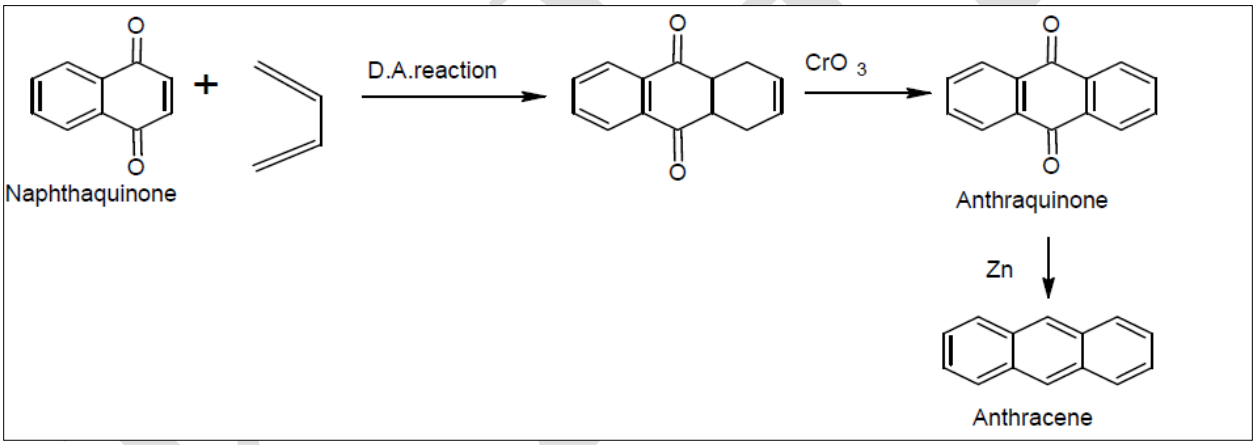


From benzene and methylene dibromide and acetylene tetrabromide:

This method involving Friedel crafts alkylation of benzene with either methylene dibromide or with acetylene tetrabromide.



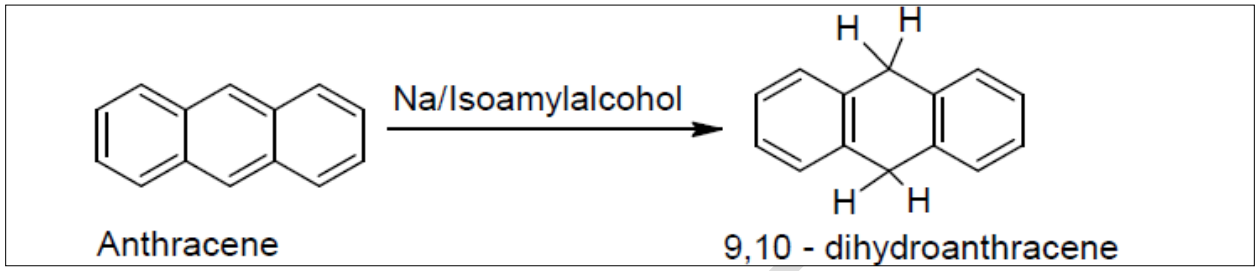
This synthesis consists in Diels-Alder reaction between naphthaquinone and butadiene followed by oxidation of the intermediate with chromic acid in glacial acetic acid to give anthraquinone which on distillation with zinc dust yields anthracene.



It is a colourless solid, m.p.489K, with a green-yellow or blue fluorescence. It is insoluble in water and sparingly soluble in organic solvents.

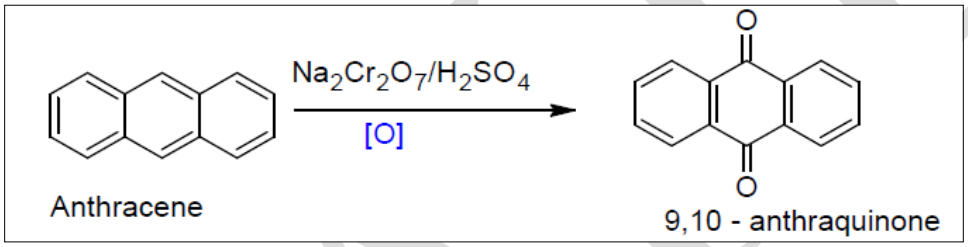
Chemical reaction: It resembles benzene and naphthalene in many of its chemical reactions. It is very reactive at positions 9- and 10.Electrophilic substitution,such as halogenations or nitration, preferably gives 9- or 9-,10-disustituted products. The greater reactivity of the 9,10-positions is readily understandable if we consider the relative stabilities of the σ-complexes formed as a result of electrophile attack 1-,2- and 9-positions. The attack at 1- or 2- position forms a carbocation having a naphthalene moiety whereas the σ-complex formed by attack at 9-position has two benzene rings. The resonance stabilization in the latter will be more since the total resonance energy of two benzene rings is greater than that of a naphthalene ring.

1. Reduction: When reduced with sodium and isoamyl alcohol it forms 9,10- dihydroanthracene which on heating or on reaction with conc. H2SO4 reforms anthracene.

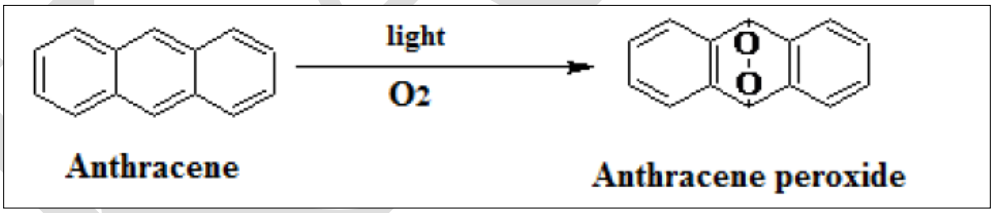


Catalytic reduction (H_2/Ni at 473-523K) gives tetra-, octa- and finally perhydroanthracene ($C_{14}H_{24}$).

2. Oxidation: It is readily oxidized with chromic acid to 9,10-anthraquinone**.**

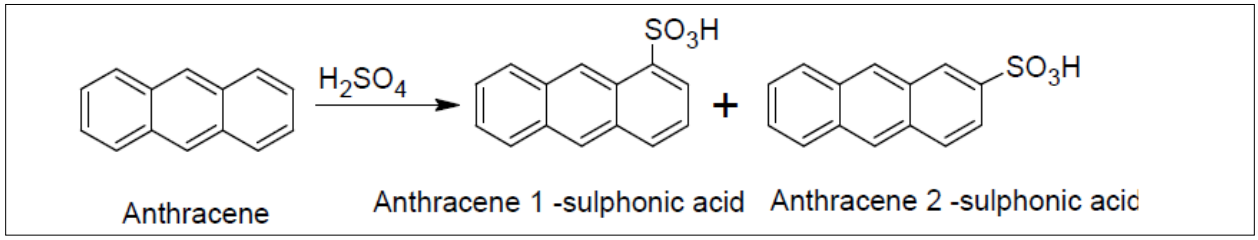


It adds one molecule of oxygen in the presence of light to form a colourless peroxide.



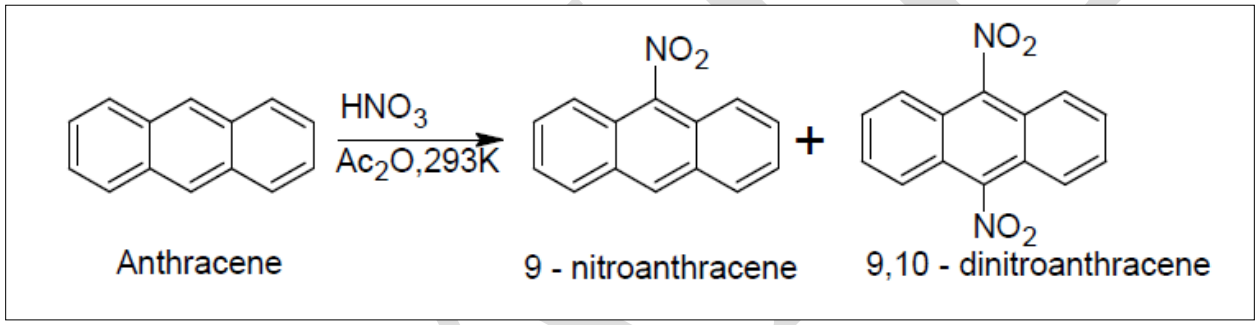
Electrophilic substitution reactions: It undergoes electrophilic substitution reactions like sulphonation,nitration, halogenations etc.

I] Sulphonation: It reacts with H_2SO_4 to form a mixture of 1-and 2- sulphonic acids.

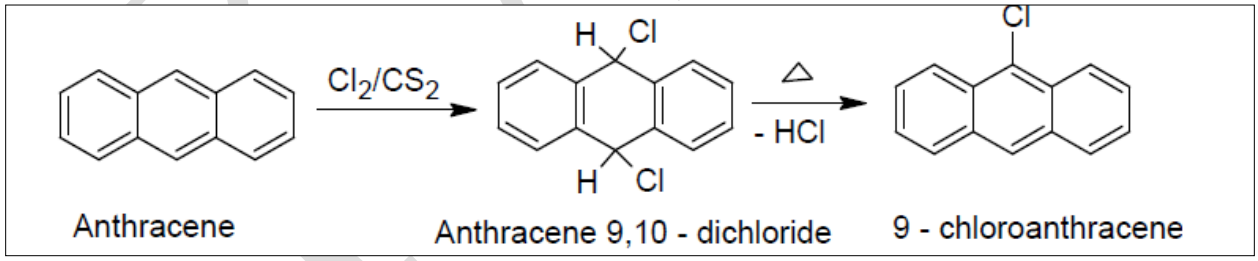


At higher temperatures the 2- sulphonic acid is the main product. However, unlike naphthalene, the 1-sulphonic acid of antharcene does not rearrange to 2- sulphonic acid. Sulphonation with conc.H2SO4 gives 1,5-and 1,8-anthracene disulphonic acids.

Nitration: Anthracene on nitration with concentrated nitric acid in the presence of acetic anhydride gives a mixture of 9-nitro anthracene and 9,10-dinitro anthracene.



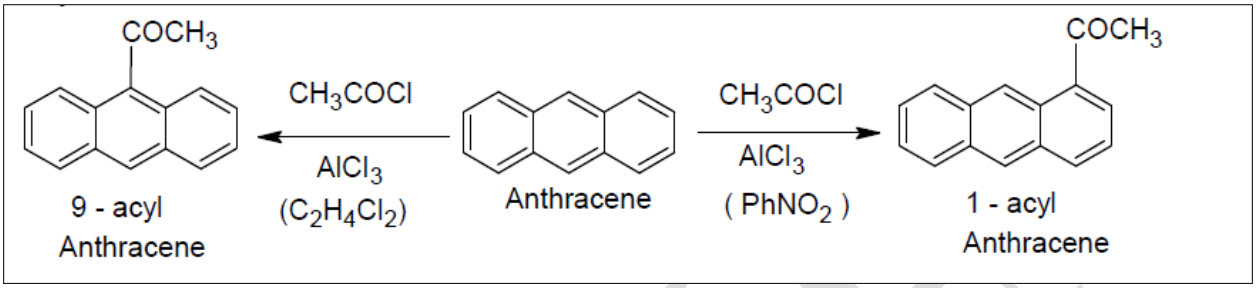
Halogenation: Chlorination with chlorine in carbon disulphide solvent in cold gives anthracene dichloride which on heating or treatment with alkali yields 9-chloroanthracene.



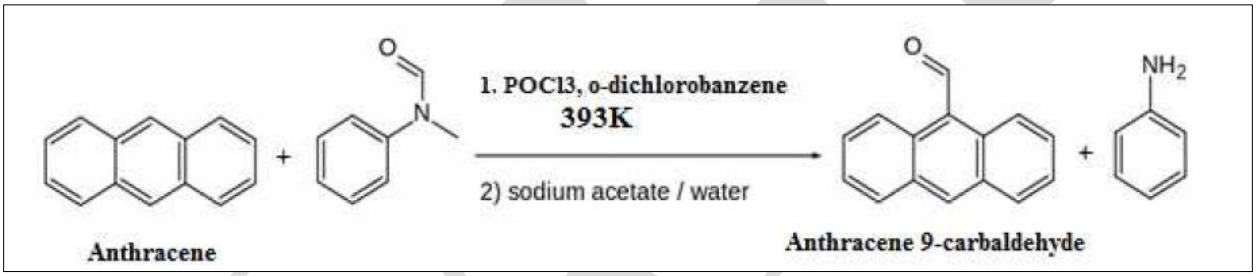
9-chloroanthracene may also be obtained by heating anthracene with cuprous chloride in carbon tetrachloride solution. Reaction of sulphuryl chloride with anthracene gives 9,10- dichloro,9,10-dihydro-anthracene. Both 9-chloroanthracene and anthracene dichloride on oxidation form anthraquinone.

Bromination in carbon tetrachloride follows the same course first forming anthracene dibromide (9,10-dibromo-9,10- dihydro anthracene which on heating yields 9-bromo anthracene.

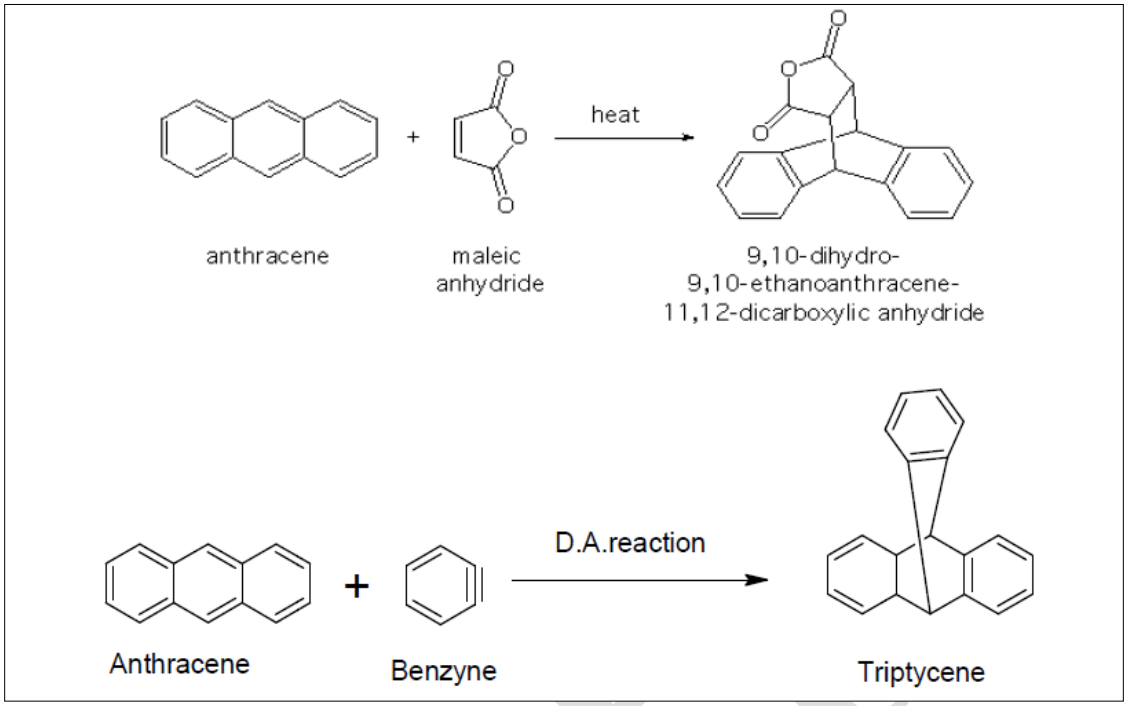
IV] Friedel craft acylation: Friedel crafts acylation of anthracene with acetyl chloride in benzene or nitrobenzene gives a complex mixture. However, the main product in nitro benzene as solvent is the 1-acetyl derivative whereas in ethylene dichloride it is the 9-acetyl derivative.



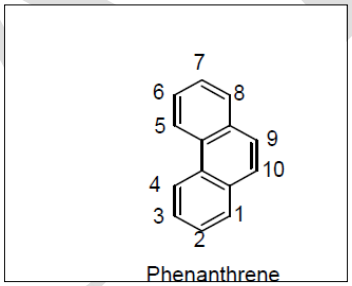
Formylation by Vilsmeier – Haack method: Anthracene can be formylated exclusively at the 9-position. The reaction of anthracene with *N*-methylformanilide, also using phosphorus oxychloride gives Anthracene 9-carbaldehyde.



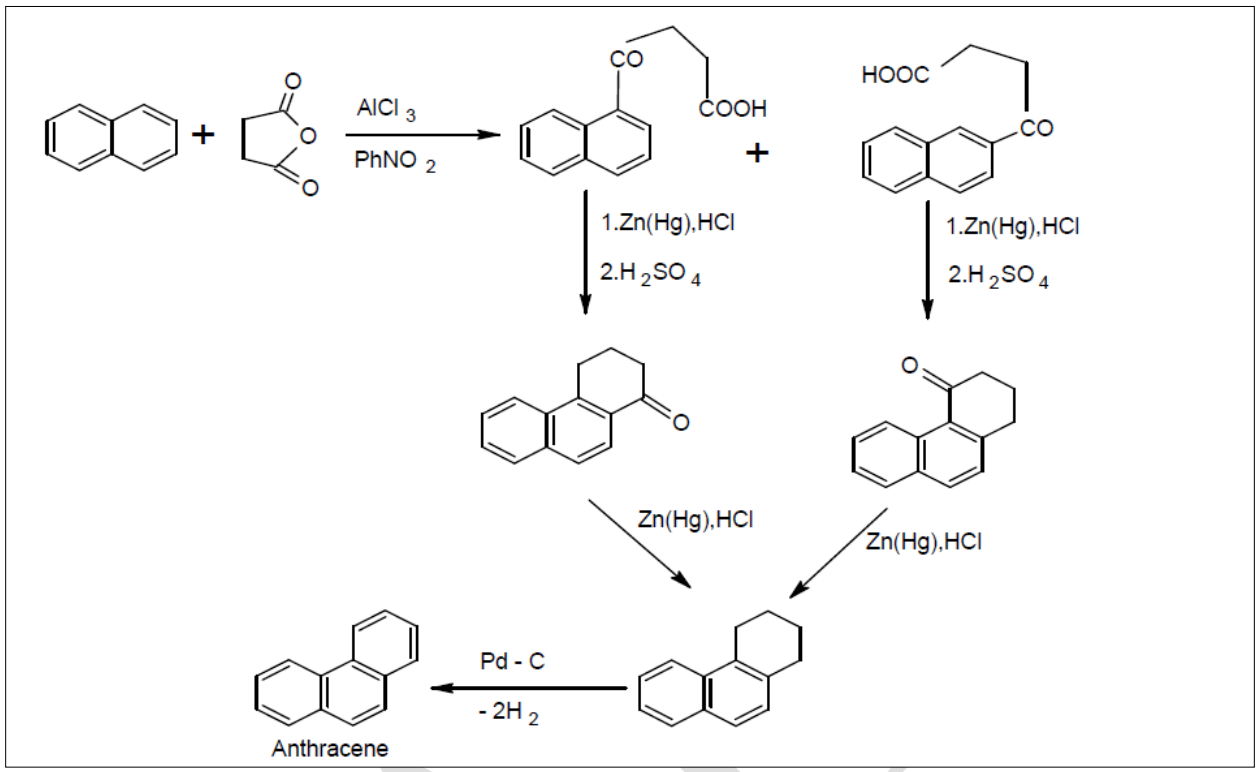
5. Diels-Alder Reaction: Anthracene undergoes facile Diels-Alder reaction with maleic anhydride and benzyne to give 1,4- addition products.



Phenanthrene –



Haworth synthesis: Succinoylation of naphthalene produces two isomeric keto acids: β- (1-naphthoyl) propionic acid and β-(2-naphthoyl) propionic acid. These two isomers can be readily separated. Clemmensen reduction affords γ-(1-naphthyl) butyric acid and γ-(2- naphthyl)-butyric acid respectively. Acid catalysed cyclisation gives 1-keto-1,2,3,4- tetrahydro- and 4-keto-1,2,3,4-tetrahydrophenanthrene. Clemmensen reduction of either isomer followed by aromatization.



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SUGGESTED MATERIALS:

Text books:

T1: Morrison, R. T. & Boyd, R. N.(1992). *Organic Chemistry*. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).
T2: Arun Bahl(2005). Advanced organic chemistry, S.Chand & Company Pvt.Ltd. Ramnagar, New Delhi.
T3: Finar, I. L. (2002). *Organic Chemistry*. Volume 1. Dorling Kindersley (India) Pvt. Ltd., (Pearson Education).

Reference Books

R1: Finar, I. L. (2002). *Organic Chemistry*: *Stereochemistry and the Chemistry of Natural Products*. Volume 2. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

POSSIBLE QUESTIONS

PART A
(1 Mark Q.No. 1 to 20)
(Online examination)

PART B (2 Marks)

1. How benzene diazonium chloride is prepared
2. Write short notes on Sandmeyer reaction
3. How phenanthrene is prepared
4. Differentiate phenanthrene and anthracene
5. Explain what is meant by coupling reaction
6.

PART C (6 Marks)

1. What are the synthetic applications of benzene diazonium chloride
2. Explain the preparation and properties of naphthalene
3. Starting from benzene diazonium chloride how to prepare
   (i) iodobenzene (ii) Phenol (iii) aminoazobenzene (iv) Benzene
4. What is diazotization? How toluene diazonium chloride is prepared in the laboratory.
5. How phenol react with diazonium salts
7. Describe five reactions of diazonium salts in which nitrogen is evolved.
7. Explain the preparation and properties of Phenanthrene
8. Elucidate the structure of naphthalene
9. How to prepare anthracene. What are its properties?
10. What are polynuclear compounds ? How they are classified ? Give examples of each group.
11. Discuss the constitution of naphthalene.
12. What is modern view regarding the structure of naphthalene ?
13. How will you show that naphthalene has two benzene rings fused in o-position ?
14. Write note on:
    i) Orientation in naphthalene ring system.
    ii) Electrophilic substitution reactions of naphthalene.
    iii) Bucherer reaction
    iv) Aromatic nature of naphthalene
    v) Sulphonation of naphthalene
    vi) Electrophilic substitution reactions of anthracene
15. How can α- and β- naphthols and naphthylamines be obtained ?
16. In what respect anthracene and phenanthrene resemble benzene? Explain why position 9,10 are reactive in them.
17. Give one synthesis for each one of the following:

i) Anthracene ii) Naphthalene c) Phenanthrene

18. Explain why α- position of naphthalene is more reactive than β-position ?
19. What product(s) are formed when naphthalene is reacted with :
    a) Cl_2/Fe b) CrO_3/AcOH at298K c) Conc.H_2SO_4 at 355K d) HNO_3/ Conc.H_2SO_4
20. Describe the isolation of anthracene from coal tar.
21. How will be establish the structure of anthracene on the basis of analytical evidence ?
22. Write the resonating structures of anthracene and naphthalene
23. How will you synthesize α- and β-naphthols?
24. Explain in Haworth synthesis, the clemmensen reduction of the keto acid is essential before cyclisation.
25. What are the methods used for synthesis of phenanthrene?
26. Explain anthracene is more reactive than naphthalene.
27. Why the 9,10-position of anthracene are very reactive ?
28. Illustrate the following:
29. i) Elbs reaction for the synthesis of anthracene
30. ii) Bardhan-Sengupta synthesis of phenanthrene
31. Comment on the modern views about the naphthalene structure.
32. What are naphthyl amines? How are they prepared ? Give their chemical reactions.
33. Why naphthalene is less aromatic than benzene
34. Give the oxidation and reduction reactions of naphthalene.
35. How will you prepared naphthalene from benzaldehyde and benzene ?
36. How will you synthesize naphthalene ? Give its chemical reactions with respect to sulphonation, chloromethylation and friedel crafts alkylation.

17CHU303

Karpagam Academy of Higher Education

Coimbatore-21

(For the candidate admitted on 2017 onwards)

Department of Chemistry

III- semester

ORGANIC CHEMISTRY-III

UNIT II- Objective Questions for online examination (Each carry 1 Marks)

Question	Option-A	Option-B	Option-C	Option-D	Answer
Which is more basic	p-nitroaniline	m-nitroaniline	aniline	ammonia	ammonia
The correct structure of benzene diazonium chloride which explain all the properties of the compound was given by	Greiss	Kekule	Bloomstrand	Huckel	Bloomstrand
Diazotisation of aniline can be carriedout at the temperature range	73-78K	173-178K	373-378K	273-278K	273-278K
$-N_2Cl$ group can be replaced by –H by means of	Hypophosphorous acid	Phosphoric acid	Phosphorous acid	Metaphosphoric acid	Hypophosphorous acid
Coupling reaction involves the reaction between benzene diazonium chloride and	ether	Carboxylic acid	Carboxylic acid derivatives	phenol	phenol
Coupling reaction involves the reaction between benzene diazonium chloride and	ether	Carboxylic acid	Carboxylic acid derivatives	aniline	aniline
Benzene diazonium chloride can be converted into fluorobenzene using	CuF	Cu/HF	HBF_4	F_2	HBF_4
The coupling reaction between benzene diazonium chloride and animine takes place in	Strongly alkaline medium	Weakly alkaline medium	Strongly acidic medium	Weakly acidic medium	Weakly alkaline medium
Sodium nitrite and dil hydrochloric acid gives	Nitric acid	Sulphuric acid	Sulphurous acid	Nitrous acid	Nitrous acid
An aromatic primary amine reacts with Sodium nitrite and dil hydrochloric acid gives	Benzene diazonium chloride	nitrosoamine	Yellow colour nitroso compound	Diazo methane	Benzene diazonium chloride
An aromatic primary amine reacts with nitrous acid to give	Benzene diazonium chloride	nitrosoamine	Yellow colour nitroso compound	Diazo methane	Benzene diazonium chloride

Benzene diazonium chloride is prepared from	An aromatic primary amine with sodium nitrite	An aromatic primary amine and nitrous acid	Aromatic primary amine with hydrochloric acid	Secondary amine with sodium nitrite	An aromatic primary amine and nitrous acid
Benzene diazonium chloride reacts with cuprous chloride to give	Chlorobenzene	aniline	Copper diazonium chloride	diazomethane	Chlorobenzene
Benzene diazonium chloride reacts with cuprous bromide to give	Bromo benzene	aniline	Copper diazonium chloride	diazomethane	Bromo benzene
Benzene diazonium chloride reacts with cuprous cyanide to give	cyano benzene	aniline	Copper diazonium chloride	diazomethane	cyano benzene
Benzene diazonium chloride reacts with copper and hydrogen chloride to give	Chlorobenzene	aniline	Copper diazonium chloride	diazomethane	Chlorobenzene
Benzene diazonium chloride reacts with cuprous bromide to give bromobenzene	Sandmeyer reaction	Gattermann reaction	Gattermann koch reaction	Clemenson reduction	Sandmeyer reaction
Benzene diazonium chloride reacts with copper and potassium cyanide to give	cyano benzene	aniline	Copper diazonium chloride	diazomethane	cyano benzene
Benzene diazonium chloride reacts with copper and hydrogen bromide to give	Bromo benzene	aniline	Copper diazonium chloride	diazomethane	Bromo benzene
Benzene diazonium chloride reacts with copper and hydrogen bromide to give	Sandmeyer reaction	Gattermann reaction	Gattermann koch reaction	Clemenson reduction	Gattermann reaction
On warming the solution diazonium salt with potassium iodide solution to give	Bromo benzene	aniline	Copper diazonium chloride	Iodo benzene	Iodo benzene
On warming the solution diazonium salt with water it gives	Bromo benzene	aniline	Copper diazonium chloride	phenol	phenol
Decomposing diazonium fluoborate with sodium nitrite solution in the presence of copper powder it gives	Bromo benzene	aniline	Copper diazonium chloride	nitrobenzene	nitrobenzene
P-amino azobenzene is obtained by reacting benzene diazonium chloride with	aniline	phenol	benzaldehyde	benzophenone	aniline
P-hydroxy azobenzene is obtained by reacting benzene diazonium chloride with	aniline	phenol	benzaldehyde	benzophenone	phenol

Compounds in which two or more rings are fused due to the sharing of two or more carbon atoms by two or more rings are called	Condensed polynuclear hydrocarbons	Aromatic compounds	Aliphatic compounds	Mixed amines	Condensed polynuclear hydrocarbons
An Example for polynuclear hydrocarbons	Napthalene	aniline	phenol	benzaldehyde	Napthalene
Phenanthrene is a	Condensed polynuclear hydrocarbons	Aromatic aldehyde	Aromatic ketone	Aromatic alcohol	Condensed polynuclear hydrocarbons
An Example for polynuclear hydrocarbons	Anthracene	aniline	phenol	benzaldehyde	Anthracene
In naphthalene benzene rings are fused in	Para positions	Meta positions	Ortho positions	Ortho and meta positions	Ortho positions
Resistant to addition reaction	Naphthalene	ethylene	propylene	butylene	Naphthalene
Undergoes electrophilic substitution reactions	Anthracene	ethylene	propylene	butylene	Naphthalene
Naphthalene on oxidation with acid permanganate gives	Benzoic acid	Furoic acid	Phthalic acid	Phthalic anhydride	Phthalic acid
Phthalic acid is obtained when oxidized with acid permangnate	Naphthalene	anthracene	phenanthrene	benzaldehyde	Naphthalene
4-phenylbutene is passed over red hot calcium oxide to give	Naphthalene	anthracene	phenanthrene	benzaldehyde	Naphthalene
Nitronaphthalene on oxidation gives	Benzoic acid	Furoic acid	Nitro Phthalic acid	Phthalic anhydride	Nitro Phthalic acid
Aminonapthalene on oxidation gives	Benzoic acid	Furoic acid	Phthalic acid	Phthalic anhydride	Phthalic acid
Alpha naphthol on distillation with Zinc gives	Naphthalene	anthracene	phenanthrene	benzaldehyde	Naphthalene
Shape of naphthalene molecule is	tetrahedral	planar	trigonal	bipyramidal	planar
The length of C1-C2 bond is	1.36A	1.40A	1.54A	1.22A	1.36A
The length of C2-C3 bond is	1.36A	1.40A	1.54A	1.22A	1.40A
The resonance enthalpy of naphthalene is	80 K cal	61 K cal	180 K cal	30 K cal	61 K cal
All the carbon atoms in naphthalene are in	SP hybridisation	SP^2 hybridisation	SP^3 hybridisation	D^2 SP hybridisation	SP^2 hybridisation
When compared to benzene naphthalene is more susceptible to	Hydrolysis	Oxidation	reduction	Oxidation and reduction	Oxidation and reduction

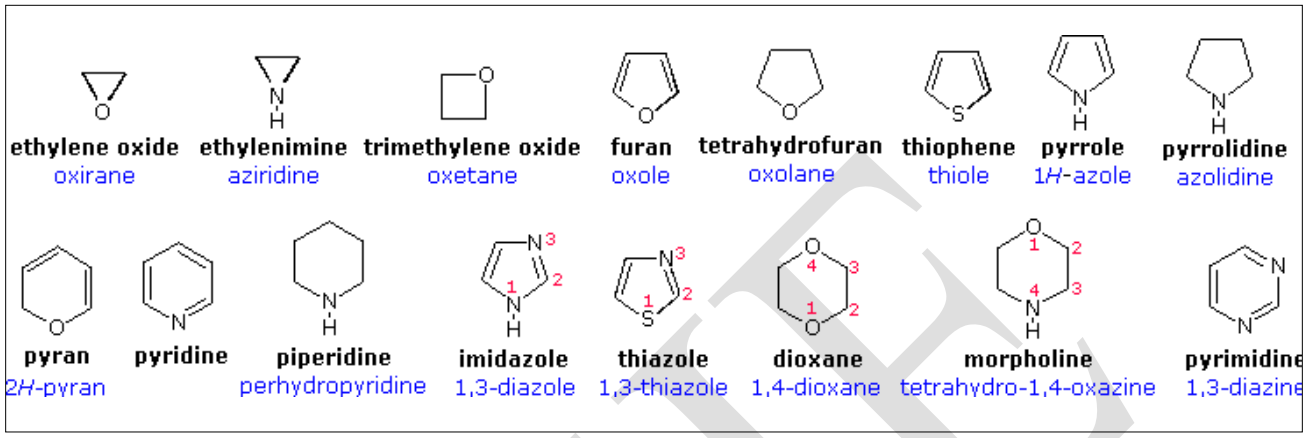
Electrophilic substitution of naphthalene takes place at	1^{st} position	2^{nd} position	1^{st} or 2^{nd} position	8^{th} position	1^{st} or 2^{nd} position
Nitration of naphthalene with con.nitric acid and sulphuric acid at higher temperature gives	1,5-di nitro naphthalene	1,8-di nitro naphthalene	A mixture of 1,5-di nitro naphthalene and 1,8-di nitro naphthalene	3- nitro naphthalene	A mixture of 1,5-di nitro naphthalene and 1,8-di nitro naphthalene
Nitration of naphthalene with con.nitric acid and sulphuric acid gives predominantly	1-nitro naphthalene	2- nitro naphthalene	3- nitro naphthalene	4- nitro naphthalene	1-nitro naphthalene
Sulphonation of naphthalene at 355K yields	1-naphthalene sulphonic acid	2- naphthalene sulphonic acid	A mixture of 1- and 2-naphthalene sulphonic acid	Cannot be sulphonated	1-naphthalene sulphonic acid
Sulphonation of naphthalene at 425K yields	1-naphthalene sulphonic acid	2- naphthalene sulphonic acid	A mixture of 1- and 2-naphthalene sulphonic acid	Cannot be sulphonated	2-naphthalene sulphonic acid
The reaction of naphthalene with sulphuryl chloride in presence of aluminium chloride gives	1-chloronaphthalene	2-chloronaphthalene	5-chloro naphthalene	1-, 2-, and 5-chloronaphthalene	1-chloronaphthalene
Chlorination of naphthalene with ferric chloride gives	1-chloronaphthalene	2-chloronaphthalene	5-chloro naphthalene	1-, 2-, and 5-chloronaphthalene	1-chloronaphthalene
Acylation of naphthalene gives	1-acyl naphthalene	2-acyl naphthalene	1- and 2- acyl naphthalene	A mixture of 1-acyl and 2-acyl naphthalene	A mixture of 1-acyl and 2-acyl naphthalene
The ratio between 1- and 2- acyl naphthalene when the reaction takes place in presence of anhydrous $AlCl_3$	3:01	1:09	2;4	3;6	3:01
The ratio between 1- and 2- acyl naphthalene when the reaction takes place in presence of nitrobenzene	3:01	1:09	2;4	3;6	1:09
Naphthalene on reaction with paraformaldehyde, HCl, acetic acid and phosphoric acid gives	1-chloromethyl naphthalene	2-chloromethyl naphthalene	1- and 2-chloromethyl naphthalene	Polymer of naphthalene	1-chloromethyl naphthalene

Naphthalene on Birch reduction gives	1,4-dihydro	1,2-dihydro Naphthalene	1,3-dihydro Naphthalene	2,4-dihydro Naphthalene	1,4-dihydro Naphthalene
Naphthalene on reduction with Na and ethyl alcohol gives	1,4-dihydro Naphthalene	1,2-dihydro Naphthalene	1,3-dihydro Naphthalene	2,4-dihydro Naphthalene	1,4-dihydro Naphthalene
Naphthalene on reduction with Na and amyl alcohol gives	1,4-dihydro Naphthalene	1,2-dihydro Naphthalene	1,3-dihydro Naphthalene	tetralin	tetralin
Naphthalene on reduction with Pt and Nickel gives	1,4-dihydro Naphthalene	1,2-dihydro Naphthalene	5-decalin	tetralin	decalin
Naphthalene on oxidation with oxygen in presence of Vanadium Pentoxide forms	Benzoic acid	Furoic acid	Phthalic acid	Phthalic anhydride	Phthalic anhydride

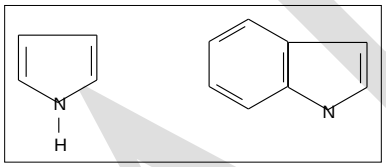
UNIT III
SYLLABUS

Classification and nomenclature, Structure, aromaticity in 5-numbered and 6-membered rings containing one heteroatom; Synthesis, reactions and mechanism of substitution reactions of: Furan, Pyrrole (Paal-Knorr synthesis, Knorr pyrrole synthesis, Hantzsch synthesis), Thiophene, Pyridine (Hantzsch synthesis),

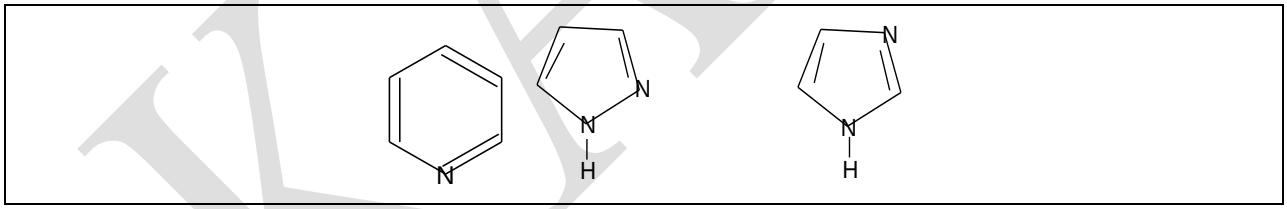
Heterocyclic compounds



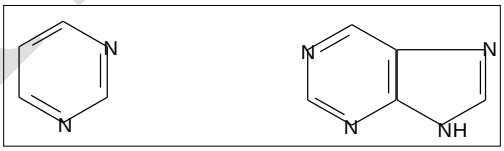
Some important heterocyclic compounds with N-heteroatom



Pyrrole **Indole**



Pyridine **Pyrazole** **Imidazole**



Pyramidine **Purine**

Nomenclature

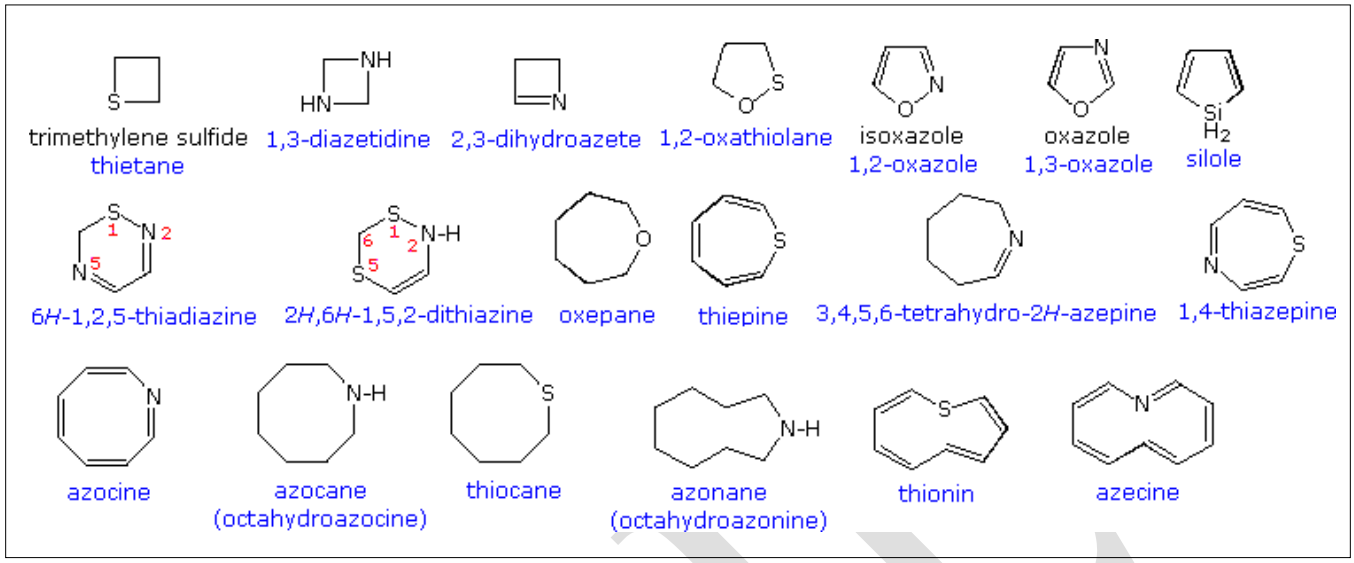
Devising a systematic nomenclature system for heterocyclic compounds presented a formidable challenge, which has not been uniformly concluded. Many heterocycles, especially amines, were identified early on, and received trivial names which are still preferred.

An easy to remember, but limited, nomenclature system makes use of an elemental prefix for the heteroatom followed by the appropriate carbocyclic name. A short list of some common prefixes is given in the following table.

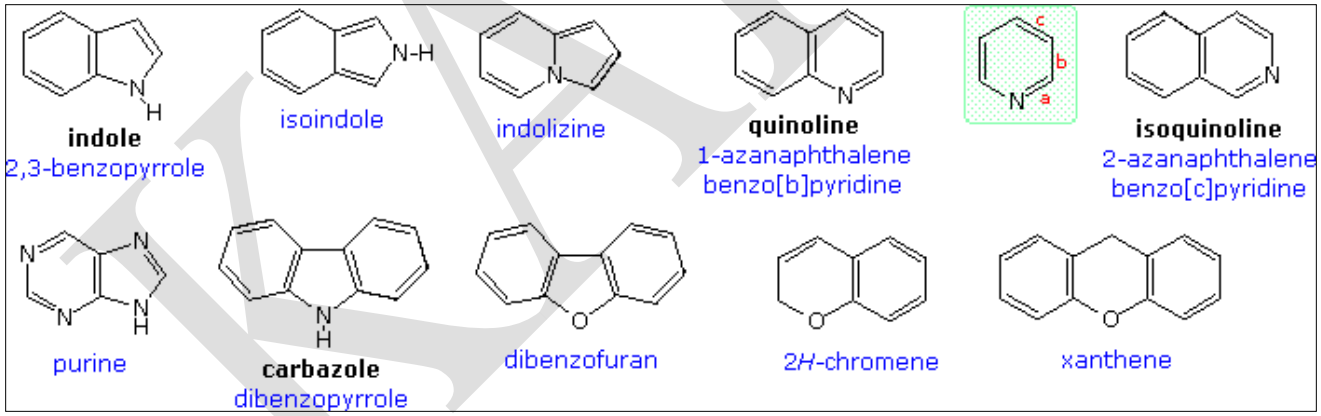
Examples of this nomenclature are:

- ethylene oxide = oxacyclopropane
- furan = oxacyclopenta-2,4-diene
- pyridine = azabenzene
- morpholine = 1-oxa-4-azacyclohexane.

Element	oxygen	sulfur	selenium	nitrogen	phosphorous	silicon	boron
Valence	II	II	II	III	III	IV	III
Prefix	Oxa	Thia	Selena	Aza	Phospha	Sila	Bora



All the previous examples have been monocyclic compounds. Polycyclic compounds incorporating one or more heterocyclic rings are well known. A few of these are shown in the following diagram. Thus, the location of a fused ring may be indicated by a lowercase letter which designates the edge of the heterocyclic ring involved in the fusion, as shown by the pyridine ring in the green shaded box.



Heterocyclic rings are found in many naturally occuring compounds. Most notably, they compose the core structures of mono and polysaccharides, and the four DNA bases that establish the genetic code

Heterocyclic compounds are:

- Heterocyclic compounds with three - membered rings
- Heterocyclic compounds with four - membered rings
- Heterocyclic compounds with five - membered rings
- Heterocyclic compounds with six - membered rings

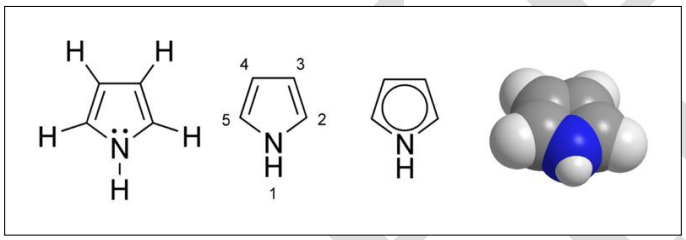
▪

Heterocyclic compounds with five-membered rings

Pyrrole

Pyrrole, is a heterocyclic aromatic organic compound, a five-membered ring with the formula C_4H_4NH. Substituted derivatives are also called ***pyrroles***. For example, $C_4H_4NCH_3$ is N-methylpyrrole. Porphobilinogen is a trisubstituted pyrrole, which is the biosynthetic precursor to many natural products.

Pyrroles are components of more complex macrocycles, including the porphyrins of heme, the chlorins and bacteriochlorins of chlorophyll, and porphyrinogens.



Pyrrole

Properties

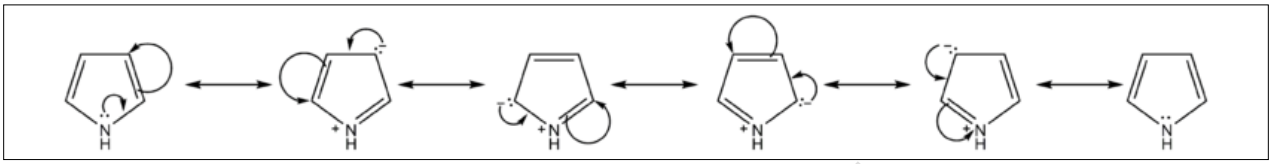
Pyrrole has very low basicity compared to amines and other aromatic compounds like pyridine, wherin the ring nitrogen is not bonded to a hydrogen atom. This decreased basicity is attributed to the delocalization of the lone pair of electrons of the nitrogen atom in the aromatic ring. Pyrrole is a very weak base with a pKaH of about −4. Protonation results in loss of aromaticity, and is, therefore, unfavorable.

Reactivity

Both NH and CH protons in pyrroles are moderately acidic and can be deprotonated with strong bases such as butyllithium and the metal hydrides. The resulting "pyrrolides" are nucleophilic. Trapping of the conjugate base with an electrophile (e.g., an alkyl or acyl halide) reveals which sites were deprotonated based on which ring positions actually react as nucleophiles. The product distribution of such a reaction can often be complex and depends on the base used (especially the counterion, such as lithium from butyllithium or sodium from sodium hydride), existing substitution of the pyrrole, and the electrophile.

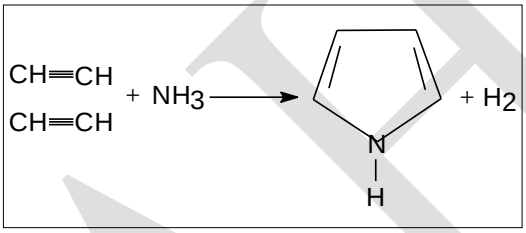
The resonance contributors of pyrrole provide insight to the reactivity of the compound. Like furan and thiophene, pyrrole is more reactive than benzene towards nucleophilic aromatic

substitution because it is able to stabilize the positive charge of the intermediate carbanion. This is because the nitrogen can donate a lone pair into the ring by resonance.



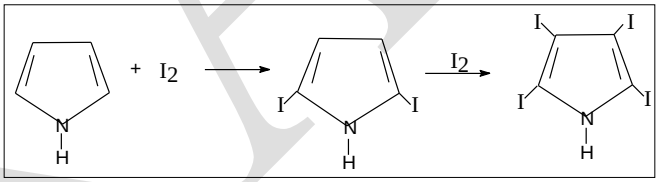
Pyrrole undergoes electrophilic aromatic substitution at the 2 and 5 positions, though the substitution product at positions 3 and 4 is obtained in low yields.

Preparation

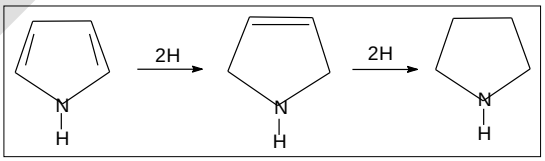


Chemical properties

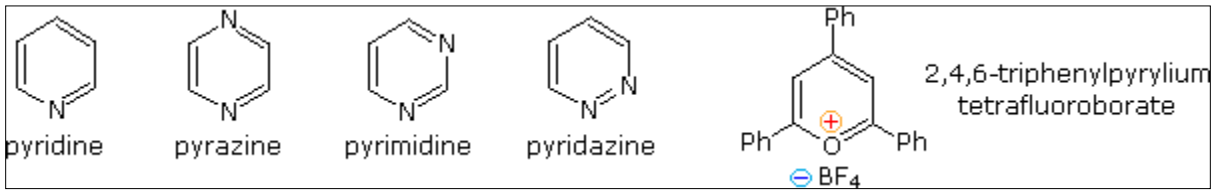
- With iodine



- Hydrogenaration

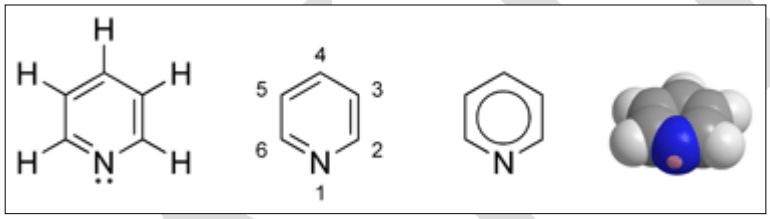


Fully unsaturated six-membered nitrogen heterocycles, such as pyridine, pyrazine, pyrimidine and pyridazine, have stable aromatic rings. Oxygen and sulfur analogs are necessarily positively charged, as in the case of 2,4,6-triphenylpyrylium tetrafluoroborate.



Pyridine

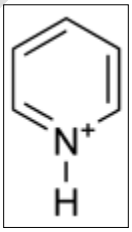
Pyridine is a simple aromatic heterocyclic organic compound with the chemical formula C_5H_5N used as a precursor to agrochemicals and pharmaceuticals, and is also an important solvent and reagent. It is structurally related to benzene, wherein one CH group in the aromatic six-membered ring is replaced by a nitrogen atom. It exists as a colorless liquid with a distinctive, unpleasant fish-like odor. The pyridine ring occurs in many important compounds, including nicotinamides.



Reactions

As a base

In organic reactions pyridine behaves both as a tertiary amine, undergoing protonation, alkylation, acylation, and N-oxidation at nitrogen, and as an aromatic compound, undergoing Nucleophilic substitutions.



Pyridinium cation

The nitrogen atom on pyridine features a basic lone pair of electrons. Because this lone pair is not delocalized into the aromatic pi-system, pyridine is basic with chemical properties similar to tertiary amines. The pKa of the conjugate acid is 5.21. Pyridine is protonated by reaction with acids and forms a positively charged aromatic polyatomic ion called pyridinium. The bond

lengths and bond angles in pyridine and the pyridinium ion are almost identical. In addition, the pyridinium cation is isoelectronic with benzene. Pyidine is widely used as a ligand in coordination chemistry. Also important are its chelating derivatives 2,2'-bipyridine, consisting of two pyridine molecules joined by a single bond, and terpyridine, a molecule of three pyridine rings linked together.

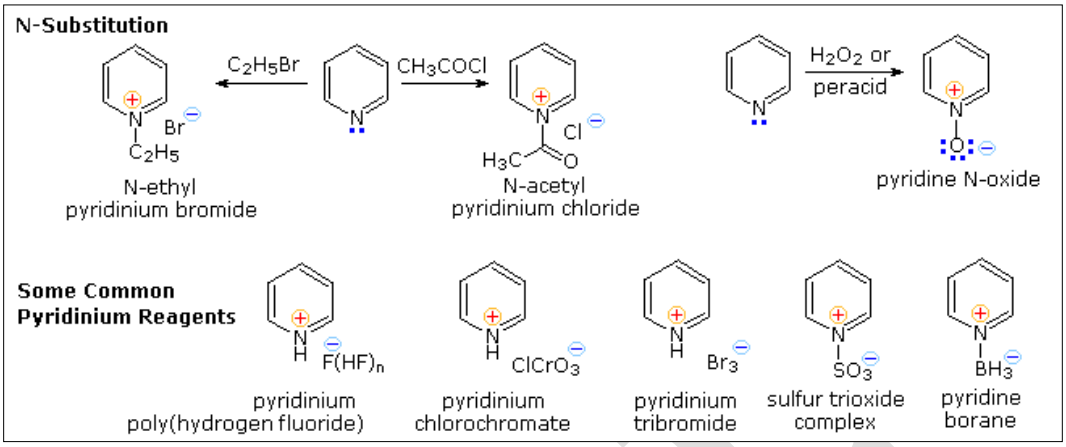
Nucleophilic reactions at the ring

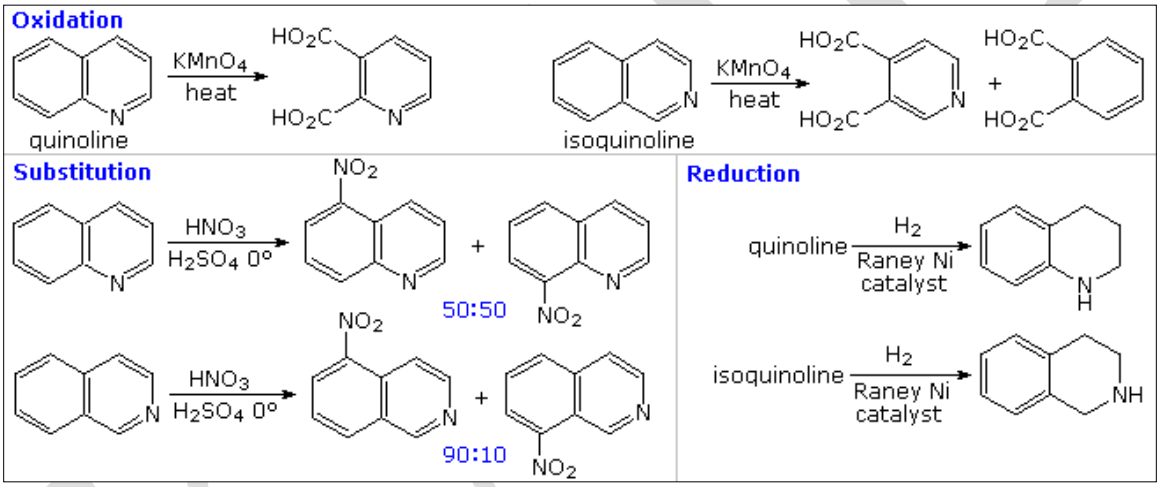
Nucleophilic aromatic substitution occurs at C-2 and at C-4. For example in the Chichibabin reaction, pyridine reacts with sodium amide to give 2-aminopyridine. In the Emmert reaction, named for Bruno Emmert), pyridine reacts with a ketone in presence of aluminium or magnesium and mercuric chloride to give the carbinol also at C_2. Pyridine is also used as a denaturant for antifreeze mixtures, for ethyl alcohol, for fungicides, and as a dyeing aid for textiles.

Electrophilic Substitution of Pyridine

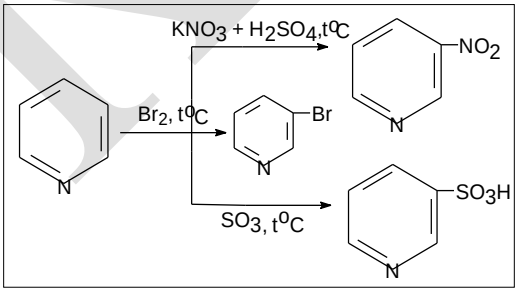
Pyridine is a modest base (pKa=5.2). Since the basic unshared electron pair is not part of the aromatic sextet, as in pyrrole, pyridinium species produced by N-substitution retain the aromaticity of pyridine. As shown below, N-alkylation and N-acylation products may be prepared as stable crystalline solids in the absence of water or other reactive nucleophiles. The N-acyl salts may serve as acyl transfer agents for the preparation of esters and amides. Because of the stability of the pyridinium cation, it has been used as a moderating component in complexes with a number of reactive inorganic compounds. Several examples of these stable and easily handled reagents are shown at the bottom of the diagram. The poly(hydrogen fluoride) salt is a convenient source of HF for addition to alkenes and conversion of alcohols to alkyl fluorides, pyridinium chlorochromate (PCC) and its related dichromate analog are versatile oxidation agents and the tribromide salt is a convenient source of bromine. Similarly, the reactive compounds sulfur trioxide and diborane are conveniently and safely handled as pyridine complexes.

Amine oxide derivatives of 3º-amines and pyridine are readily prepared by oxidation with peracids or peroxides, as shown by the upper right equation. Reduction back to the amine can usually be achieved by treatment with zinc (or other reactive metals) in dilute acid.

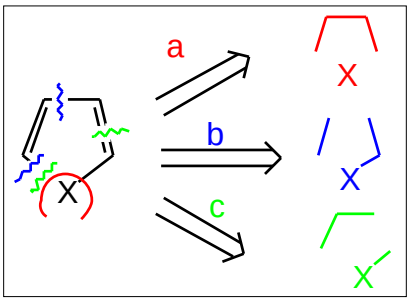




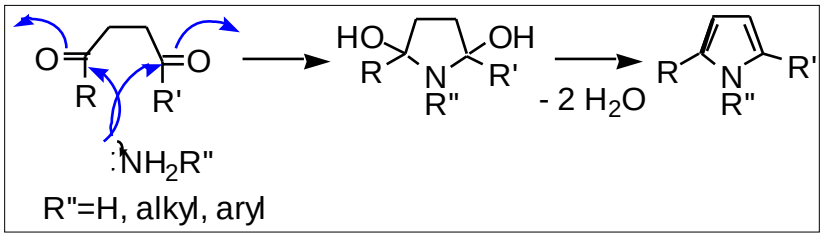
N-subtitution

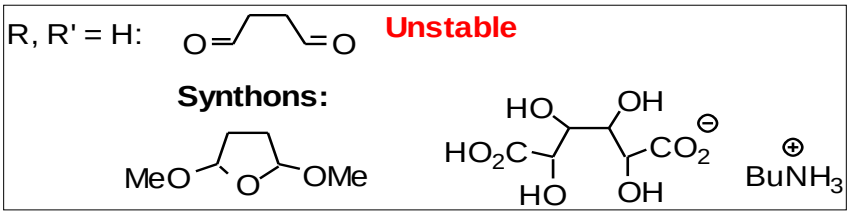


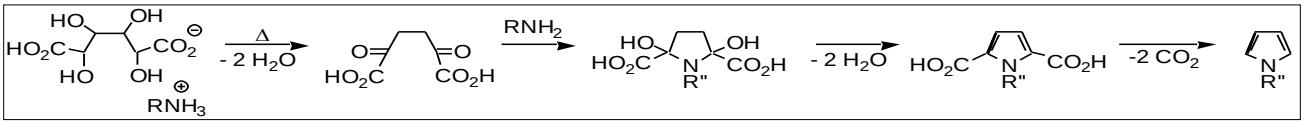
Pyrrole



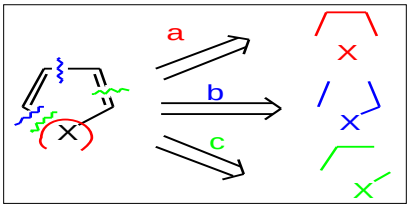
Strategy a: Paal – Knorr Synthesis

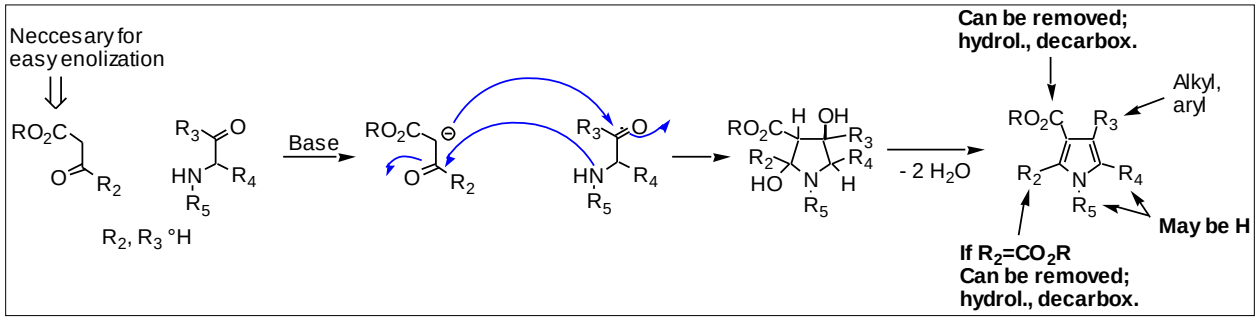




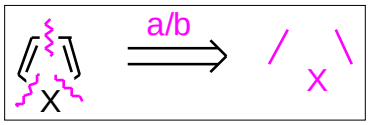


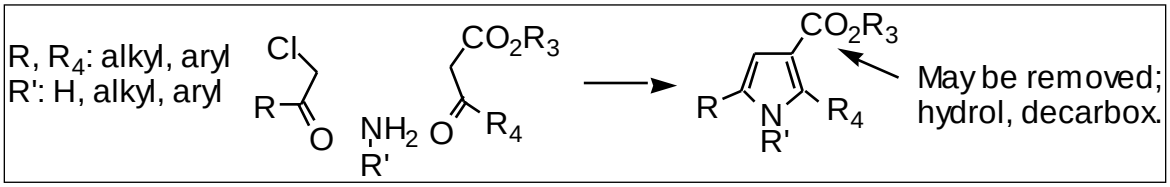
Strategy b; Knorr synth

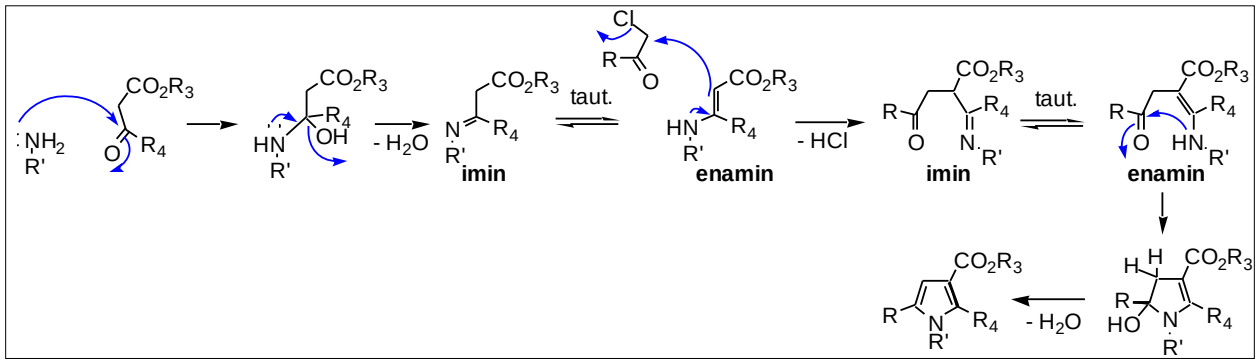




Strategy a and b combined; Hantzsch synth.







SUGGESTED MATERIALS:

Text books:

T1: Morrison, R. T. & Boyd, R. N.(1992). *Organic Chemistry*. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).
T2: Arun Bahl(2005). Advanced organic chemistry, S.Chand & Company Pvt.Ltd. Ramnagar, New Delhi.

T3: Finar, I. L. (2002). *Organic Chemistry*. Volume 1. Dorling Kindersley (India) Pvt. Ltd., (Pearson Education).

Reference Books

R1: Finar, I. L. (2002). *Organic Chemistry*: *Stereochemistry and the Chemistry of Natural Products*. Volume 2. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

POSSIBLE QUESTIONS

PART A

(1 Mark Q.No.1 to 20)
(Online examination)

PART B (2 Marks)

1. Write any one synthesis of pyrrole
2. Write any one synthesis of furan
3. Write any synthesis of thiophene
4. Why pyrrole is more aromatic than furan
5. Why pyridine is more basic than pyrrole.

PART C(6 Marks)

1. Discuss the electrophilic aromatic substitution reactions of furan
2. Discuss the aromaticity present in furan, thiophene and pyrrole.
3. Explain Paal-Knorr synthesis to prepare furan and pyrrole.
4. How pyridine is prepared by Hantzsch synthesis
5. Discuss the electrophilic reactions of furan
6. Explain how pyrrole is prepared by (i) Paal-Knorr synthesis, (ii) Knorr pyrrole synthesis, (iii) Hantzsch synthesis
7. Explain the following reactions in detail (i) Gattermann Koch Synthesis (ii) Friedelcrafts acylation of furan (iii) pyrrole is acidic in nature
8. Discuss the aromaticity present in furan thiophene and pyrrole.

17CHU303

Karpagam Academy of Higher Education

Coimbatore-21

(For the candidate admitted on 2017 onwards)

Department of Chemistry

III- semester

ORGANIC CHEMISTRY-III

UNIT III- Objective Questions for online examination (Each carry 1 Marks)

Question	Option-A	Option-B	Option-C	Option-D	Answer
Naphthalene on oxidation chromic acid in acetic acid forms	1,4 napthoquinone	Furoic acid	Phthalic acid	Phthalic anhydride	1,4 napthoquinone
Pyridine has a delocalized pi molecular orbital containing	8 electrons	6 electrons	4 electrons	12 electrons	6 electrons
Pyrrole has a delocalized pi molecular orbital containing	4 electrons	6 electrons	8 electrons	12 electrons	6 electrons
Furan has a delocalized pi molecular orbital containing	6 electrons	4 electrons	8 electrons	12 electrons	6 electrons
Thiophene has a delocalized pi molecular orbital containing	4 electrons	6 electrons	8 electrons	12 electrons	6 electrons
Furan reacts with ammonia in the presence of alumina at 400 C to give	Pyridine	Furfural	Pyrrole	Furoic acid	Pyrrole
When aniline is heated with glycerol in the presence of sulphuric acid and nitrobenzene, it gives quinoline. The reaction is called	Fischer synthesis	Skraup synthesis	Diazotisation	Corey-House synthesis	Skraup synthesis
Cyclic compounds having atleast one atom other than carbon in the ring are termed as	Heterocyclic compounds	Carbocyclic compounds	Alicyclic compounds	Polycyclic compounds	Heterocyclic compounds
Example for an hetero atom	Hydrogen	Carbon	Oxygen	silicon	Oxygen

Pickup an hetero atom from the following	Hydrogen	Carbon	Nitrogen	silicon	Nitrogen
One among the following is called an hetero atom	Hydrogen	Carbon	Sulphur	silicon	Sulphur
Most stable heterocyclic compounds are	5 or 6 membered compounds	4 membered compounds	7 membered compounds	12 membered compounds	5 or 6 membered compounds
Five membered heterocyclic compound are derived from benzene by replacement of	a C=C by a hetero atom	A carbon of benzene by an hetero atom	Reaction with ammonia	Reaction of benzene with sulphur trioxide	A carbon of benzene by an hetero atom
Five membered heterocyclic compound are derived from benzene by replacement of	a C=C by a hetero atom	A carbon of benzene by an hetero atom	Reaction with ammonia	Reaction of benzene with sulphur trioxide	A C=C by a hetero atom
Example for an five membered heterocyclic compound	Indole	Pyridine	Furan	Pyrimidine	Furan
Choose an five membered heterocyclic compound	Indole	Pyridine	Pyrrole	Pyrimidine	Pyrrole
One among the following is an 5-membered heterocyclic compound	Indole	Pyridine	Thiophene	Pyrimidine	Thiophene
Example for an six membered heterocyclic compound	Indole	Pyridine	Furan	Pyrimidine	Pyridine
Choose an six membered heterocyclic compound	Indole	Pyran	Pyrrole	Pyrimidine	Pyran
One among the following is an 6-membered heterocyclic compound	Indole	Thiopyran	Thiophene	Pyrimidine	Thiopyran
Example for an condensed heterocyclic compound	Indole	Pyridine	Furan	Pyrimidine	Indole

Choose a condensed heterocyclic compound	Quinoline	Pyran	Pyrrole	Pyrimidine	Quinoline
One among the following is a condensed heterocyclic compound	Isoquinoline	Thiopyran	Thiophene	Pyrimidine	Isoquinoline
The first priority is given to the hetero atom	Oxygen	Nitrogen	Sulphur	Phosphorous	Oxygen
Least priority is given to	Oxygen	Nitrogen	Sulphur	Phosphorous	Phosphorous
The prefix used to IUPAC name a 5-membered oxygen containing heterocyclic compound is	oxa	thia	aza	Phospha	oxa
The prefix used to IUPAC name a sulphur containing heterocyclic compound is	oxa	thia	aza	Phospha	thia
The prefix used to IUPAC name a nitrogen containing heterocyclic compound is	oxa	thia	aza	Phospha	aza
The suffix used to IUPAC name a 5-membered oxygen containing heterocyclic compound is	-ole	-ine	-epine	-aza	-ole
The suffix used to IUPAC name a 6-membered oxygen containing heterocyclic compound is	-ole	-ine	-epine	-aza	-ine
The suffix used to IUPAC name a 7-membered oxygen containing heterocyclic compound is	-ole	-ine	-epine	-aza	-epine
The IUPAC name of Pyrrole is	azole	oxole	thiole	azine	azole
The IUPAC name of Furan is	azole	oxole	thiole	azine	oxole
The IUPAC name of thiophene is	azole	oxole	thiole	azine	thiole
The IUPAC name of pyridine is	azole	oxole	thiole	azine	azine
Dry distillation of mucic acid gives	Furan	pyrrole	thiophene	pyridine	Furan

Furfural and steam passed over a catalyst consisting of Zn and Mn chromites at 673 K, it gives	Furan	pyrrole	thiophene	pyridine	Furan
Acetonyl acetone on dehydration with phosphorous pentoxide gives	Furan	pyrrole	thiophene	pyridine	Furan
Furan treated with acetyl nitrate to form	2-nitrofuran	3-nitrofuran	4-nitrofuran	3 and 4-nitro furan	2-nitrofuran
Electrophilic substitution in furan takes place at	1,2 position	2, 5 position	3,4 position	2 and 3 position	2, 5 position
Furan treated with pyridine-Sulphur trioxide gives	Furan-2-sulphonic acid	Furan-pyridine adduct	Pyridine 2-sulphonic acid	3-furan sulphonic acid	Furan-2-sulphonic acid
Furan treated with HCN and HCl in presence of aluminium chloride to form	Furoic acid	furfural	Aryl furan	2-acetyl furan	furfural
Nitrogen analog of furan is called	Pyrrole	Pyridine	pyrimidine	dihydropyrrole	Pyrrole
Distillation of succinimide with zinc dust gives	Furan	pyrrole	thiophene	pyridine	Pyrrole
Ammonium mucate is distilled in the presence of glycerol gives	Furan	pyrrole	thiophene	pyridine	Pyrrole
Acetonyl acetone on heating with ammonia gives	Furan	pyrrole	thiophene	pyridine	Pyrrole
Which is more aromatic	Furan	pyrrole	thiophene	Allyl chloride	Thiophene
Hantsch synthesis is to prepare	Furan	pyrrole	thiophene	pyridine	pyridine
Process of heating 2 moles of ethylacetoacetate, acetaldehyde and ammonia to form pyridine is called	Hantsch synthesis	Clemenson reduction	Hoffmann degradation	Hoffmann elimination	Hantsch synthesis
Heating of sodium succinate with phosphorous sulphide gives	Furan	pyrrole	thiophene	pyridine	thiophene
Acetonyl acetone reacts with phosphorous pentasulphide to form	Furan	pyrrole	Dimethyl thiophene	pyridine	Dimethyl thiophene

Which of the following reagents will re react with pyrrole to form 2-formylpyrrole	Formic acid	Chloroform/KOH	Hydrogen peroxide	Acetic anhydride	Chloroform/KOH
Which of the following reagents will react with furan to form 2-furansulphonic acid	SO_3 in pyridine 100 C	Dil sulphuric acid at 200 C	Sulphur dioxide at 100 c	Dil sulphuric acid at 100 C	SO_3 in pyridine 100 C
Pyridine reacts with a mixture of KNO_3 and H_2SO_4 at 300 C to give	1-nitropyridine	2-nitropyridine	3-nitropyridine	4-nitropyridine	3-nitropyridine
Pyridine reacts with HCl to form	Pyridinium chloride	2-chloropyridine	3-chloropyridine	5-chloropyridine	Pyridinium chloride
Pyrrole is less basic than pyridine because the lone pair of electrons on N-atom in pyrrole	Is part of the delocalized pi molecular orbital	Is not part of the delocalized pi molecular orbital	Resides in SP hybrid orbital	Resides in SP^2 hybrid orbital	Is part of the delocalized pi molecular orbital
Furan is less aromatic than pyrrole because	Oxygen is more electronegative than Nitrogen	Oxygen is less electronegative than Nitrogen	Nitrogen is more electronegative than oxygen	Nothing to do with electronegativity	Oxygen is more electronegative than Nitrogen
Furan is less aromatic than thiophene because	Oxygen is more electronegative than sulphur	Oxygen is less electronegative than Sulphur	Sulphur is more electronegative than oxygen	Nothing to do with electronegativity	Oxygen is more electronegative than Sulphur

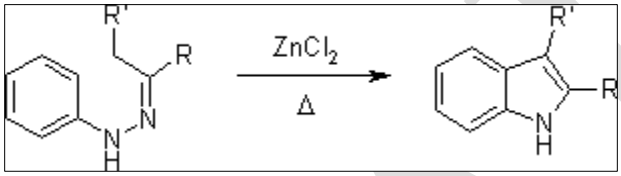
Diels Alder adduct is formed when furan react with	Succinic anhydride	Maleic anhydride	Maleic acid	Succinic acid	Maleic anhydride
Furan when reduced with Nickel in presence of hydrogen to form	Dihydrofuran	Tetrahydrofuran	1,6 diamino hexane	Adipic acid	Tetrahydrofuran

UNIT IV
SYLLABUS

Indole(Fischer indole synthesis and Madelung synthesis), Quinoline and isoquinoline, (Skraup synthesis, Friedlander's synthesis, Knorr quinoline synthesis, Doebner- Miller synthesis, Bischler-Napieralski reaction, Pictet-Spengler reaction, Pomeranz-Fritsch reaction)

Fischer Indole Synthesis

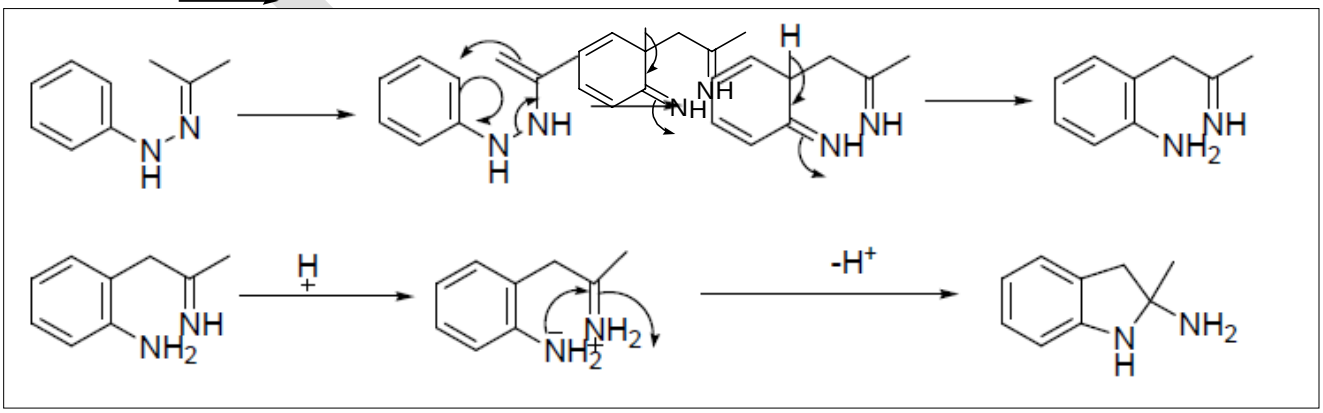
Fischer indole synthesis – this is the oldest way known to make indoles. The reaction is catalyzed by acid. The starting material is phenylhydrazone, and it is formed from the condensation of phenyl hydrazine and a ketone:

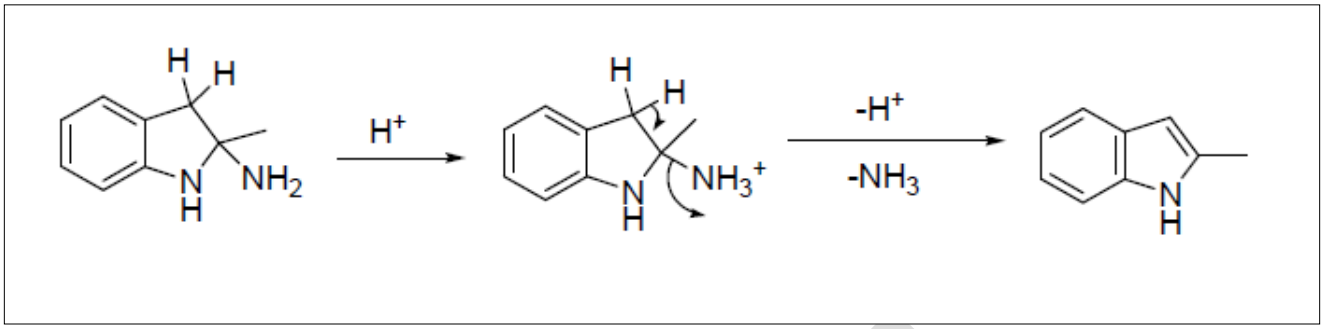


The conversion of aryl hydrazones to indoles; requires elevated temperatures and the addition of Brønsted or Lewis acids. Some interesting enhancements have been published recently; for example a milder conversion when *N*-trifluoroacetyl enehydrazines are used as substrates.

To convert this compound into an indole, the reaction follows the mechanism shown below:

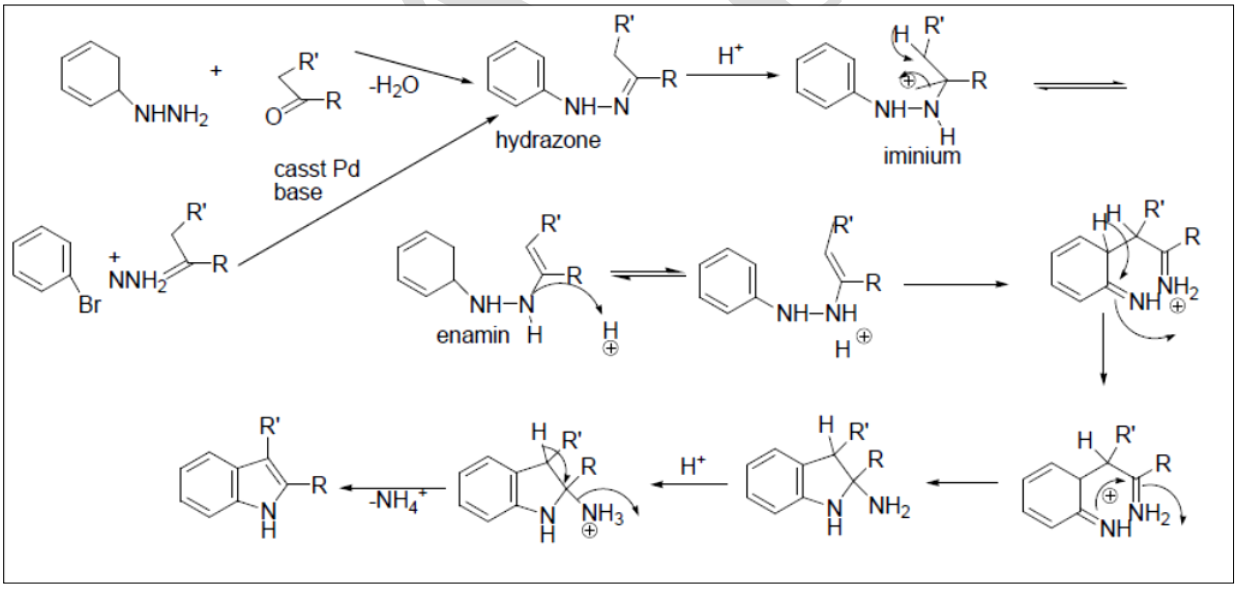
Mechanism of the Fischer Indole Synthesis





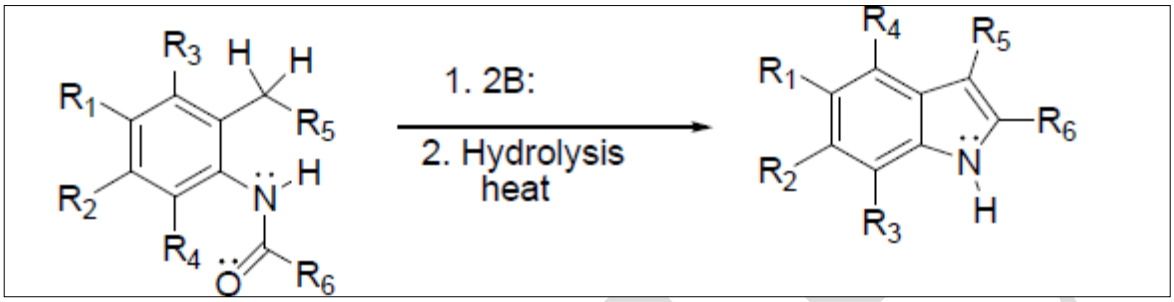
The key step is this reaction is the [3,3] sigmatropic rearrangement, and the driving force for that rearrangement is that you are forming new carbon-carbon bonds (strong) at the expense of breaking NN bonds (weak).

In general, a "sigmatropic rearrangement" refers to something where the only reaction involves moving sigma bonds. The product and the starting material have the same number and same types of atoms; the only difference is where the sigma bonds are located. Also, the rearrangement occurs via a concerted moving of electrons- all the bonds move at once. This particular rearrangement is called a 3,3 rearrangement. This reaction was discovered in 1883. Since then there have been a few advances in indole synthesis.



The **Madelung synthesis** is a chemical reaction that produces (substituted or unsubstituted) indoles by the intramolecular cyclization of N-phenylamides using strong base at high temperature.The Madelung synthesis was reported in 1912 by Walter Madelung, when he observed that 2-phenylindole was synthesized using N-benzoyl-o-toluidine and two equivalents of sodium

ethoxide in a heated, airless, reaction. Common reaction conditions include use of sodium or potassium alkoxide as base in hexane or tetrahydrofuran solvents, at temperatures ranging between 200-400 °C. A hydrolysis step is also required in the synthesis. The Madelung synthesis is important because it is one of few known reactions that produce indoles from a base- catalyzed thermal cyclization of N-acyl-o-toluidines. The overall reaction for the Madelung synthesis follows.

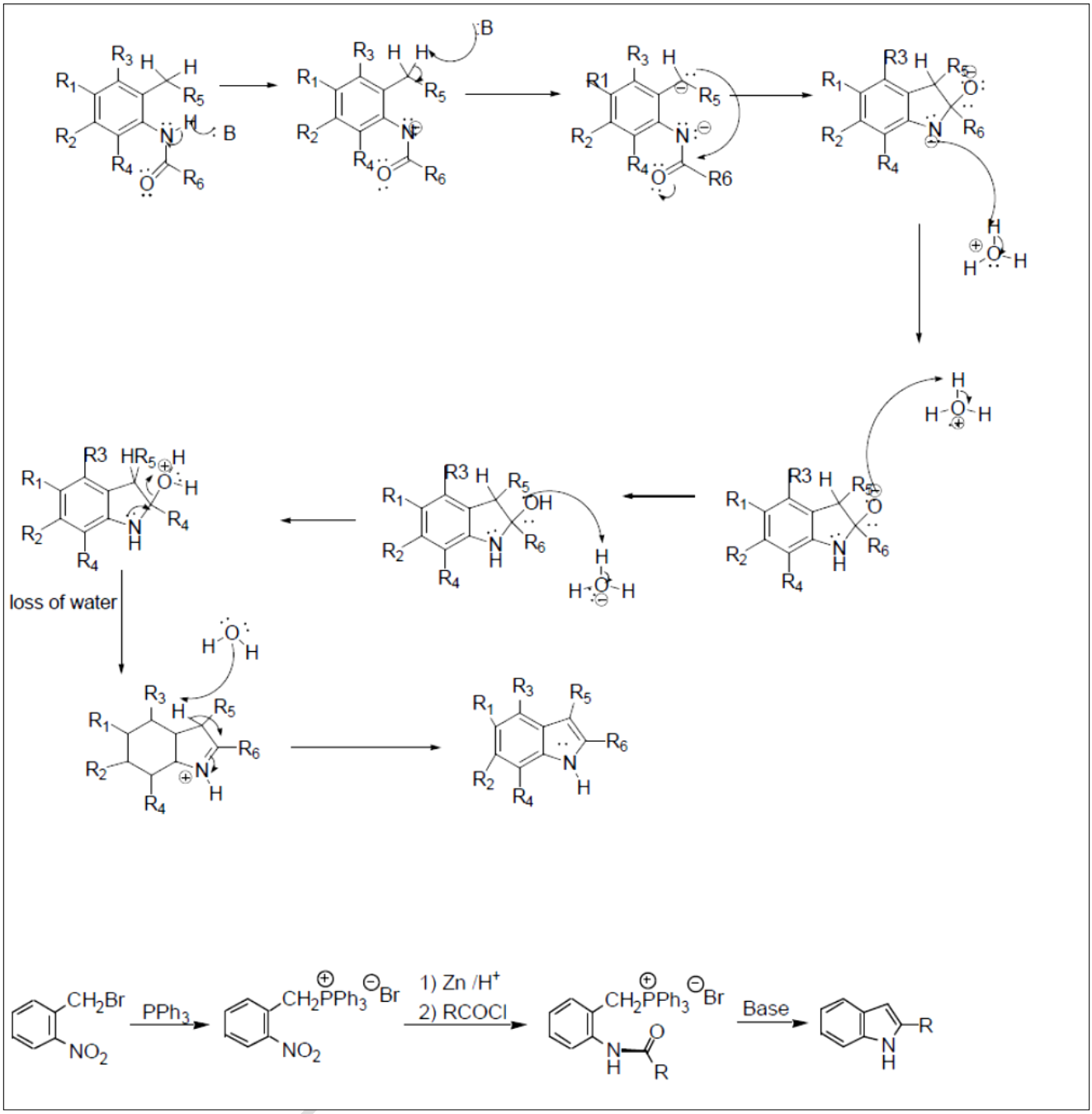


This method is essentially confined to the preparation of 2-alkinylindoles (not easily accessible through electrophilic aromatic substitution) because of the vigorous reaction conditions. A detailed reaction mechanism for the Madelung synthesis follows.

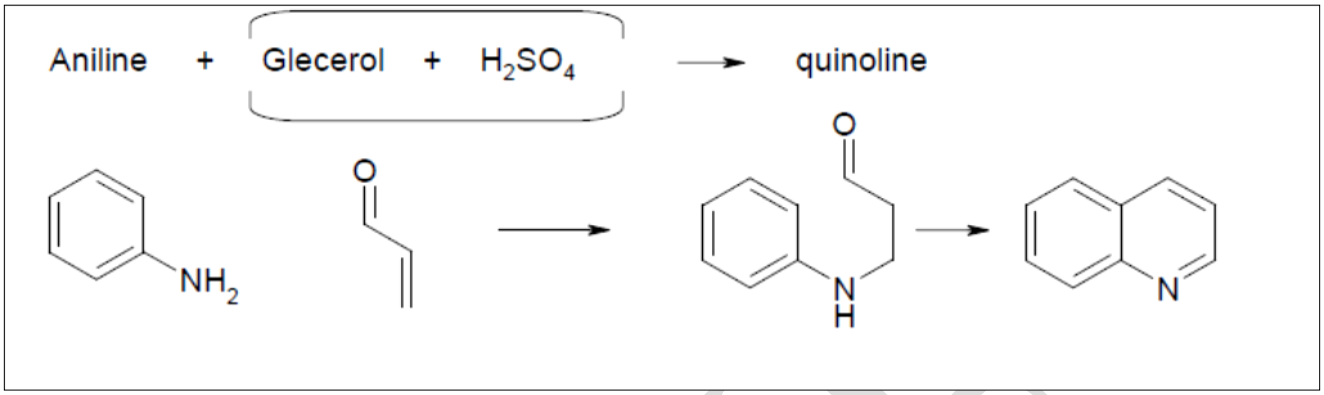
Mechanism of the reaction

The reaction begins with the extraction of a hydrogen from the nitrogen of the amide substituent and the extraction of a benzylic hydrogen from the substituent ortho to the amide substituent by a strong base. Next, the carbanion resulting from the benzylic hydrogen extraction performs
a nucleophilic attack on the electrophilic carbonyl carbon of the amide group. When this occurs, the pi-bond of the amide is converted into a lone pair, creating a negatively charged oxygen.

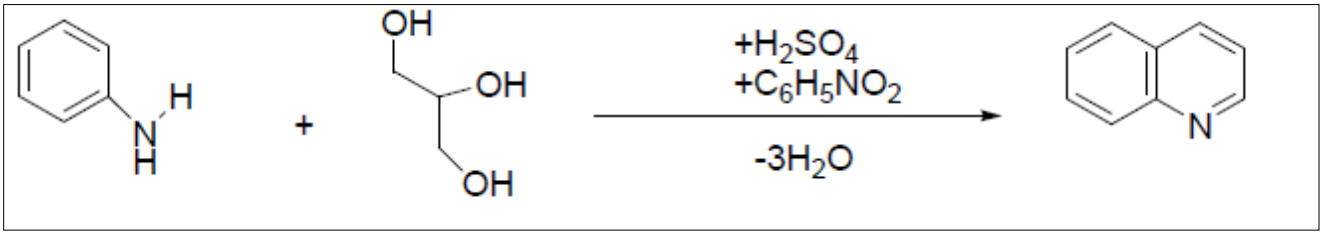
After these initial steps, strong base is no longer required and hydrolysis must occur. The negatively charged nitrogen is protonated to regain its neutral charge, and the oxygen is protonated twice to harbor a positive charge in order to become a good leaving group. A lone pair from the nitrogen forms a pi-bond to expel the positively charged leaving group, and also causes the nitrogen to harbor a positive charge. The final step of the reaction is an elimination reaction (specifically an E2 reaction), which involves the extraction of the other hydrogen that was once benzylic, before the bicyclic compound was formed, whose electrons are converted into a new pi-bond in the ring system. This allows the pi-bond formed by nitrogen in the preceding step to be converted back into a lone pair on nitrogen to restore nitrogen's neutral charge.


loss of water
CH2Br
NO2
PPh3
CH2PPh3 Br
1) Zn /H+
2) RCOCl
Base

Quinoline Skraup Synthesis

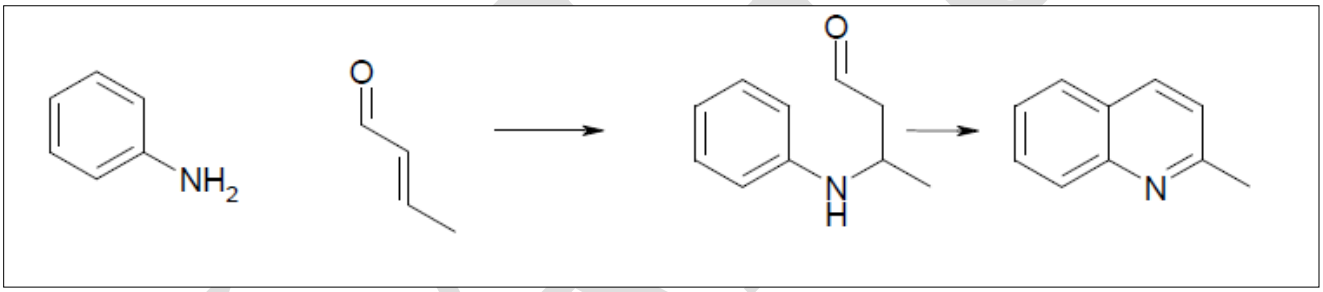


In the archetypal Skraup reaction, aniline is heated with sulfuric acid, glycerol, and an oxidizing agent such as nitrobenzene to yield quinoline.

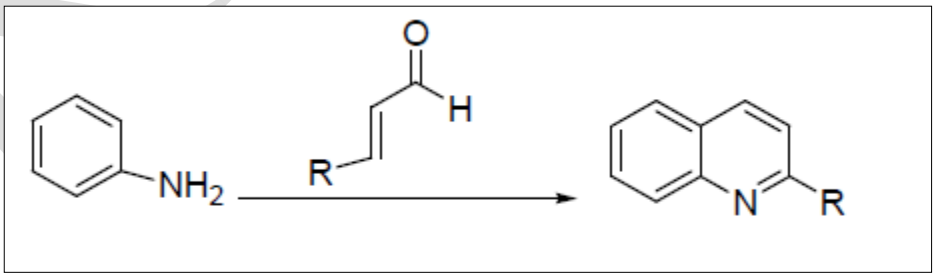


In this example, nitrobenzene serves as both the solvent and the oxidizing agent. The reaction, which otherwise has a reputation for being violent, is typically conducted in the presence of ferrous sulfate. Arsenic acid may be used instead of nitrobenzene and the former is better since the reaction is less violent

Doebner-von Millar



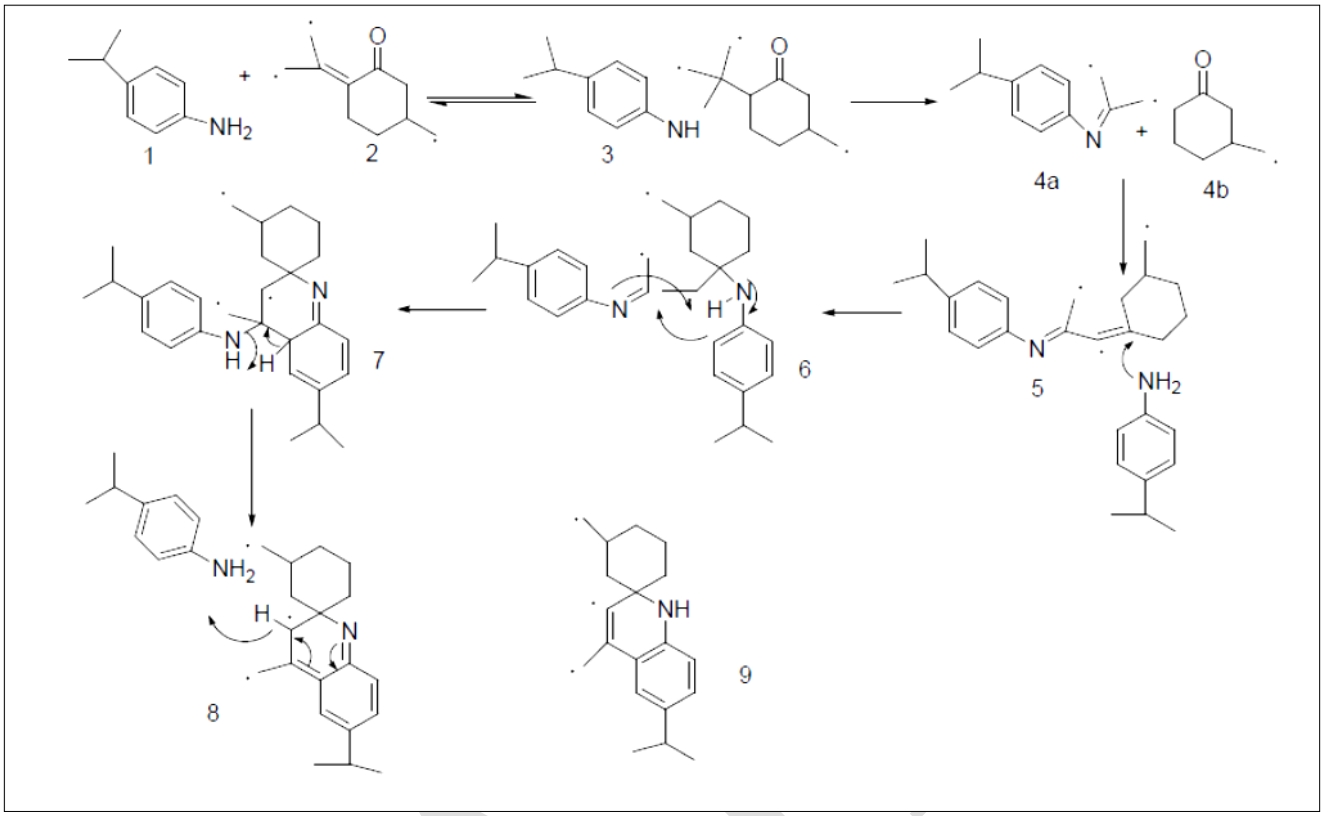
The **Doebner–Miller reaction** is the organic reaction of an aniline with α,β-unsaturated carbonyl compounds to form quinolines.



This reaction is also known as the **Skraup-Doebner-Von Miller quinoline synthesis**, and is named after the Czech chemist Zdenko Hans Skraup (1850–1910), and the Germans Oscar Döbner (Doebner) (1850–1907) and Wilhelm von Miller (1848–1899). When the α,β- unsaturated

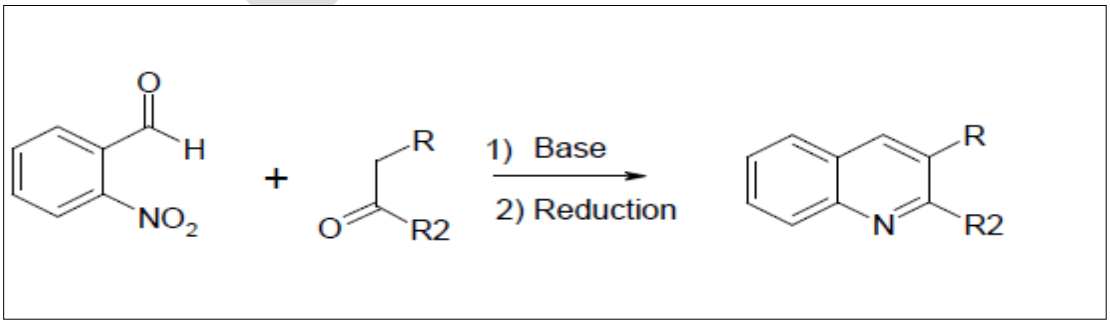
carbonyl compound is prepared in situ from two carbonyl compounds (via an Aldol condensation), the reaction is known as the **Beyer method for quinolines**. The reaction is catalyzed by Lewis acids such as tin tetrachloride and scandium(III) triflate and Brønsted acids such as *p*-toluenesulfonic acid, perchloric acid, amberlite and iodine.

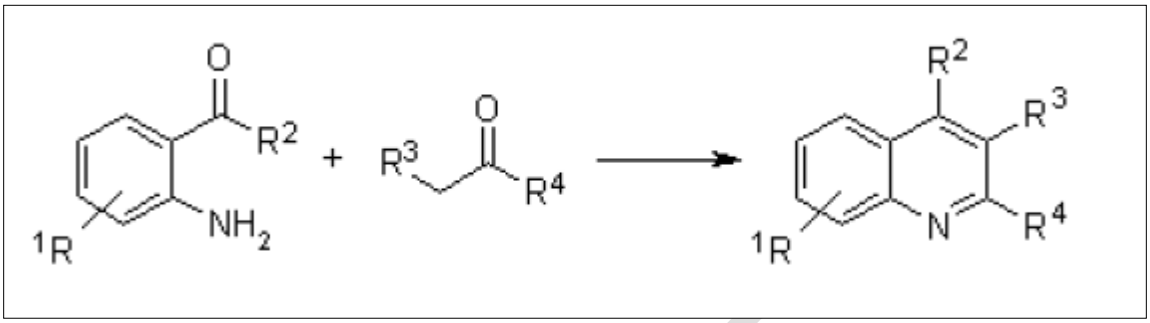
The reaction mechanism for this reaction and the related Skraup synthesis is a matter of debate. A 2006 study proposes a fragmentation-recombination mechanism based on carbon isotope scrambling experiments. In this study 4-isopropylaniline **1** is reacted with a mixture (50:50)of ordinary pulegone and the ^{13}C-enriched isomer **2** and the reaction mechanism is outlined in *scheme 2* with the labeled carbon identified with a red dot. The first step is a nucleophilic conjugate addition of the amine with the enol to the amine ketone **3** in a reversible reaction. This intermediate then fragmentates to the imine **4a** and the saturated cyclohexanone **4b** in a non-reversible reaction and both fragments recombine in a condensation reaction to the conjugated imine **5**. In the next step **5** reacts with a second aniline molecule in a nucleophilic conjugate addition to imine **6** and subsequent electrophilic addition and proton transfer to leads to **7**. elimination of one aniline molecule through **8** and rearomatization leads to final product **9**. Because α-amino protons are not available in this model compound the reaction is not taken to the fully fledged quinoline.



The fragmentation to **4a** and **4b** is key to this mechanism because it explains the isotope scrambling results. In the reaction only half the pulegone reactant (**2**) is labeled and on recombining a labeled imine fragment can react with another labeled ketone fragment or an unlabeled fragment and likewise a labeled ketone fragment can react with a labeled or unlabeled imine fragment. The resulting product distribution is confirmed by mass spectrometry of the final product

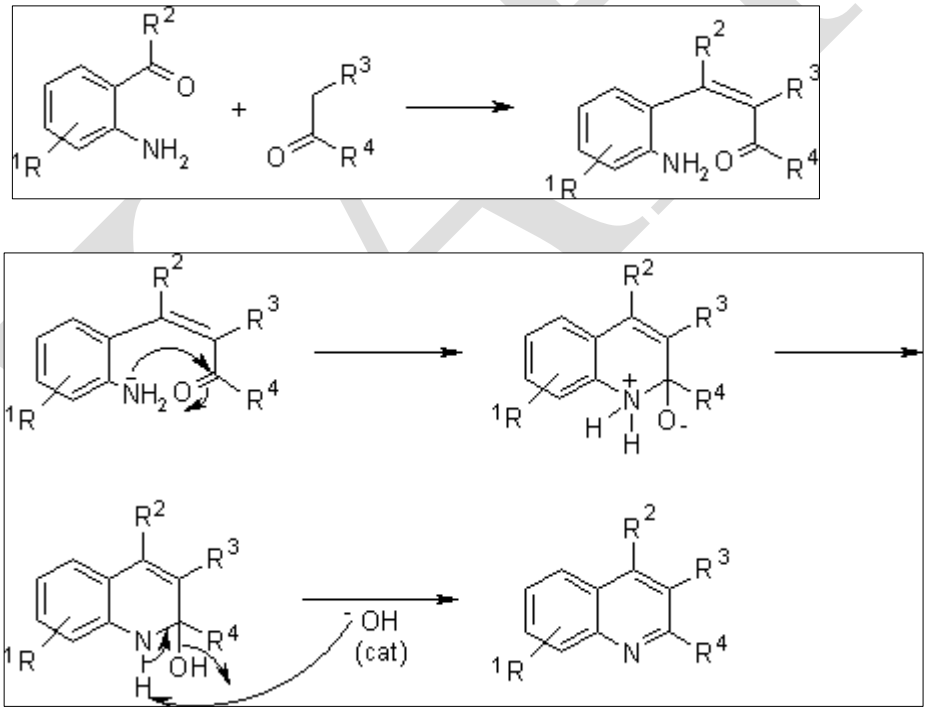
Friedlaender Synthesis



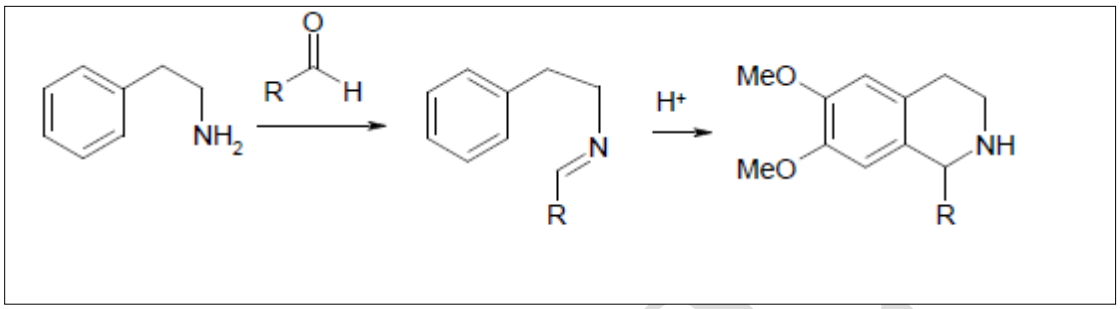


The starting materials for this quinoline synthesis are *o*-aminoaryl aldehydes or ketones and a ketone possessing an α-methylene group. After an initial amino-ketone condensation, the intermediate undergoes base- or acid-catalyzed cyclocondensation to produce a quinoline derivative.

Mechanism of the Friedlaender Synthesis

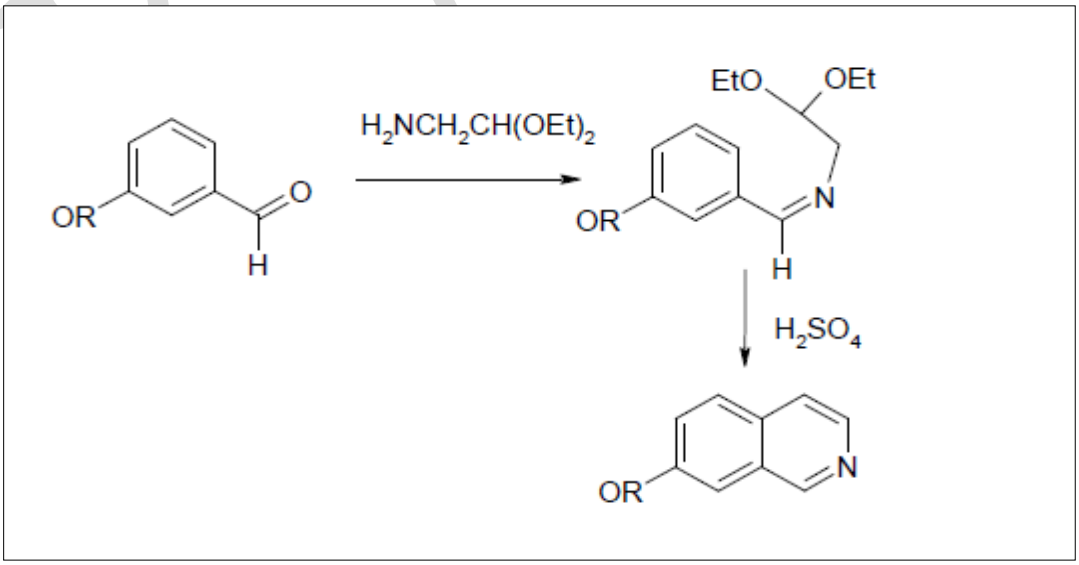


Pictet-Spengler Synthesis

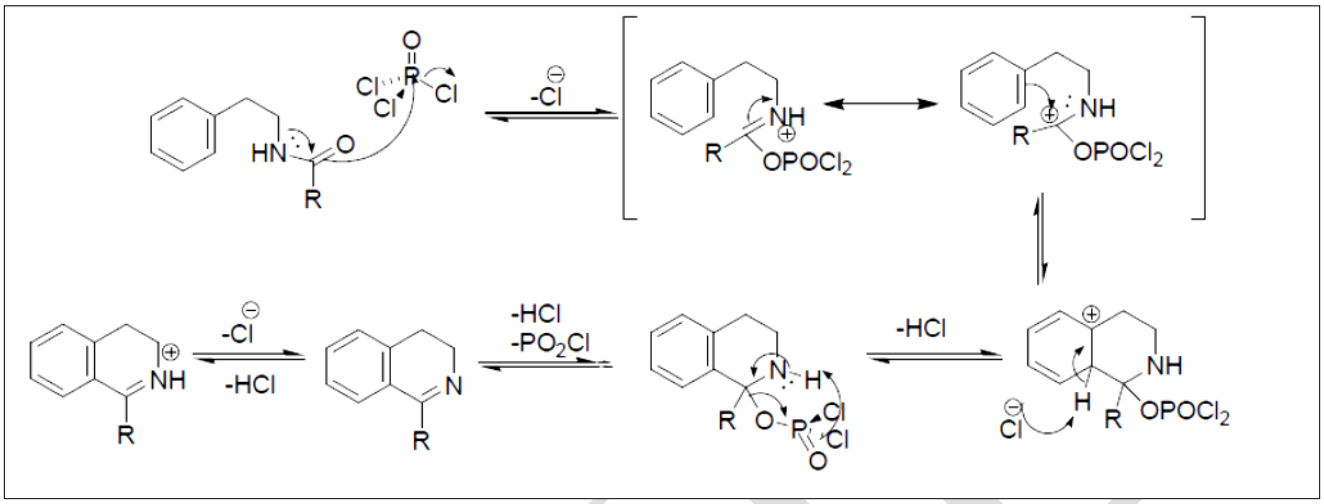


The Pictet-Spengler reaction is an organic reaction used to convert a β-arylenylamine and an aldehyde or ketone to a tetrahydroisoquinoline using an acid catalyst. The mechanism begins with protonation of the carbonyl oxygen by the acid which is subsequently attacked by the amine reagent. Proton transfer steps and the release of a water molecule results in a protonated imine intermediate, which then undergoes a 6-endo-trig cyclization reaction with loss of aromaticity of the aryl ring. A final deprotonation step restores the aromaticity and results in the tetrahydroisoquinoline product.

Pomeranz-Fritsch Synthysis



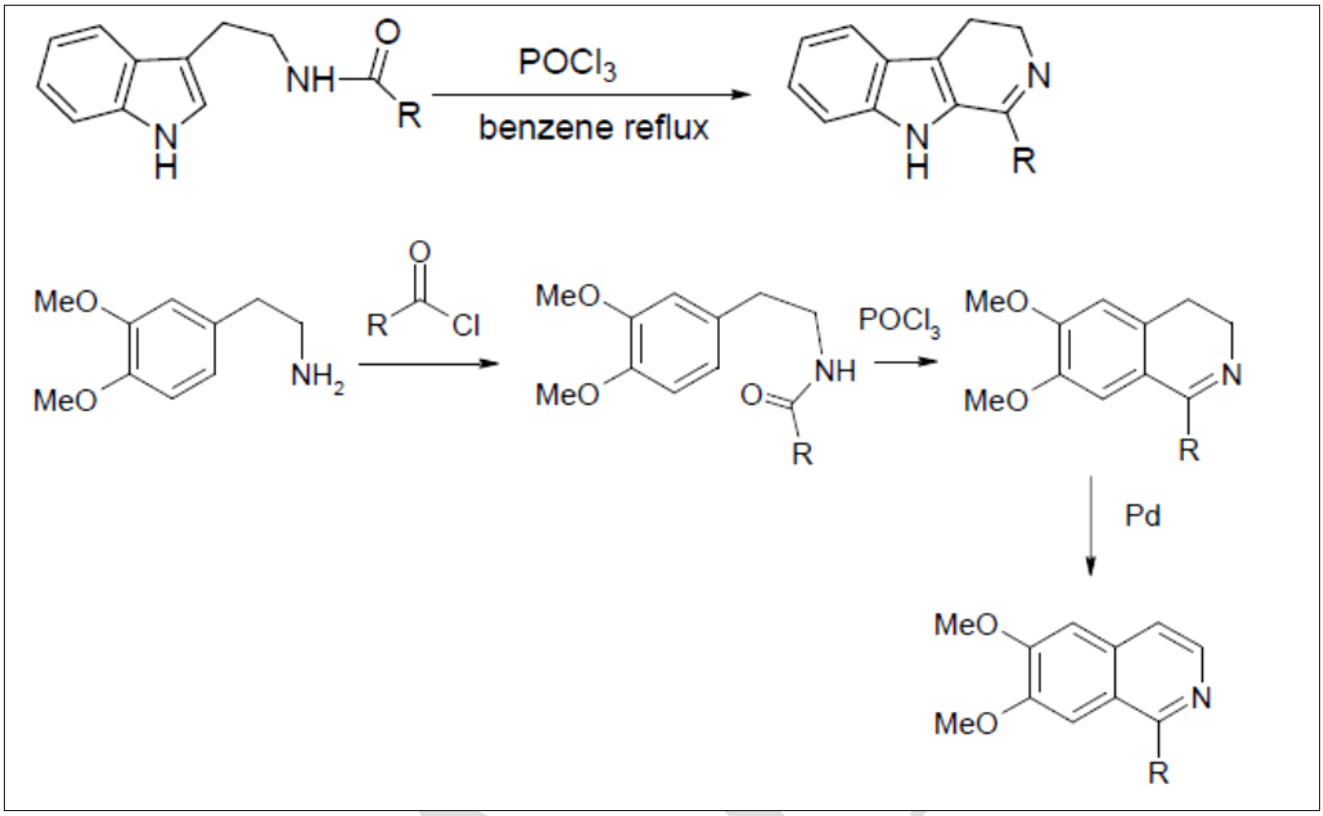
Mechanism



Isoquinoline Synthesis

Bischler-Napierlaski

The **Bischler–Napieralski reaction** is an intramolecular electrophilic aromatic substitution reaction that allows for the cyclization of β-arylethylamides or β-arylethylcarbamates. It was first discovered in 1893 by August Bischler and Bernard Napieralski, in affiliation with Basle Chemical Works and the University of Zurich. The reaction is most notably used in the synthesis of dihydroisoquinolines, which can be subsequently oxidized to isoquinolines.



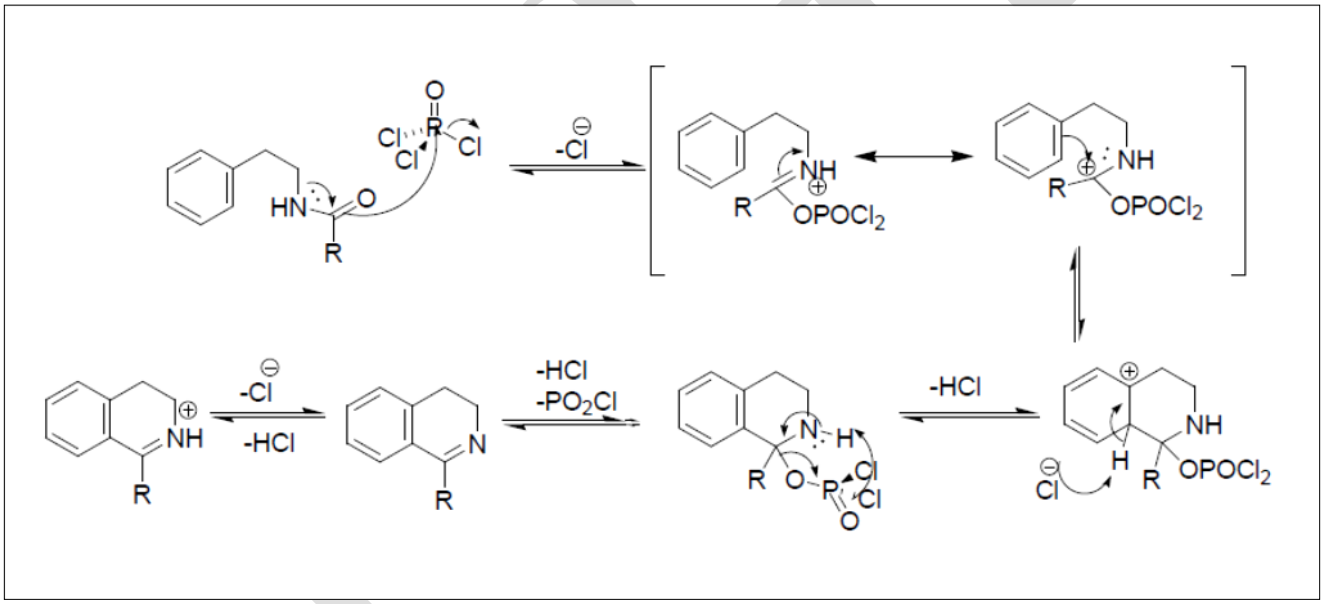
Two types of mechanisms have appeared in the literature for the Bischler–Napieralski reaction. Mechanism I involves a dichlorophosphoryl imine-ester intermediate, while Mechanism II involves a nitrilium ion intermediate (both shown in brackets). This mechanistic variance stems from the ambiguity over the timing for the elimination of the carbonyl oxygen in the starting amide. In Mechanism I, the elimination occurs with imine formation *after* cyclization; while in Mechanism II, the elimination yields the nitrilium intermediate *prior* to cyclization. Currently, it is believed that different reaction conditions affect the prevalence of one mechanism over the other (see reaction conditions).

In certain literature, Mechanism II is augmented with the formation of an imidoyl chloride intermediate produced by the substitution of chloride for the Lewis acid group just prior to the nitrilium ion. Because the dihydroisoquinoline nitrogen is basic, neutralization is necessary to obtain the deprotonated product.

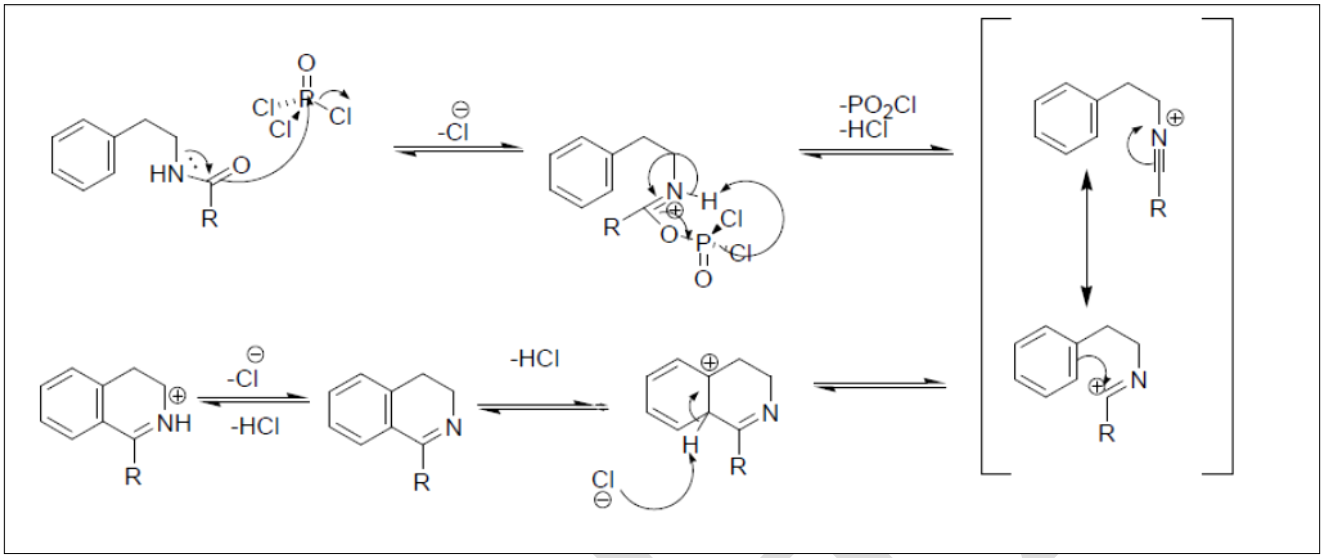
General reagents and reaction conditions

The Bischler–Napieralski reaction is carried out in refluxing acidic conditions and requires a dehydrating agent. Phosphoryl chloride ($POCl_3$) is widely used and cited for this purpose. Additionally, $SnCl_4$ and BF_3 etherate have been used with phenethylamides, while Tf_2O and polyphosphoric acid (PPA) have been used with phenethylcarbamates. For reactants lacking electron-donating groups on the benzene ring, phosphorus pentoxide (P_2O_5) in refluxing $POCl_3$ is most effective. Depending on the dehydrating reagent used, the reaction temperature varies from room temperature to 100 °C.

MECHANISM I



MECHANISM II



SUGGESTED MATERIALS:

Text books:

T1: Morrison, R. T. & Boyd, R. N.(1992). *Organic Chemistry*. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

T2: Arun Bahl(2005). Advanced organic chemistry, S.Chand & Company Pvt.Ltd. Ramnagar, New Delhi.

T3: Finar, I. L. (2002). *Organic Chemistry*. Volume 1. Dorling Kindersley (India) Pvt. Ltd., (Pearson Education).

Reference Books

R1: Finar, I. L. (2002). *Organic Chemistry*: *Stereochemistry and the Chemistry of Natural Products*. Volume 2. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

POSSIBLE QUESTIONS

PART A
(1 Mark Q.No.1 to 20)
(Online examination)

PART B

1. How indole is prepared by Lipps synthesis
2. Explain with suitable examples what are five and six membered heterocycles
3. How quinoline is prepared from Friedlander's synthesis
4. How isoquinoline is prepared from cinnamaldehyde
5. What is Pomeranz-Fritsch reaction

PART C

1. How quinoline is prepared by (i) Skraup synthesis (ii) The Dobner-Miller synthesis
2. Write note on Pictet-Spengler reaction and Pomeranz-Fritsch reaction.
3. How indole is prepared by Fischer indole synthesis. Explain the mechanism
4. How isoquinoline is prepared by BischlerNapieralski synthesis. Explain its mechanism
5. What is meant by BischlerNapieralski synthesis. Explain its mechanism
6. Discuss in detail about the Fischer indole synthesis. How heterocyclic compounds are prepared from that.
7. Explain the mechanisms of Pictet-Spengler reaction, Pomeranz-Fritsch reaction
8. How indole is prepared by (i) Madelung synthesis (ii) Bischler synthesis

17CHU303

Karpagam Academy of Higher Education

Coimbatore-21

(For the candidate admitted on 2017 onwards)

Department of Chemistry

III- semester

ORGANIC CHEMISTRY-III

UNIT IV- Objective Questions for online examination (Each carry 1 Marks)

Question	Option-A	Option-B	Option-C	Option-D	Answer
Furan undergoes cycloaddition reaction with carbenes to form	Cyclopropane derivative	Cyclobutane derivative	Diels alder adduct	tetrahydofuran	Cyclopropane derivative
Numbering of ring atoms starts at the hetero atom except	Quinoline	Isoquinoline	benzofuran	indole	isoquinoline
The alternate name of indole is	Quinoline	Isoquinoline	benzopyrrole	indole	benzopyrrole
The alternate name of benzopyrrole is	Quinoline	Isoquinoline	indole	indole	indole
In the Fischer indole synthesis the starting material is	benzaldehyde	benzophenone	Phenyl acetate	Phenyl hydrazone of acetaldehyde	Phenyl hydrazone of acetaldehyde
The catalyst used in the Fischer indole synthesis is	Zinc chloride	Vanadium pentoxide	Chromium oxide	Sulphuric acid	Zinc chloride
In the Fischer indole synthesis the starting material to prepare 2-methyl indole is	benzaldehyde	benzophenone	Phenyl acetate	Phenyl hydrazone of acetone	Phenyl hydrazone of acetone
Heating phenyl hydrazone of acetaldehyde with zinc chloride gives	Quinoline	Isoquinoline	indole	indole	indole
Heating phenyl hydrazone of acetone with zinc chloride gives	Quinoline	Isoquinoline	2-methyl indole	indole	2-methylindole
To prepare indole, phenyl hydrazone of acetone has to be heated with	Zinc chloride	Vanadium pentoxide	Chromium oxide	Sulphuric acid	Zinc chloride

Preparation of indole from Heating phenyl hydrazone of acetaldehyde with zinc chloride is called	Fischer indole synthesis	Madelung synthesis	Lipps synthesis	Wolf kishner reduction	Fischer indole synthesis
To prepare indole, zinc chloride has to be heated with	benzaldehyde	benzophenone	Phenyl acetate	Phenyl hydrazone of acetone	Phenyl hydrazone of acetone
In Lipps synthesis of indole the starting material is	o-amino chlorostyrene	o-hydroxy chlorostyrene	o-nitro chlorostyrene	o-chloro chlorostyrene	o-amino chlorostyrene
In Lipps synthesis of indole the catalyst used is	Sodium ethoxide	Zinc chloride	sodamide	Tin and HCl	Sodium ethoxide
Preperation of indole from o-amino chlorostyrene and Sodium ethoxide is called	Fischer indole synthesis	Madelung synthesis	Lipps synthesis	Wolf kishner reduction	Lipps synthesis
In Lipps synthesis of indole o-amino chlorostyrene is heated with	Sodium ethoxide	Zinc chloride	sodamide	Tin and HCl	Sodium ethoxide
In Lipps synthesis of indole sodium ethoxide is heated with	o-amino chlorostyrene	o-hydroxy chlorostyrene	o-nitro chlorostyrene	o-chloro chlorostyrene	o-amino chlorostyrene
In Lipps synthesis indole is from from o-amino chlorostyrene and	Sodium ethoxide	Zinc chloride	sodamide	Tin and HCl	Sodium ethoxide
In Lipps synthesis indole is from from sodium ethoxide and	o-amino chlorostyrene	o-hydroxy chlorostyrene	o-nitro chlorostyrene	o-chloro chlorostyrene	o-amino chlorostyrene
The method used to prepare 2-alkyl indole by the cyclodehydration of 0-acyl amidotoluene is	Fischer indole synthesis	Madelung synthesis	Lipps synthesis	Wolf kishner reduction	Madelung synthesis
To prepare 2-alkyl indole by the cyclodehydration of 0-acyl amidotoluene is carried out with	Sodium ethoxide	Zinc chloride	sodamide	Tin and HCl	sodamide
To prepare 2-alkyl indole by the cyclodehydration of 0-acyl amidotoluene is carried out with	Sodium ethoxide	Zinc chloride	Potassium tertiary butoxide	Tin and HCl	Potassium tertiary butoxide
The reaction involved in the conversion of 0-acyl amidotoluene into indole is	cyclodehydration	dehydration	hydrolysis	condensation	cyclodehydration

cyclodehydration of 0-acyl amidotoluene with sodamide gives	Quinoline	Isoquinoline	pyrans	indole	indole
cyclodehydration of 0-acyl amidotoluene with Potassium tertiary butoxide gives	Quinoline	Isoquinoline	pyrans	indole	indole
Reaction of o-amino benzaldehyde with acetaldehyde in NaOH is	Fischer indole synthesis	Madelung synthesis	Lipps synthesis	Friedlander's synthesis	Friedlander's synthesis
In the synthesis of quinoline o-amino benzaldehyde reacs with	Acetaldehyde	o-amino chlorostyrene	o-hydroxy chlorostyrene	o-nitro chlorostyrene	Acetaldehyde
In the synthesis of quinoline acealdehyde reacs with	o-amino benzaldehyde	o-amino chlorostyrene	o-hydroxy chlorostyrene	o-nitro chlorostyrene	o-amino benzaldehyde
o-amino benzaldehyde reacts with acetaldehyde in presence of ---------- to give quinoline	Sodium ethoxide	Zinc chloride	Potassium tertiary butoxide	Sodium hydroxide	Sodium hydroxide
Friedlander synthesis is used to synthesis	Quinoline	Isoquinoline	indole	pyrans	Quinoline
Madelung synthesis is used to prepare	Quinoline	Isoquinoline	indole	pyrans	indole
Fischer,s synthesis is used to prepare	Quinoline	Isoquinoline	indole	pyrans	indole
Lipps synthesis is concerned with	Quinoline	Isoquinoline	indole	pyrans	indole
In Friedlander synthesis the chief material used to synthesis quinoline is	o-amino benzaldehyde	o-amino chlorostyrene	Phenyl hydrazone	o-acylamidotoluene	o-amino benzaldehyde
In Madelung synthesis the chief raw material is	o-amino benzaldehyde	o-amino chlorostyrene	Phenyl hydrazone	o-acylamidotoluene	o-acylamidotoluene
In Fischer,s synthesis the chief raw material is	o-amino benzaldehyde	o-amino chlorostyrene	Phenyl hydrazone	o-acylamidotoluene	Phenyl hydrazone
In Lipps synthesis the chief raw material is	o-amino benzaldehyde	o-amino chlorostyrene	Phenyl hydrazone	o-acylamidotoluene	o-amino chlorostyrene
In Skraup synthesis nitrobenzene is used as a	Oxidising agent	Condensing agent	Dehydrating agent	Drying agent	Oxidising agent

Aniline and glycerol reacts in presence of sulphuric acid and nitrobenzene to give	Quinoline	Isoquinoline	indole	pyrans	quinoline
The process where Aniline and glycerol reacts in presence of sulphuric acid and nitrobenzene to give quinoline is	Fischer indole synthesis	Madelung synthesis	Skraup synthesis	Friedlander's synthesis	Skraup synthesis
The catalyst used to prepare quinoline in Skraup synthesis is	Sodium ethoxide	Zinc chloride	Potassium tertiary butoxide	Sulphuric acid	Sulphuric acid
For the synthesis of quinoline, in presence of sulphuric acid and nitrobenzene glycerol reacts with	o-amino chlorostyrene	Phenyl hydrazone	o-acylamidotoluene	aniline	aniline
For the synthesis of quinoline, in presence of sulphuric acid and nitrobenzene aniline reacts with	o-amino chlorostyrene	Phenyl hydrazone	o-acylamidotoluene	glycerol	glycerol
α, β-unsaturated carbonyl compounds are prepared from	aldehydes	nitrocompounds	alcohols	phenols	aldehydes
Modified form of Skraup synthesis is called	Fischer indole synthesis	Madelung synthesis	Dobner-Miller synthesis	Friedlander's synthesis	Dobner Miller synthesis
The reaction to prepare α, β-unsaturated carbonyl compounds from aldehydes is	Aldol condensation	Knorr synthesis	Claisen condensation	Reimer-Tieman	Aldol condensation
Dobner-Miller synthesis is the modified form of	Fischer indole synthesis	Madelung synthesis	Skraup synthesis	Friedlander's synthesis	Skraup synthesis
In Dobner- Miller synthesis aniline reacts with	o-amino chlorostyrene	Phenyl hydrazone	o-acylamidotoluene	α, β-unsaturated carbonyl compounds	α, β-unsaturated carbonyl compounds
In Dobner- Miller synthesis α, β-unsaturated carbonyl compounds reacts with	o-amino chlorostyrene	Phenyl hydrazone	o-acylamidotoluene	aniline	aniline
Isoquinoline can be prepared from	Bischler Napieralski synthesis	Fischer indole synthesis	Madelung synthesis	Skraup synthesis	Bischler Napieralski synthesis

Isoquinoline can be prepared from	Pomeranz Fritsch synthesis	Fischer indole synthesis	Madelung synthesis	Skraup synthesis	Pomeranz Fritsch synthesis
Isoquinoline can be prepared from	Pictet-Spengaler synthesis	Fischer indole synthesis	Madelung synthesis	Skraup synthesis	Pictet-Spengaler synthesis
The starting material in Pictet-Spengaler synthesis is	Phenyl ethyl amine	aminoacetal	Aryl ethylamine and an aldehyde	aniline	Aryl ethylamine and an aldehyde
The starting material in Pomeranz Fritsch synthesis is	Phenyl ethyl amine	aminoacetal	Aryl ethylamine and an aldehyde	aniline	Aryl ethylamine and an aldehyde
The starting material in Bischler Napieralski synthesis is	Phenyl ethyl amine	aminoacetal	Aryl ethylamine and an aldehyde	aniline	Phenyl ethyl amine
Bischler Napieralski synthesis is	Phenylethylamine reacts with formyl chloride, followed by reaction with P_2O_5 and Se	Benzaldehyde reacts with aminoacetal followed by reaction with sulphuric acid	Reaction of phenyl ethylamine with acetaldehyde followed with reduction	Cinnamaldehyde reacts with hydroxylamine	Phenylethylamine reacts with formyl chloride, followed by reaction with P_2O_5 and Se
Pomeranz Fritsch synthesis is	Phenylethylamine reacts with formyl chloride, followed by reaction with P_2O_5 and Se	Benzaldehyde reacts with aminoacetal followed by reaction with sulphuric acid	Reaction of phenyl ethylamine with acetaldehyde followed with reduction	Cinnamaldehyde reacts with hydroxylamine	Reaction of phenyl ethylamine with acetaldehyde followed with reduction

Pomeranz Fritsch synthesis involves	Phenylethylamine reacts with formyl chloride, followed by reaction with P_2O_5 and Se	Benzaldehyde reacts with aminoacetal followed by reaction with sulphuric acid	Reaction of phenyl ethylamine with acetaldehyde followed with reduction	Cinnamaldehyde reacts with hydroxylamine	Benzaldehyde reacts with aminoacetal followed by reaction with sulphuric acid
Phenylethylamine reacts with formyl chloride, followed by reaction with P_2O_5 and Se to give	Quinoline	Isoquinoline	indole	pyrans	isoquinoline
Benzaldehyde reacts with aminoacetal followed by reaction with sulphuric acid to give	Quinoline	Isoquinoline	indole	pyrans	isoquinoline

UNIT V
SYLLABUS

Alkaloids
Natural occurrence, General structural features, Isolation and their physiological action, Hoffmann's exhaustive methylation, Emde's modification; Structure elucidation and synthesis of Nicotine. Medicinal importance of Nicotine, Hygrine, Quinine, Morphine, Cocaine, and Reserpine.

Terpenes
Occurrence, classification, isoprene rule; Elucidation of stucture and synthesis of Citral.

ALKALOIDS
Introduction

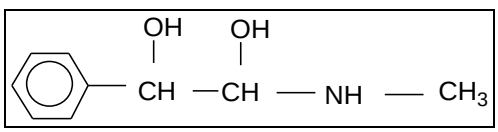
- The term alkaloid meaning, 'alkali-like' has been used to designate.
- The compounds of plant origin having one or more basic nitrogen atoms in heterocyclic ring systems, which induce pronounced physiological activity in aeimals and man
- The above definition of the alkaloids is by no means perfect and does not cover all compounds classed as alkaloids

1) piperine , the alkaloid of pepper, is not basic and has practically no physiological activity.

2) purines such as caffeine (in coffee and tea) and 1herobromine (in cocoa bean), which stimulate the nervous system, and are heterocycles containing nitrogens ,conform to the definition of alkaloids but are frequently not included in this class

3) Opium (containing the alkaloid morphine) and hashish or bhang, are both habit forming drugs ,yet the active principle of the latter does latter does not contain nitrogen .

4) Ephedrine is a straight-chain alkaloid that is produced by animal glands , and has marked physiological activity



In fast, no precise definition of the term "alkaloid" is possible but in general it designates compounds having the following common features

a) they are found in plants ,although a few are of animal origin

b) they are basic in character and show marked physiological activity

c) they have heterocyclic rings containing nitrogen as a part of their structures

Occurrence And Isolation

- Alkaloids occur chiefly in plants of the dicotyledons families and are localised in seeds, leaves , bark, or root of the plant .Each site may contain several closely related alkaloids
- They occur largely as sets of common plants acids such as acetic acid ,oxalic acid ,lactic acid, malic acid, tartaric acid ,citric acid or of certain special organic acid
- For extraction of alkaloid ,the plant material is macerated
- If the material is rich in fat (seeds) it is first extracted with ligroin or petroleum ether for their removal
- The plant residue is then extracted with methanol and the cellulosic material separated by filtration
- The filtrate is evaporated to give the crude plant extract
- This is then dissolved in dilute acid and extracted with ether
- The acid solution of alkaloid salts is then basified and extracted with ether
- Evaporation of ether solution gives a solid mixture of crude alkaloids, it is then subjected to fractional crystallization for separation into individual pure alkaloids
- In modern practice the isolation is effected by column chromatography, gas chromatography and by counter current distribution →
- The general scheme for the extraction of alkaloids

Macerated plant

↓

Step 1

1, extract with ligroin

2, filter

Filtrate $\underline{\quad rate .> \quad}$ FATS

↓

PLANT RESIDUE

↓

STEP 2

1. extract with CH_3OH
2. filter out cellulosic material
3. evaporate filtrate

crude plant extract

↓

step 3

1. Dissolved in dil. inorganic acid
2. Extract with ether

↓

Ether solution evaporate> non basic material

acid solution of alkaloid salts

↓

step 4

1. NAOH solution
2. Extract with either

↓ → aqueous residue

Ether solution

↓

Step 5

1. Evaporate

Alkaloids

Procedure for the isolation alkaloids from plants

General Properties

1) Alkaloids are usually colourless , crystalline ,non-volatile solids ,while a few of them (coniine nicotine) are liquids
2) Expect the liquid alkaloids which are soluble in water but dissolve readily in ethanol ,ether, chloroform, and benzene.
3) They are basic with bitter taste, and dissolve in mineral acids to form salts

4) They are optically active , the majority being leavo-rotatory

5) Physiological activity

*most of them possess marked physiological activity when orally administered
*coniine is a violet poison
*quinine is an antimalarial
*cocaine acts as local anaesthetic
*morphine relieves pain
*atrophine dilates pupil of the eye

6) **Basic character**

- The molecule of alkaloid contains one or more basic nitrogen
- Most alkaloids are tertiary monoacid, while a few are secondary bases
- These they form well defined crystalline salts with mineral acids, the hydrochloride and nitrate being generally readily soluble in water

Alkaloidal reagent

The solutions of alkaloids in dilute mineral acids when treated with certain reagents form insoluble precipitates, after having characteristics colour and melting points such reagents as are frequently spoken of as alkaloidal reagents

The common ones are;-

Chloroplatinic acid H_2PtCl_6, phoshphomolybdic acid, phosphotungstic acid, picric acid tannic acid, etc

Classification of Alkaloids

- They are classified according to the heterocyclic ring system

They are

1) Pyrrolidine
2) Piperidine alkaloids
3) Pyridine-pyrrolidine alkaloids
4) Piperidine piperidine alkaloids
5) Quinoline alkaloids
6) Isoquinoline alkaloids
7) Iodole alkaloids

By the advent of the latest separation techniques and the copious volume of informations accumulated through the intensive and extensive research carried out with regard to the

conventional processes essentially associated with the separation as well as isolation of the hundreds of **alkaloids** from the natural plant sources, the following *five* steps are most important and vital, namely:

(*i*) Sample preparation
(*ii*) Liberation of free alkaloidal base
(*iii*) Extraction of alkaloidal base with organic solvent
(*iv*) Purification of crude alkaloidal extract
(*v*) Fractionation of crude alkaloids

All these *five* steps shall be discussed individually as under:

Sample Preparation

The first and foremost step is the sample preparation. The plant material is reduced to a moderately coarse powder by appropriate means using grinders and sieves, to facilitate maximum effective contact of the solvent with the ruptured alkaloid bearing tissues and cells. In the case of plant substances that are rich in oils and fats, such as: seeds, kernels, these non-alkaloidal chemical components need to be eliminated completely by extraction with a suitable non-polarsolvent like nhexane, light petroleum ether, in a soxhlet apparatus, which would not extract the alkaloids in question.

However, it is always advisable to shake the light-petroleum ether or n-hexane fraction with a dilute mineral acid and subsequently test the acidic solution for the presence of alkaloids.

Liberation of Free Alkaloidal Base

It has been observed that the **alkaloids** invariably occur in the plant sources as the salt of acids, such as: oxalates, tannates etc. Therefore, when the plant substance is exposed to an alkaline medium, the alkaloidal salts are readily converted to the corresponding alkaloid bases.

Choice of Alkali Indeed, the choice of a suitable *mineral base* (alkali) for the ease of liberation of the alkaloid from the salts is not only very vital but also equally significant and largely depend on the following factors, namely:

(*a*) **Natural state of the alkaloids:** It has been observed that the salt of a *strongly basic alkaloid* with a mineral acid usually tends to undergo cleavage under the influences of a stronger base. Likewise, the corresponding salt of a *weakly basic alkaloid* and a relatively weak organic acid shall require a rather weaker base for its cleavage.

(*b*) **Chemical characteristics of the alkaloidal base:** The usage of strong alkali *e.g.*, NaOH or KOH should be avoided as far as possible by virtue of the fact that certain alkaloids undergo hydrolysis on prolonged contact with a strong base.

Example

(*i*) **Hydrolysis of ester-alkaloids,** *e.g.*, **cocaine, hyoscyamine;**

(*ii*) **Phenolic alkaloids** *e.g.*, **cephaeline, morphine.** These **alkaloids** normally get solubilized while in contact with a strong alkali and, therefore milder alkaline reagents *e.g.*, dilute ammonia solution are necessary for their liberation.

(a) **Presence of fatty substances:** The usage of strong alkali is strictly prohibited in the case of fat containing plant materials because of the formation of saponified products causing troublesome emulsions. In such cases, it is always preferred to defat the plant substance before proceeding for the liberation of free alkaloids.

Ammonium Hydroxide Solution Dilute aqueous ammonium hydroxide solution is one of the choicest alkali most frequently used for the liberation of alkaloids from the plant sources. It enjoys a two-fold advantage. First, being its adequate alkalinity to liberate most of the common alkaloids, and second by, its volatile nature so that it may be removed by evaporation of the solvent. As it has a tendency to be extracted by solvent ether from the aqueous solution, therefore, it is almost necessary to get rid of it by evaporation and subsequent washing repeatedly. In normal practice, usually even the last traces of ammonia are removed when the combined ethereal extract is reduced to half of its original volume under vacuum.

NaOH or KOH Solution The alkaloids that occur naturally as their tannate salts specially require either NaOH or KOH solution for their subsequent liberation. In certain typical instance even the use of KOH or NaOH fails to cleave the tannate salts because of their intimately strong bondage with the alkaloid and extremely insoluble nature.

Example

(*i*) **Cinchona Bark:** It has got to be treated first by heating with dilute HCl so as to decompose the salts and liberate the alkaloids in the form of water soluble hydrochlorides, and

(*ii*) **Pomegranate Bark:** It does not have the tannin so tenaciously bound to the alkaloids as in the case of cinchona bark. Hence, NaOH solution is strong enough to cause on effective split of the alkaloidal salts. It also acts to control the solubility of the water-soluble pomegranate alkaloids by preventing their dissociation.

Extraction of Alkaloidal Base

The extraction of alkaloidal base may be accomplished by *three* different types of solvents that are discussed below, namely:

[A] Extraction with Water-Miscible Solvents A plethora of **alkaloids** and their respective salts are soluble in alcohols, such as: methanol, ethanol, isopropanol; therefore, these very solvents may also be employed for the extraction of the plant substances. The usual pretreatment of the crude drug with alkali may be avoided completely, because alcohol appears to affect dissolution of not only the *alkaloidal salts* but also the *free bases* found in the plant substances. It is, however, believed that alcohol predominantly exerts a *hydrolyzing effect* upon the alkaloidal tannates and other salts. In actual practice, neither pretreatment of the crude drug with an alkali nor acidification of the alcohol with a small amount of a mineral acid or an organic acid is required.

Note

1. The penetration and hence the subsequent extraction of the crude drug is almost complete with the help of four successive extractions with an alcohol. Further, the loss of solvent is comparatively less than the chlorinated solvents e.g., chloroform.

2. The extraction of total alkaloids with alcohol is highly recommended because of its maximum efficiency and economical viability.

[B] Extraction with Water-Immiscible Solvents In reality, the most widely used water-immiscible solvents for the extraction of alkaloids are: chloroform, diethyl ether (solvent ether) and isopropyl ether. However, a few other specific organic solvents, namely: ethylene chloride, carbon tetrachloride and **benzene*** may be employed with an evident advantage for certain specific alkaloids. Interestingly, *chloroform* is regarded as the choicest water-immiscible solvent for a broad-spectrum of alkaloids present in the plant kingdom and extracts them with varying degrees of ease.

Note: Chloroform is not suitable for the extraction of quaternary alkaloids e.g., tubocurarine.

[C] Extraction with Water The crude drug is subjected to extraction with water previously acidified with dilute solution of HCl, H_2SO_4 or CH_3COOH, which is subsequently rendered alkaline, preferably with dilute NH_4OH solution and finally extracted with a water-immiscible solvent as stated in [B] above.

Undoubtedly, water being an excellent and absolutely inexpensive polar solvent for the extraction of alkaloids, but if offers an enormous volume of disadvantages because it carries along with it a large number of other plant components, for instance: sugar, pigments (*e.g.*, **chlorophylls**), starches, tannins, proteins etc., which ultimately puts across a collosal waste of time, energy and chemicals. Hence, its usage has been resulting to a bear minimum level.

In general, the alkaloids may be extracted by any of the following *three* well-defined and widely accepted processes, namely:

(*a*) Soxhlet Extraction Process

(*b*) Stas-Otto Process, and

(*c*) Kippenberger's Process.

All these three processes shall now be discussed briefly in the sections that follows:

(a) **Soxhlet Extraction Process:** The soxhlet assembly is a continuous extractor which is generally suitable for the extraction of alkaloids from powdered plant materials with the help of organic solvents. In this instance, the powdered drug is usually moistened with dilute ammonia

solution and then packed loosely in the thimble of the Soxhlet apparatus; and the organic solvent affords a deep penetration of the moist drug thereby allowing the greatest possible extraction of the alkaloids from the exposed surfaces of the cells and tissues of the crude drug. Once, the extraction is ascertained to have completed, the solvent is filtered and evaporated in a **Rotary Thin-Film Evaporator** and the residue is treated further for the isolation of individual alkaloids.

(b) **Stas-Otto Process:** The **Stas-Otto process** essentially consists of treating the powdered and sieved drug substance with 90–95% (v/v) ethanol, previously acidified with tartaric acid. The proportion of crude drug to solvent should be maintained as 1 Kg to 1 L. The alcohol is distilled off under vacuum and the resulting aqueous residue is treated with petroleum-ether (60-80°C) to remove the fatty components completely. If any alkaloid is removed by the petroleum ether, it must be recovered by treating it with dilute mineral acid. Thus, the resulting aqueous extract is mixed with the main bulk of aqueous extract. The combined aqueous extract is filtered and evaporated to dryness preferably in a **Rotary *Thin*-Film Evaporator** under vacuum. The residue is extracted with absolute ethanol thereby dissolving the total alkaloids.

(c) **Kippenberger's Process:** In Kippenberger's process the powdered and sieved plant substance is first and foremost digested with solution of tannin (100 g) in glycerol (500 g) at a constant temperature of 40°C for a duration of 48 hours. The resulting mixture is further heated to 50°C so as to help in the complete coagnlation of proteinous substances, cooled to ambient temperature and finally filtered. The resulting filtrate is thoroughly shaken with petroleum ether to get rid of faulty materials (oils, fats and waxes), and the last traces of petroleum ether is removed from the extract by heating either on a water-bath (electric) or exposure to Infra-Red Lamp. The fat-free crude plant extract is subsequently acidified and shaken with chloroform, successively to remove the bulk of the alkaloids, namely, atropine, codeine, colchicine, narcotine, nicotine, papaverine, spartenine and thebaine.

The resulting residual extract may still contain narceine, curarine and morphine. However, narceine and morphine may be isolated by passing freshly generated CO2 directly into extract so as to convert the alkali hydroxide into their corresponding carbonate, which is then ultimately subjected to solvent extraction using a mixture of alcohol and chloroform. Finally, the third alkaloid, curarine, may be extracted by agitation with a mixture of equal volumes of ether and chloroform.

However, a combination of **Kippenberger's process** and **Stas-Otto process** by its application to the final alcoholic extract obtained by the latter process is found to give better separation of alkaloids.

Purification of Alkaloidal Extract

The main bulk of the **crude alkaloidal extract** is invariably subjected to further purification by means of either anyone or combination of the following methods:

(*a*) Extraction with Acid Solution The extraction of the **alkaloid** from the bulk of the crude alkaloid solution in immiscible organic solvent is invariably carried out by shaking with an acid solution. In usual practice, the use of HCl is restricted when chloroform remains as the solvent because of the fact that quite a few alkaloidal hydrochlorides are distinctly soluble in the latter. However, dilute H_2SO_4 is always preferred over HCl for general use in the extraction of alkaloids. Subsequently, the acid solution is rendered alkaline with dilute NH4OH solution to liberate the alkaloids which is then extracted with an organic solvent. The solvent is removed under reduced pressure and the traces of moisture is removed with anhydrous sodium sulphate.

Note: The following two precautions may be observed, namely

(*i*) To avoid the formation of stubborn and troublesome emulsions a solution of gumtragacanth is often added to the aqueous-phase. In case, it still persists the two phases may be got separated by centrifugation, and

(*ii*) To discard the presence of foreign interfering extractive components present in plant substances, such as: pigments, resins, waxes, oils and fats, the use of a 2.5-5% (w/v) solution of lead acetate is made to the alkaloidal extract which precipitates them effectively. The excess of lead present in the filtrate is removed by either passing H_2S gas through the Kipp's Apparatus or by adding sodium phosphate.

(b) **Precipitation of Alkaloid with Precipitating Reagent** The usual precipitation of the **alkaloid** as a complex compound is accomplished by the addition of a suitable precipitating reagent. The resulting alkaloidal complex is further purified by filtration, recrystallization and ultimately decomposed to obtain the desired free alkaloid(s).

Example

(*i*) **Tannic-acid Complex:** It is normally decomposed by treatment with freshly prepared $Pb(OH)_2$ or $Pb(CO_3)_2$.

(*ii*) **Precipitates obtained with $HgCl_2$, $AuCl_3$, $PtCl_4$, Mayer's Reagent:** These precipitates are decomposed by passing a stream of H_2S gas through its suspension.

(*iii*) **Precipitates with Double Salts:** The double salt obtained with Dragendorff's Regent is quickly boiled with 5% (w/v) $BaCO_3$ solution.

(*iv*) **Precipitates with Nitrogenous Acids:** The precipitates obtained with nitrogenous acids like picric acid and picrolonic acid are normally decomposed by treatment with either NH_4OH or NaOH.

(*v*) **Reineckate Complex:** The complex obtained from alkaloid with *Reinecke Salt*, NH_4 [$Cr(NH3)_2(SCN)_4$], is normally decomposed by treating its solution in a mixture of acetone and water (1:1) with a silver sulphate solution. It is pertinent to mention here that the **free liberated alkaloid** from the complexes stated above, (*i*) through (*v*), may be further extracted for its final recovery with an appropriate organic solvent, such as: chloroform.

(*c*) The purification of **alkaloids** may also be accomplished by the formation of its crystallised alkaloidal salt by the addition of an appropriate mineral or organic acid, such as: hydrochloric, hydrobromic, perchloric, sulphuric, oxalic and tartaric acids.

(*d*) Various known **separation techniques,** namely: **partition, ion-exchange** and **column chromatography** are invariably used for the purification of a host of alkaloids.

Besides, various physical parameters like: specific rotation, melting point, solubility are frequently used as a definite criteria of ascertaining the purity of alkaloids.

Fractionation of Crude Alkaloids

It has been observed largely that most of the alkaloid-bearing plant materials usually contain a mixture of closely-related alkaloids. Therefore, it has become almost necessary to carry out an effective fractionation of crude alkaloids from the extract or solution of total crude alkaloids.

However, the traditional and orthodox methods of separation are not only difficult but also tedious and cumbersome. The commonly employed techniques of separation that were found to the reliable and dependable may be short-listed as follows:

(*i*) Fractional crystallization,

(*ii*) Fractional distillation, and

(*iii*) Derivatization with low solubility products.

The latest methods employed for the separation of **alkaloids** are the preparative **high performance liquid chromatography (HPLC), high performance thin-layer chromatography (HPTLC),** chromatotron, counter-current distribution and other chromatographic techniques including columnchromatography, ion-exchange chromatography.

Following are some of the typical situations whereby the mixture of **alkaloids** may be separated effectively, such as:

(*a*) A larger section of the **alkaloids** are easily soluble in chloroform and relatively less soluble in other organic solvents. In general, the order of solubility is as stated below chloroform > acetone > ethanol > methanol > ethyl acetate > ether > n-hexane. Keeping in view the above solubility profile of alkaloids in organic solvents, if one of the alkaloids is much less soluble in ethanol than chloroform, the fractional crystallization of this alkaloid is possible. In this particular instance the chloroform-fraction is concentrated to an appropriate level, and hot ethanol added in small proportions at intervals. Thus, upon cooling the alkaloid, which is less soluble in ethanol, separates out conveniently.

(*b*) In case, the fractional crystallization of the mixture of closely related alkaloids become tedious and ineffective, one may try to form their respective salts,** and then carry out the separation indicated above.

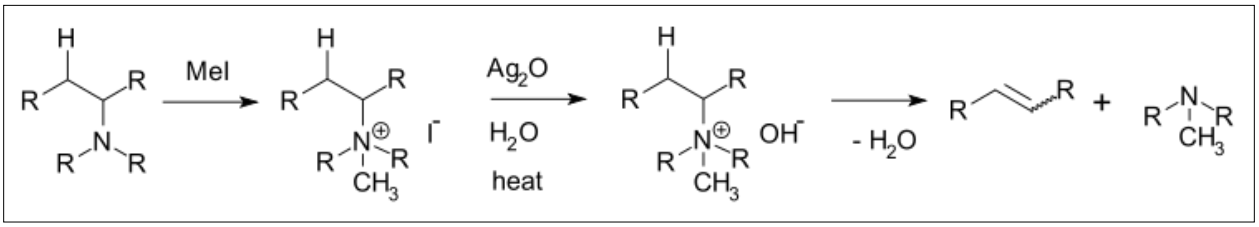
(*c*) The various acids, namely: HCl, HBr, HI, $HClO_4$, HNO_3, $C_2H_2O_4$, and $C_6H_3N_3O_7$, may either be employed in aqueous or methanolic solution. Thus, from the resulting methanolic solution, the salts of the respective alkaloids may be precipitated by the addition of ether. The precipitated crude alkaloidal salts may be further recrystallized from hot acetone containing a small proportion of methanol.

(*d*) In certain other specific instances, the salts of the respective oxalates, picrates and perchlorates may be precipitated from their solutions in acetone, by the addition of ethyl acetate.

Hofmann's Exhaustive Methylation Method:

The principle of this method is that compounds, which contain the structural unit =CH=C–N+R_3OH , eliminate a trialkylamine on pyrolysis at 200 °C or above to yield an olefin.

Hofmann elimination, also known as exhaustive methylation, is a process where a quaternary amine is reacted to create a Tertiary amine and an alkene by treatment with excess methyl iodide followed by treatment with silver oxide, water, and heat.

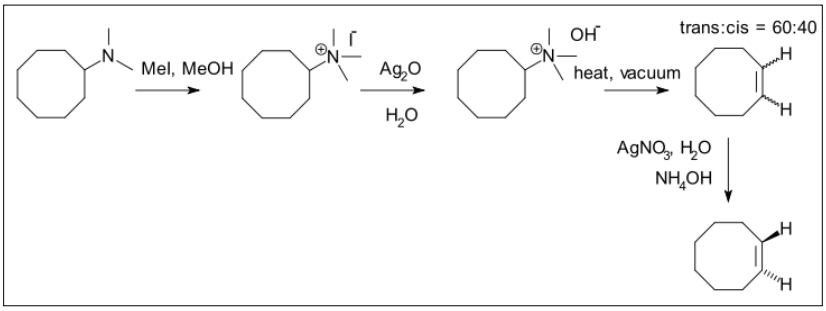


After the first step, a quaternary ammonium iodide salt is created. After replacement of iodine by an hydroxyl anion, an elimination reaction takes place to the alkene.

With asymmetrical amines, the major alkene product is the least substituted and generally the least stable, an observation known as the **Hofmann rule**. This is in direct contrast to normal elimination reactions where the more substituted, stable product is dominant (Zaitsev's rule).

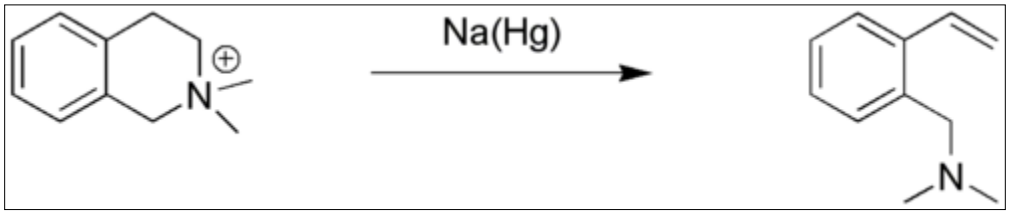
The reaction is named after its discoverer, August Wilhelm von Hofmann.[1]

An example is the synthesis of trans-cyclooctene:



In a related chemical test called **Herzig–Meyer alkimide group determination** a tertiary amine with at least one methyl group and lacking a beta-proton is allowed to react with hydrogen iodide to the quaternary ammonium salt which when heated degrades to iodomethane and the secondary amine

The **Emde degradation** (also called **Emde-reaction** or **Emde-reduction**) is a method for the reduction of a quaternary ammonium cation to a tertiary amine with sodium amalgam.



This organic reaction was first described in 1909 by the German chemist Hermann Emde and was for a long time of great importance in structure elucidation of many alkaloids, for example that of ephedrine. Alternative reducing agents exist for this reaction; for instance, lithium aluminium hydride.

Alkaloids are naturally-occurring organic compounds containing nitrogen moiety, and are usually heterocyclic in nature. They are nitrogen based organic compounds, with nitrogen enclosed in an heterocyclic ring. The alkyl amines are referred to as proalkaloids. Characteristics of alkaloids (1)They are basic in nature due to the presence of nitrogen in their ring. (2) They have complex structures. (3) They have bitter principles. (4) They are mostly obtained from plant materials. (5) They have high pharmacological and physiological activities. Examples of alkaloids are: (1) Quinine — an antimalarial drug isolated from a plant called Cinchonia officialis

Nicotine

i. The molecular formula of nicotine is C_{10} H_{14} N_2.
ii. With HCI it forms the crystalline salt, nicotine dihydrochloride. This proves that nicotine is a diacid base.
iii. On treatment with CH3I, it forms dimethiodide. This suggests that nicotine is a ditertiary base
iv. Herzig - Meyer determination proves that nicotine contains one (-NCH3) group.
v. Nicotine on oxidation with KNnO4 or chromic acid gives nicotinic acid (Pyridine – 3-carboxylic acid).

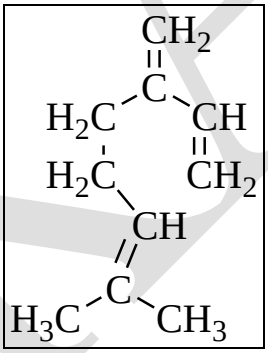
The reaction shows that the side chain is saturated

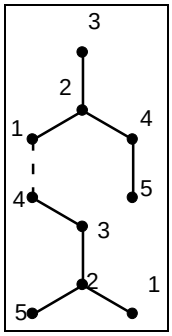
The structure of nicotine is also proved by the following reaction. Nicotine when treated with bromine, forms dibromo nicotine. This on heating with barium hedroxide, breaks down to give nicotinic acid, malonic acid and methyl amine.

Introduction of Terpenoids

Definition

- Originally, the term "terpene" was employed to describe a mixture of isomeric hydrocarbons of the molecular formula $C_{10}H_{16}$ occurring in the terpentine and many essential oils which are obtained from the sap and tissues of certain plants and trees.
- The oxygenated derivatives like alcohols, aldehydes, ketones, etc. at the time were called camphor's.
- As more compounds relating to terpenes and camphor's were discovered with the pace of time, both the terms "terpenes" and "camphors" were amalgamated into a single term called "terpenoids".
- The *Modern definition* of this term is,
  It includes hydrocarbons of plant origin of the general formula $(C_5H_8)_n$ as well as their oxygenated, hydrogenated and dehydrogenated derivatives.
- As terpenoids are composed of isoprene units, these are sometimes called "isoterpenoids".
- Not only the carbon skeletons of terpenoids are divisible into isoprene units but the terpene hydrocarbons are usually exact multiplies of C_5H_8.
- An example is mycerene ($C_{10}H_{16}$) which has a carbon skeleton divisible into 2 isoprene units.



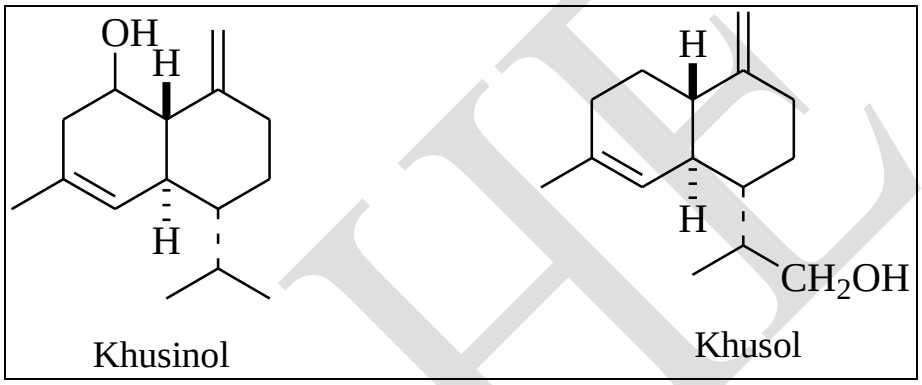


Nomenclature

- Many terpenoids are known by their trivial names because these were isolated and described in the literature long before their structures were elucidated.
- Generally these trivial names are derived from their botanical origins.

- For eg: the crystalline sesquiterpene secondary alcohol belonging to the cadinane group was isolated from vetiver oil (Vetiveria Zizaniodides) and named 'khus' oil in India.

  Therefore, Its alcohol was called khusinol and another crystalline alcohol with also belonged to the same group and isolated from the same source was called khusol.



Importance

- In the recent part, biological activity of various substances has been related with terpenoids.
- Many sesquiterpenes have been found to be active against experimental tumours and the plant growth hormones like gibberellins and diterpenoids.
- As some terpenoids exhibit biological activity viz insecticidal anthelmintic or antiseptic activity. These are used in pharmacy.

Occurrence

- Terpenoids are most widespread, chemically interesting and provide structure of great diversity.
- Although the majority of terpenoids occur in plant kingdom, a few of them have also been obtained from other source.
- Most of the fragment components of plants are volatile with steam distillation, solvent extraction or other treatment of the plant. These components are called essential oils.
- These have been used in perfumery from the earliest times

- The simple mono and sesquiterpenoids are the chief constituents of the essential oils.
- However, the di, tri-terpenoids, which are not steam volatile are obtained from plant and resins.
- Unlike mono and sesquiterpenoids, these compounds donot possess any perfumery value.
- The tetraterpenoids constitute a group of compounds called carotenoids.

Important Essential oils with their terpenoids constituents:-

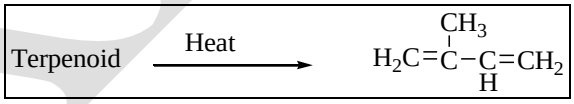
S.NO	Essential Oil	Constituent Terpenoid
1.	Bay	Eugenol
2.	Bergamot	Linalool and its acetate
3.	Caraway	Limonene, Carvone
4.	Camphor	Camphor
5.	Cardamon cajeput	Terpineol
6.	Citronella	Farnesol, citronellal and geraniol
7.	Clove	Eugenol
8.	Coriander	Linalool, α-pinene
9.	Eucalyptus	Cineole
10.	Geranium	Geraniol esters, cintronellol
11.	Ginger	Zinziberene
12.	Jasmine	Linalool
13.	Lavender	Linalool
14.	Lemon	d, l- limonene, citral
15.	Neroli	Nerolidol
16.	Peppermint	Menthol and its esters
17.	Rose	Geraniol, citronellol and Farnesol
18.	Sandal wood	Santalol
19.	Sweet orange	d- limonene

General Properties of Terpenoids:-

- Most of them are colourless liquids which are lighter than water and boil between 150-180ºC.
- A few are solids which are lighter than water, volatile in steam, usually highly refractive and insoluble in water but soluble in organic solvents.
- Many of them are optically active.

Chemical Properties

- They are unsaturated compounds (Open chain or cyclic with one or more carbon atom rings) having one or more double bonds.
  - It undergoes addition reactions with hydrogen, halogen and halogen acids, etc.
  - Some of them form hydrates
  - They also form characteristic addition products with NO_2, NOCl and NOBr. These addition products are found ti be useful in the identification of terpenoids.
  - A number of addition products have antiseptic properties.
- They undergo polymerization and also dehydrogenation in the ring.
- As they have olefinic bonds, they are very easily oxidized nearly by all the oxidizing agents.
- A number of terpenoids are labile and hence readily isomerised in the presence of acids in two more stable forms.
- On thermal decomposition, most of the terpenoids yield isoprene as one of the product.



Isolation

Due to their wide occurrence in nature, all the terpenoids could not be isolated and separated by a general method.

However, mono and sesqui-terpenoids have a common source. ie, essential oils and therefore isolation has been generalized, this is carried out in 2 steps.

1. Isolation of essential oils.
2. Separation of terpenoids from essential oils. Let us discuss these steps one by one.

1. Isolation of essential oils

As a plant having essential oils generally possess maximum concentration at some particular time.

Eg. Jasmine at sun-set, it becomes desirable to take the plant parts having essential oil at this particular time.

In general, our methods based on different principles have been developed for the extraction of oils.

These methods are discussed as follows:

a) **Expression method**

- This method is not used these days. However, it has the historical importance only.
- In this method, the plant material is cut in to small pieces. These pieces are then crushed to get the juice which is screened to remove longer the large particles.
- After screening, the juice is centrifuged in a high speed centrifugal machine when one-half of the oil is extracted and the rest half of the essential oil remains with the residue.
- From this residue, inferior quality of the oil is obtained by distillation.
- Expression method is generally used to extract citrus, lemon and grass oils.

b) **Steam distillation method**

- This method is one of the most widely used methods. In this method the plant materials are macerated and then steam distilled to get the essential oils into the distillate from which these are extracted by using pure organic volatile solvents like light petroleum and the solvent is then removed by distillation under reduced pressure.
- One should employ steam distillation method carefully because it suffers from the following demerits:-
  - i) Some essential oils undergo decomposition during steam distillation.
  - ii) Some constituents of essential oils eg. Esters, which are responsible for the odour and fragrance of the oil may undergo decomposition resulting in a perfume of inferior industry.

c) **Extraction by mean of volatile solvents**

- This method is widely used in a perfume industry. This method is generally used for such plants which yields oil or give low quantities of oil on steam distillation due to decomposition of essential oils.

- In such cases, the plant material is directly treated with light petrol at 50ºC. Under these conditions the oil is taken up by the solvent along with soluble colouring materials.
- The essential oils from this extract are separated by removing the solvent by distillation under reduced pressure.

d) **Adsorption in purified fats**

- This method is also known as enfluerage method and is widely employed in france.
- By this method, the yield of the essential oil is generally higher. This method is used to extract a large number of essential oils like rose and jasmine.
- In this method, the fat is warmed to 50ºC on glass plates. Then, the surface of the fat is covered with flower petals and it is allowed to be kept as such for several days until it becomes saturated with essential oils.
- Then the old petals are replaced by fresh petals and this process is repeated.
- After removing the petals, the fat is digested with ethyl alcohol when all the essential oils present in fat are dissolved in alcohol.
- Some quantity of fat is also dissolved in alcohol. This can be removed by cooling the alcohol extract at 20ºC, when the fat separates out.
- The alcohol distillate is then finally fractionally distilled under reduced pressure to remove the solvent.
- Recently, the fat has been replaced by coconut charcoal due to its greater stability and higher adsorptive capacity.
- After keeping the coconut charcoal in contact with petals for a number of days, the charcoal is submitted to steam distillation to get essential oils.
- This method is superior to the enfluerage method.

2. Separation of terpenoids from essential oils

The essential oils obtained from the step 1 generally contain a number of terpenoids and these are separated contain a number of terpenoids and these are separated by various physical and chemical methods.

a) Chemical methods

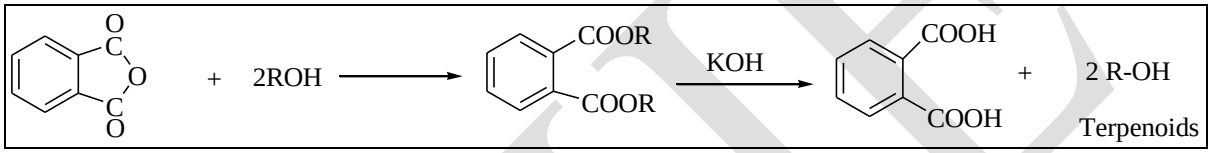
These methods are not used these days to separate various terpenoids from essential oils.

i) When essential oils containing terpenoid hydrocarbons are treated with nitrosyl chloride in chloroform, crystalline adducts of hydrocarbons having sharp melting points are obtained.

These are separated and decomposed in to their corresponding hydrocarbons.

ii) When the essential oils containing alcohols are treated with phthalic anhydride to form diesters, the primary alcohols react with phthalic anhydride readily, secondary alcohols less readily and tertiary alcohols do not react at all.

After extracting with sodiumbi carbonate, diesters are decomposed by alkali to the parent terpenoid alcohols.



iii) Terpenoid aldehyde and ketones are separated from essential oils by forming their adducts with the common carbonyl reagents like $NaHSO_3$, 2,4-dinitrophenyl hydrazine, phenyl hydrazine, semicarbozide, etc.
After separation, these are decomposed to regenerate terpenoid aldehydes and ketones.

b) Physical Methods

The various physical methods are as follows:-

i) Fractional Distillation method

- The various terpenoids present in essential oils are separated by fractionaldistillation method.
- The terpenoid-hydrocarbons distill over first, followed by the oxygenated derivatives.
- Distillation of the residue under reduced pressure yields the sesquiterpenoids and these are separated by fractional distillation.
- On an industrial scale, especially designed stills are employed and an efficient condensing system is necessary to minimize loss of more volatile hydrocarbons.
- Many times, the fractional distillation has to be carried out under reduced pressure and in the presence of an inert gas. These conditions are essential because many terpenes are sensitive to heat and atmospheric oxygen.

ii) Chromatography

- More recently, chromatography in its various forms has been widely used both for isolation and separation of terpenoids.
- In adsorption chromatography, the essential oil is made to flow through a particular adsorbent when the different types of terpenoids are adsorbed at different places on the adsorbent to form different chromatograms.
- Then, the various chromatograms are eluted by different solvent systems to get different eluates (each eluate is having terpenoids of a single group).
- Each eluate is then subjected separately to adsorption chromatography when different bands due to the various terpenoids present in eluate are obtained which are then eluted to yield different terpenoids.
- In adsorption chromatographic method, alumina and silica gel are generally used as adsorbents for separating the terpenoids, particularly triterpenoids.
- Other chromatographic techniques such as vapour phase chromatography, partition chromatography and counter-current separation method have been used for the separation of terpenoids.
- Gas chromatography has been particularly useful for isolating pure configurational forms of a given terpenoid from mixtures produced by synthesis.

Isoprene Rule

In 1887, Wallach enunciated the famous isoprene rule which may be stated as follows:-

"The skeleton structures of all naturally occurring terpenoids are built up of isoprene units".

From the above rule it follows that the divisibility into isoprene unit is regarded as a necessary condition to be satisfied by every naturally occurring terpenoid.

The isoprene rue has been deduced from the following facts:-

a) The empirical formula of almost all the naturally occurring terpenoids is C_5H_8.
b) The thermal decomposition of almost all terpenoids gives isoprene as one of the products.
For example, rubber (polyterpenoid) on destructive distillation yields isoprene as one of the decomposition products.

$$(C_5H_8)_n \xrightarrow[\text{Distillation}]{\text{Destructive}} nC_5H_8$$
Isoprene

c) Isoprene rule has been confirmed by the fact that under special experimental conditions, isoprene undergoes polymerization to yield various terpenoids.
For example,

i) Isoprene, when heated to 280ºC get dimerised to yield a widely distributed terpenoid called dipentene.

$$2\ C_5H_8 \xrightarrow{\text{Polymerization}} C_{10}H_{16}$$

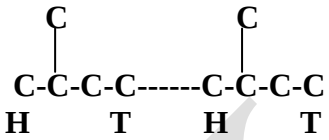
ii) Isoprene may be polymerized to yield a rubber like product.

$$n\ C_5H_8 \xrightarrow{\text{Polymerization}} (C_5H_8)n$$

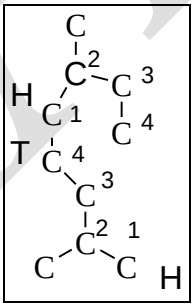
Rubber (Polyterpenoid)

Special Isoprene Rule:-

- This rule proposed by ingold (1925), shows how the isoprene units in the terpenoid molecule are linked together.
- For this purpose, the branched end of the isoprene unit is considered as the head and the other end as the tail.
- According to the special isoprene rule, the isoprene units in terpenoids are linked in a head to tail fashion.
- Thus the basic carbon skeleton of a monoterpene according to the special isoprene rule will be as follows.



or **Where** H = Head
T = Tail



- It should be noted, however that this rule, which has proved very useful can only be used as a guiding principle and not as a fixed rule.
- Therefore, there are departures and violations of this rule in many compounds.

For example,

i) Certain terpenoids are known whose carbon content is not a multiple of five. For example,

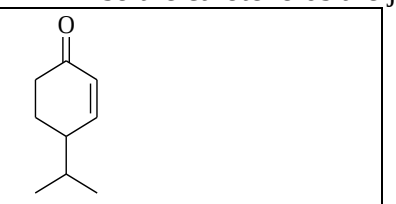
Cryptone, a naturally occurring ketonic terpenoid contains nine carbon atoms and therefore, it cannot be divided into two isoprene units.

ii) Certain terpenoids are known whose carbon content is a multiple of five but cannot be divided in to two isoprene units.

iii) Certain terpenoids are also known in which the special isoprene rule is violated.

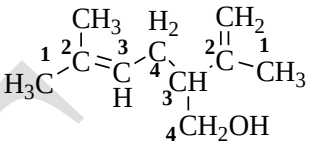
For example,

- Lavandulol is composed of two isoprene units of isoprene with the unusual linkage of tail to tail but not head to tail linkage.
- Also the carotenoids are joined tail to tail at their centre.

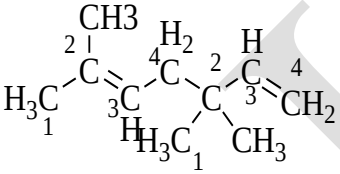


Cryptone

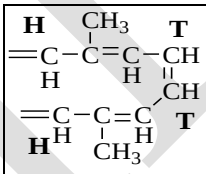
(Contains only 9 carbon atoms instead of 10)



Lavandulol(3,4-linkage)two isoprene units are linked through C_3 and C_4)

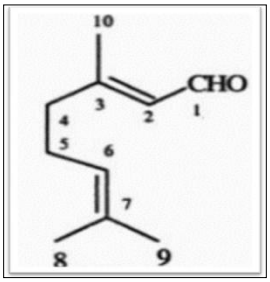


Atemisia alcohol (2,4-Union)

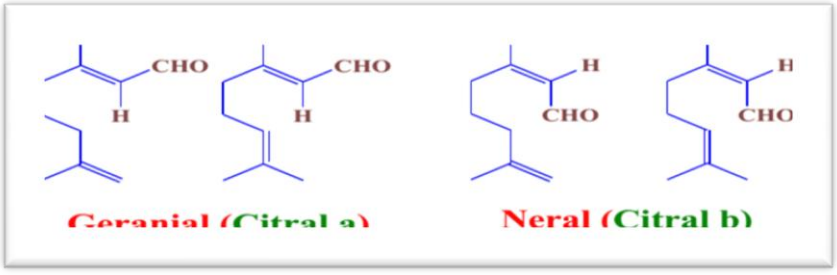


Part Structure of the Carotenoids showing tail to tail arrangement of the 2 isoprene units.

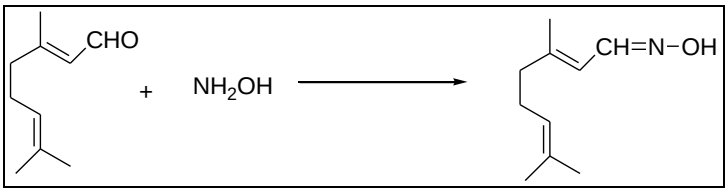
Citral



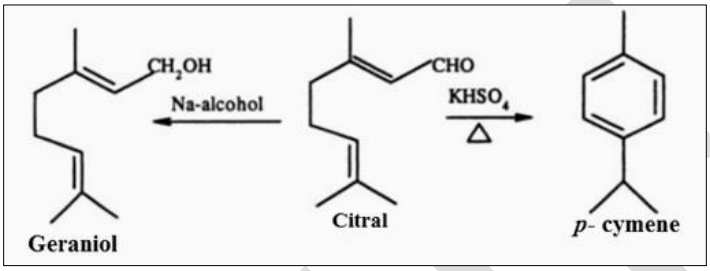
Mixture of at least 4 geometrical isomers of di-olefinic aldehydes



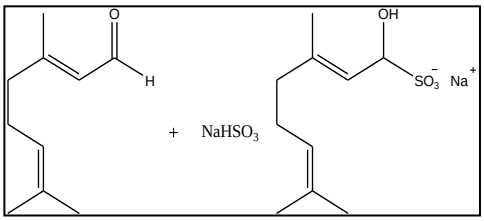
- **Formation of an oxime of citral indicated the presence of an oxo group in citral.**



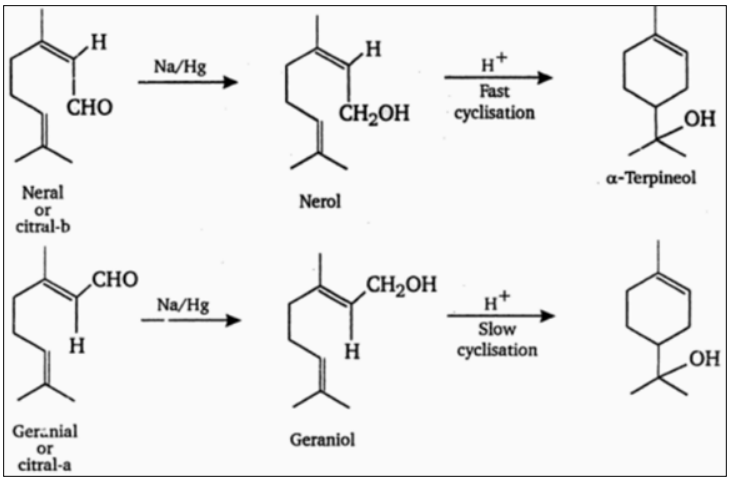
Citral when heated with potassium hydrogen sulphate afforded the known aromatic hydrocarbon, p-cymene, which fixed the position of methyl and isopropyl groups in citral.



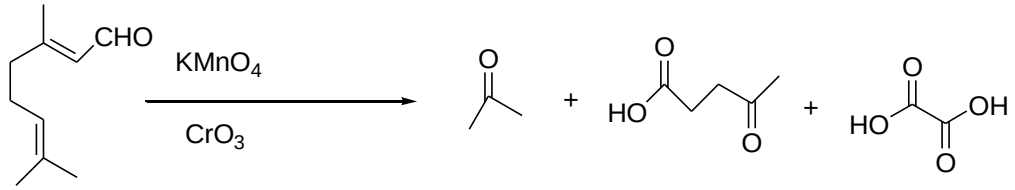
Citral formed both mono- and di- bisulphites by the addition of sodium bisulfite to reveal the presence of a **conjugated aldehyde** group. Its UV spectrum displayed a band at 238 nm to confirm this.



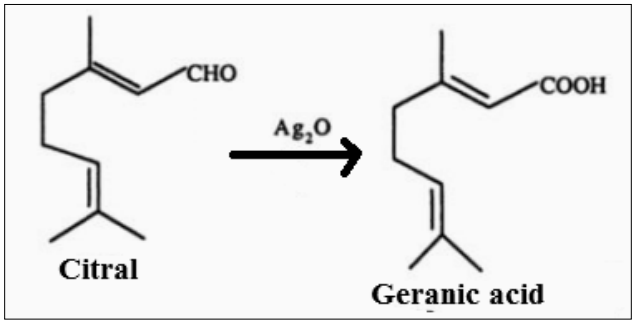
Citral on reduction with **sodium-amalgam** citral gave an alcohol, **geraniol,** $C_{10}H_{18}O$



Citral on oxidation with alkaline permanganate, yielded **acetone**, **oxalic** and **levulenic acid**.



Citral oxidation with silver oxide afforded an acid **geranic acid**, $C_{10}H_{16}O_2$ containing the same number of carbon atoms suggesting that citral had an aldehyde group.



Based on the above data and coupled with the biogenetic considerations that **citral** is formed by the joining of **two isoprene** units in the head to tail fashion, structure of **citral** was assigned tentatively.

This structure was further supported by the degradation of **citral** on treatment with aqueous **potassium carbonate** when **6-methyl-hept-5-en-2-one** and **acetaldehyde** were obtained. The structure of **citral** was finally confirmed by its synthesis

SUGGESTED MATERIALS:

Text books:

T1: Morrison, R. T. & Boyd, R. N.(1992). *Organic Chemistry*. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

T2: Arun Bahl(2005). Advanced organic chemistry, S.Chand & Company Pvt.Ltd. Ramnagar, New Delhi.

T3: Finar, I. L. (2002). *Organic Chemistry*. Volume 1. Dorling Kindersley (India) Pvt. Ltd., (Pearson Education).

Reference Books

R1: Finar, I. L. (2002). *Organic Chemistry*: *Stereochemistry and the Chemistry of Natural Products*. Volume 2. Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).

POSSIBLE QUESTIONS

PART A

(1 Marks Q.No. 1 to 20)

(Online Examination)

PART B (2 Marks)

1. What is an alkaloid? Give examples
2. What is a terpene. Give an example
3. What is meant by isoprene rule?
4. What is meant by Emdes degradation
5. What is meant by Hoffmann exhaustive methylation

PART C (6 Marks)

1. Explain the Occurrence, classification, isoprene rule in terpenes.
2. Explain with suitable examples (i) Hoffmann's exhaustive methylation, (ii) Emde'smodification.
3. Explain how alkaloids are extracted from plant materials
4. Explain the structure elucidation and synthesis of nicotine
5. Elucidate the structure of citral
6. Explain the natural occurrence, general structural features, isolation and their physiological action of alkaloids.
7. Explain the structure elucidation and synthesis of nicotine
8. Explain the medicinal importance of Medicinal importance of Nicotine, Hygrine, Quinine, Morphine, Cocaine, and Reserpine.

17CHU303

Karpagam Academy of Higher Education

Coimbatore-21

(For the candidate admitted on 2017 onwards)

Department of Chemistry

III- semester

ORGANIC CHEMISTRY-III

UNIT V- Objective Questions for online examination (Each carry 1 Marks)

Question	Option-A	Option-B	Option-C	Option-D	Answer
Reaction of phenyl ethylamine with acetaldehyde followed with reduction gives	Quinoline	Isoquinoline	indole	pyrans	isoquinoline
Monoterpenes consists of	10 carbon atoms	15 carbon atoms	20 carbon atoms	30 carbon atoms	10 carbon atoms
Sesquiterpenes consists of	10 carbon atoms	15 carbon atoms	20 carbon atoms	30 carbon atoms	15 carbon atoms
Diterpenes consists of	10 carbon atoms	15 carbon atoms	20 carbon atoms	30 carbon atoms	20 carbon atoms
Triterpenes consists of	10 carbon atoms	15 carbon atoms	20 carbon atoms	30 carbon atoms	30 carbon atoms
If a terpene consists of 10 carbon atoms then it is called	Monoterpenes	Sesquiterpenes	Diterpenes	Triterpenes	Monoterpenes
If a terpene consists of 20 carbon atoms then it is called	Monoterpenes	Sesquiterpenes	Diterpenes	Triterpenes	Diterpenes
If a terpene consists of 15 carbon atoms then it is called	Monoterpenes	Sesquiterpenes	Diterpenes	Triterpenes	sesquiterpenes
If a terpene consists of 30 carbon atoms then it is called	Monoterpenes	Sesquiterpenes	Diterpenes	Triterpenes	Triterpenes
Polyterpenes consists of	10 carbon atoms	15 carbon atoms	20 carbon atoms	Many isoprene units	Many isoprene units

Isoprene consists of	10 carbon atoms	15 carbon atoms	20 carbon atoms	5 carbon atoms	5 carbon atoms
In terpenes the isoprene units are joined together by	Head-tail fashion	Tail-head fashion	By amide linkages	By ether linkages	Head-tail fashion
Carotinoids are otherwise called as	Monoterpenes	Sesquiterpenes	Diterpenes	tetraterpenes	tetraterpenes
The chief constituents of essential oils are	Monoterpenes and sesquiterpenes	Diterpenes	triterpenes	tetraterpenes	Monoterpenes and sesquiterpenes
Monoterpenes and sesquiterpenes are usually	Volatile liquids	Low melting solids	High melting solids	Crystalline substances at room temperature	Volatile liquids
Terpenes are built up by condensation of isoprene units by either a 1-4 linkage(head to tail) is called	Hofmann rule	Isoprene rule	Zaysteff rule	Flemings rule	Isoprene rule
Example for an antimalarial drug	Quinine	Morphine	Terpineol	cymene	Quinine
Quinine is used as an	Antimalarial drug	antibiotic	Diabetes inhibitor	Anticancer drug	Antimalarial drug
Emde degradation is	reduction of a quaternary ammonium cation to a tertiary amine	reduction of a tertiary amine to a quaternary ammonium cation	reduction of a quaternary ammonium cation to a alkene	reduction of a quaternary ammonium cation to a tertiary alcohol	reduction of a quaternary ammonium cation to a tertiary amine
The reagent used in the Emde degradation is	sodium amalgam	Sodium/ethanol	Sodium nitrate	Fe/HCl	sodium amalgam
Emde degradation is used in the structure elucidation of	Alkaloids	terpenes	steroids	flavanoids	Alkaloids
In Emde degradation instead of sodium amalgam what can be used	Lithium aluminium hydride	Sodium boro hydride	Sn/HCl	Zinc amalgam	Lithium aluminium hydride

reduction of a quaternary ammonium cation to a tertiary amine in presence of sodium amalgam is	Emde degradation	Hoffmann exhaustive methylation	Hoffmann degradation	Clemensen reduction	Emde degradation
Example for Pyrrolidine type alkaloids	Hygrine	Quinine	Atropine	Caffeine	Hygrine
Example for Quinoline alkaloids	Hygrine	Quinine	Atropine	Caffeine	Quinine
Example for Tropane alkaloids	Hygrine	Quinine	Atropine	Caffeine	Atropine
Example for Purine alkaloids	Hygrine	Quinine	Atropine	Caffeine	Caffeine
Hygrine alkaloid is an example for	Pyrrolidine type alkaloids	Quinoline alkaloid	Tropane alkaloids	Purine alkaloids	Pyrrolidine type alkaloids
Quinine alkaloid is an example for	Pyrrolidine type alkaloids	Quinoline alkaloid	Tropane alkaloids	Purine alkaloids	Quinoline alkaloid
Atropine is an example for	Pyrrolidine type alkaloids	Quinoline alkaloid	Tropane alkaloids	Purine alkaloids	Tropane alkaloids
Caffeine is an example for	Pyrrolidine type alkaloids	Quinoline alkaloid	Tropane alkaloids	Purine alkaloids	Purine alkaloids
Morphine is a	Pyrrolidine type alkaloids	Quinoline alkaloid	Tropane alkaloids	Isoquinoline alkaloid	Isoquinoline alkaloid
Nicotine is used as a	parasympathomimetic stimulant	Metabolic enhancer	depressant	halucinogen	parasympathomimetic stimulant
Hygrine is found in	Coca leaves	Chincona bark	Opium	plectranthus	Coca leaves
Quinine is found in	Coca leaves	Chincona bark	Opium	plectranthus	Chincona bark
Morphine is found in	Coca leaves	Chincona bark	Opium	plectranthus	Opium
Cocaine is a	CNS drug-stimulants	CNS drug-Depressants	CNS drug-Hallucinogens	Psycho-active drug	CNS drug-stimulants
Pseudoephidrine is a	CNS drug-stimulants	CNS drug-Depressants	CNS drug-Hallucinogens	Psycho-active drug	CNS drug-stimulants

Nicotine is a	CNS drug- stimulants	CNS drug- Depressants	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- stimulants
Caffeine is a	CNS drug- stimulants	CNS drug- Depressants	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- stimulants
Tranquillisers are	CNS drug- stimulants	CNS drug- Depressant	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- Depressant
Heroin is a	CNS drug- stimulants	CNS drug- Depressant	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- Depressant
Morphine is a	CNS drug- stimulants	CNS drug- Depressant	CNS drug- Hallucinogens	Psycho-active drug	CNS drug- Depressant
Example for CNS drug- stimulants	Cocaine	Benzodiazepines	Psilocybin	Cannabis	Cocaine
Example for CNS drug- stimulants	Pseudoephidrine	Benzodiazepines	Psilocybin	Cannabis	Pseudoephidrine
Example for CNS drug- stimulants	Nicotine	Benzodiazepines	Psilocybin	Cannabis	Nicotine
Example for CNS drug- stimulants	Caffeine	Benzodiazepines	Psilocybin	Cannabis	Caffeine
Example for CNS drug- Depressants	Caffeine	tranquillisers	Psilocybin	Cannabis	tranquillisers
Example for CNS drug- Depressants	Caffeine	Benzodiazepines	Psilocybin	Cannabis	Benzodiazepines
Occur in the plant sources as the salt of acids, such as: oxalates, tannates	alkaloids	terpenes	steroids	carbohydrates	alkaloids
Alkaloids are	Weakly basic	Strongly basic	Weakly acidic	Strongly acidic	Weakly basic
Alkaloids on prolonged contact with strong bases results in	condensation	dehydration	hydrolysis	Cyclic dehydration	hydrolysis
Example for ester alkaloid	cocaine,	cephaeline	morphine	Nicotine	cocaine,

Example for ester alkaloid	hyoscyamine	cephaeline	morphine	Nicotine	hyoscyamine
Example for phenolic alkaloid	cocaine,	cephaeline	Nicotine	hyoscyamine	cephaeline
Example for phenolic alkaloid	morphine	cocaine	Nicotine	hyoscyamine	morphine
Alkaloids are converted into quarternary salt using	Methyl iodide	Sodium iodide	Sodium chlride	Petroleum ether	Methyl iodide
A quaternary amine is reacted to create a Tertiary amine and an alkene in	Hoffmann exhaustive methylation	Fischer synthesis	Synthesis of quinoline	In the synthesis of morphine	Hoffmann exhaustive methylation
In Hoffmann exhaustive methylation, the first step is	Formation of quarternary salt	Conversion of quarternary salt in to hydroxide	Heating the quarternary hydroxide	Elimination of alkene	Formation of quarternary salt
In Hoffmann exhaustive methylation, the Second step is	Formation of quarternary salt	Conversion of quarternary salt in to hydroxide	Heating the quarternary hydroxide	Elimination of alkene	Conversion of quarternary salt in to hydroxide
In Hoffmann exhaustive methylation, the Third step is	Formation of quarternary salt	Conversion of quarternary salt in to hydroxide	Heating the quarternary hydroxide	Elimination of alkene	Heating the quarternary hydroxide

Reg. No.: ---------- [17CHU303]

KARPAGAM ACADEMY OF HIGHER EDUCATION
Deemed to be University
(Established Under Section 3 of UGC Act 1956)
COIMBATORE-641 021

B.Sc., Degree Examination
(For the candidates admitted from 2017 & onwards)

II- B.Sc., Chemistry

Ist Internal Test

Organic Chemistry-III
(Nitrogen containing functional groups, Heterocyclic compounds and Natural Products)

Time: 2 Hours Maximum: 50 marks

Date:

Section-A 20X1=20

Answer all the questions

1. Nitration of propane gives
   a. Propyl nitrite b. Nitro propane c. Propyl amine d. Isopropyl amine
2. On boiling an aqueous solution of sodium nitrite with an alpha halogen carboxylic acid, it gives
   a. Nitro compound b. Alkyl nitrites c. Alkyl amines d. Chloro methyl amines
3. Catalytic reduction of nitrocompounds in presence of Hydrogen and nickel gives
   a. Primary amine b. Hydroxyl amines c. Nitroso amines
   d. N-alkyl hydroxylamine
4. In neutral reducing medium nitro compounds are reduced to
   a. Mixture of amine b. Hydroxyl aniline c. aniline d. N-alkyl hydroxylamine
5. Primary nitro alkanes react with nitrous acid to form
   a. Carboxylin acid b. Nitrolic acid c. Pseudo nitrole d. Hydroxyl amine
6. Which one of the following reaction give nitro alkanes as a product
   a. Oxidation of oximes b. Oxidation of aldehydes c. Nitration of ketones
   d. Nitration of oximes
7. Nitrolic acid dissolves in sodium hydroxide to give
   a. Blue colour solution b. Red colour solution c. Colour less precipitate
   d. Pink colour turbid solution
8. Nitro methane react with nitrous acid to form
   a. Acetic acid b. Nitrolic acid c. Pseudo nitrole d. Hydroxyl amine
9. In the following compounds which one is more basic
   a. Trimethyl amine b. Dimethyl amine c. Methylamine d. Ammonia

10. A primary amine when heated with chloroform and alcoholic potassium hydroxide gives
    a. Isocyanides b. Alkyl cyanides c. Amino aldehydes d. Amino ketones
11. Which one of the following is answered in Carbylamine test
    a. Primary amine b. Secondary amine c. Tertiary amine d. Quarternary salt
12. Carbylamine reaction, primary amine gives
    a. An offensive smell b. Pleasant smell c. A red precipitate d. Rotten egg smell
13. All the carbon atoms in naphthalene are in
    a. SP hybridization b. SP^2 hybridisation c. SP^3 hybridisation
    d. D^2 SP hybridisation
14. Nitration of naphthalene with con.nitric acid and sulphuric acid gives predominantly
    a. 1-nitro naphthalene b. 2- nitro naphthalene c. 3- nitro naphthalene
    d. 4- nitro naphthalene
15. Chlorination of naphthalene with ferric chloride gives
    a. 1-chloronaphthalene b. 2-chloronaphthalene c. 5-chloro naphthalene
    d. 1-, 2-, and 5-chloronaphthalene
16. The ratio between 1- and 2- acyl naphthalene when the reaction takes place in presence of nitrobenzene
    a. 3:01 b. 1:09 c. 2:4 d. 3:6
17. Naphthalene on reduction with Pt and Nickel gives
    a. 1,4-dihydro Naphthalene b. 1,2-dihydro Naphthalene c. decalin d. tetralin
18. Sulphonation of naphthalene at 425K yields
    a. 1-naphthalene sulphonic acid b. 2- naphthalene sulphonic acid
    c. A mixture of 1- and 2-naphthalene sulphonic acid
    d. Cannot be sulphonated
19. Electrophilic substitution of naphthalene takes place at
    a. 1^{st} position b. 2^{nd} position c. 1^{st} or 2^{nd} position d. 8^{th} position
20. The resonance enthalpy of naphthalene is
    a. 80 K cal/mol b. 61 K cal/mol c. 180 K cal/mol d. 30 K cal/mol

Section B **3x2 = 6**

Answer all the questions

21. What are nitroalkanes?

22. Give any four physical properties of nitro alkanes?

23. How 1° amines are identified?

Section C **3x8 = 24**

Answer all the questions

24. (a) Write a note on chemical properties of Aromatic Nitroalkanes?

(or)

(b) How will you distinquish 1°,2° and 3° amines by using Nitrous acid and Hinsberg's method ?

25. (a) Give an account of Hofmann's degradation with mechanism?

(or)

(b) Explain the preparation and physical properties of aliphatic nitro compounds?

26. (a) Briefly explain the structure, preparation and properties of benzene diazonium chloride?

(or)

(b) Starting with benzene outline the synthesis of following compounds using diazonium salts as intermediates?

a. Phenol
b. Bromobenzene
c. Phenylhydrazine
d. Parahydroxyazobenzene

[17CHU303] **Reg. No……**

KARPAGAM ACADEMY OF HIGHER EDUCATION
COIMBATORE-641 021

(For the candidates admitted from 2016 & Onwards)
B.Sc., DEGREE INTERNAL EXAMINATION, AUGUST 2018
CHEMISTRY
INTERNAL TEST-II
Organic Chemistry-III
(Nitrogen containing functional groups, heterocyclic compounds and Natural products)

Time: 2 Hours **Maximum: 50 marks**

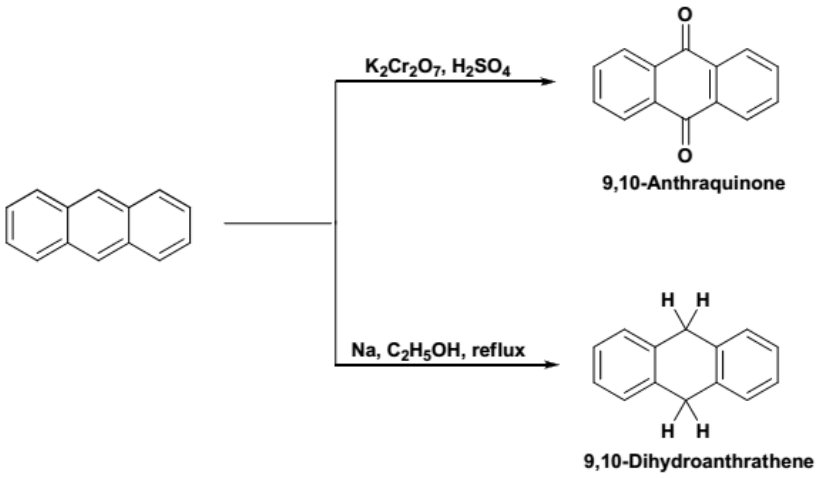
PART A **(20 x 1 =20)**
Answer all Questions

1. Sandmeyer reaction
2. Cyano benzene
3. Aniline
4. Condensed polynuclear hydrocarbons
5. Anthracene
6. Naphthalene
7. 61 K cal
8. 1-naphthalene sulphonic acid
9. A mixture of 1- acyl and 2-acyl naphthalene
10. Tetralin
11. 6 electrons
12. Skraup synthesis
13. Nitrogen
14. A carbon of benzene by an hetero atom
15. Thiophene
16. Aza
17. –epine
18. 2, 5 position
19. Pyrrole
20. Oxygen is more electronegative than Nitrogen

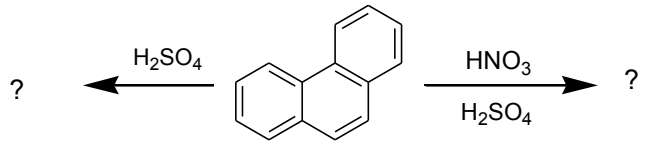
PART - B **(3 x 2 =6)**

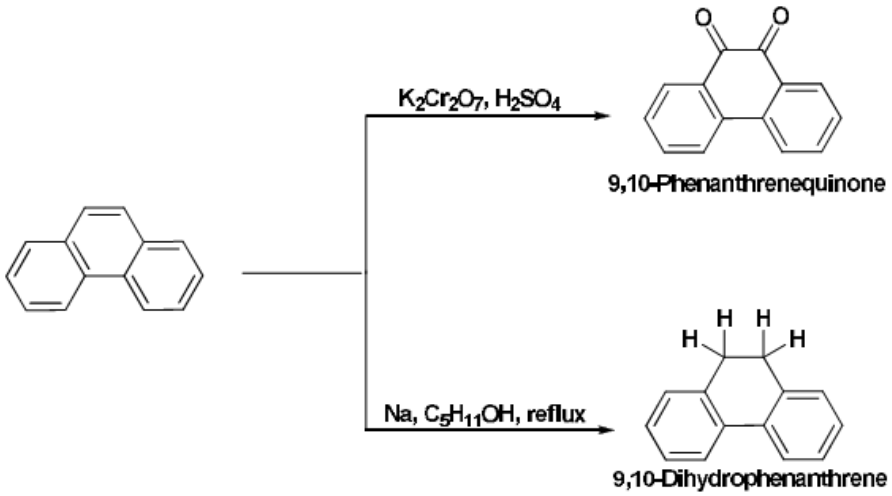
Answer all Questions

21. What is the product of oxidation of phenanthrene by $K_2Cr_2O_7/H_2SO_4$?



22. Predict the product of the following reaction





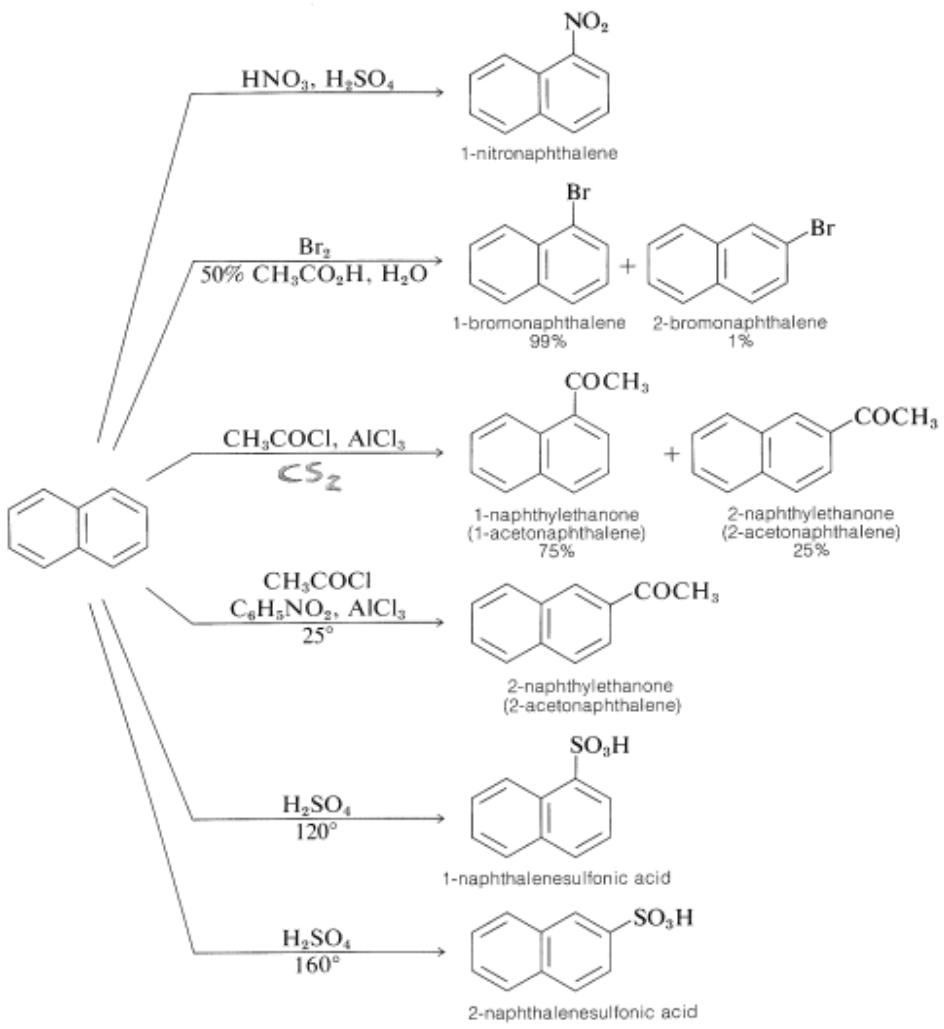
23. Define Huckel's rule?

Huckel's Rule (4n+2 rule): In order to be aromatic, a molecule must have a certain number of pi electrons (electrons with pi bonds, or lone pairs within p orbitals) within a closed loop of parallel, adjacent p orbitals.

PART - C **(3 x 8 =24)**

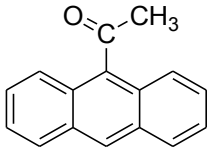
Answer all Questions

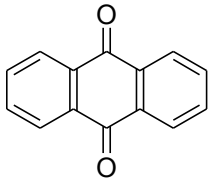
24. (a) Write a note on: Electrophilic substitution reactions in naphthalene?



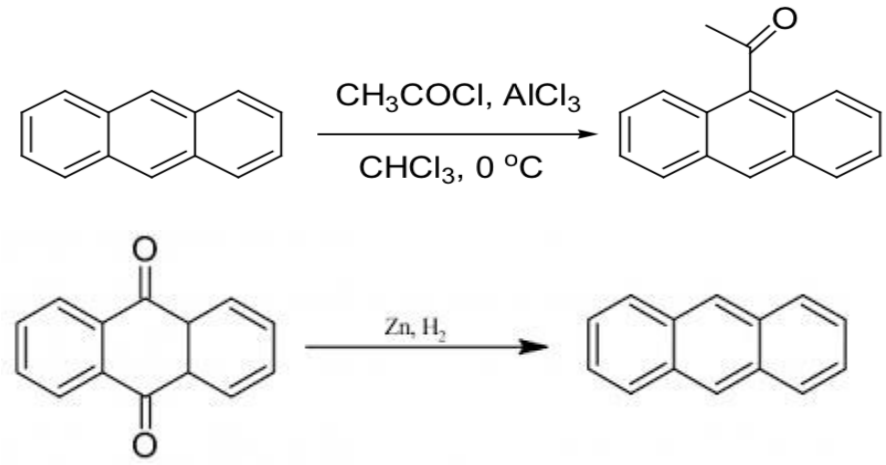
(Or)

(b) How will you synthesis the following compounds from anthracene

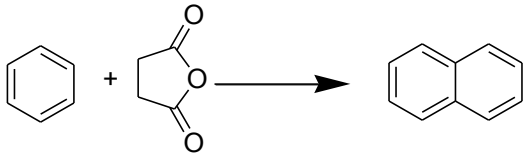
(i) 

(ii) 

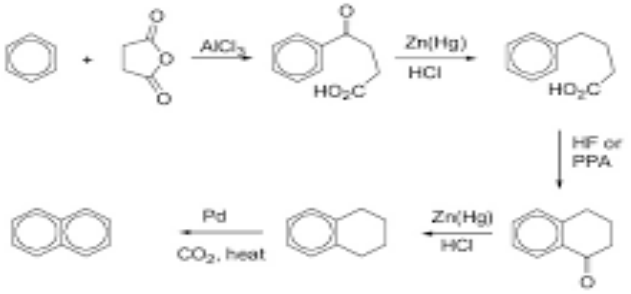
(i)



25. (a) Explain the steps involved in the following conversion



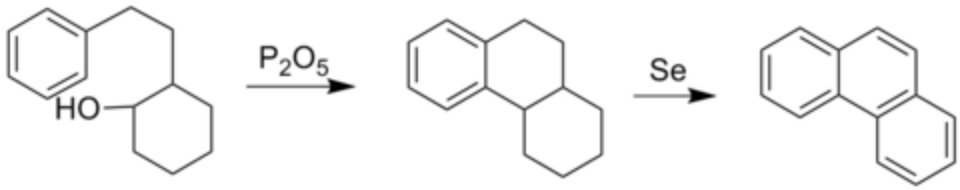
4. Haworth Synthesis of naphthalene



(Or)

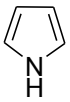
(b) Discuss the structure of phenanthrene?

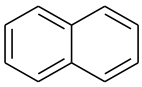
Phenanthrene is nearly insoluble in water but is soluble in most low polarity organic solvents such as toluene, carbon tetrachloride, ether, chloroform, acetic acid and benzene. The Bardhan–Sengupta phenanthrene synthesis is a classic way to make phenanthrenes.

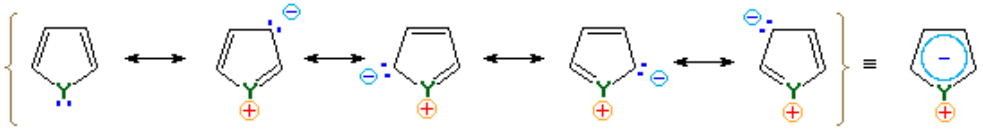


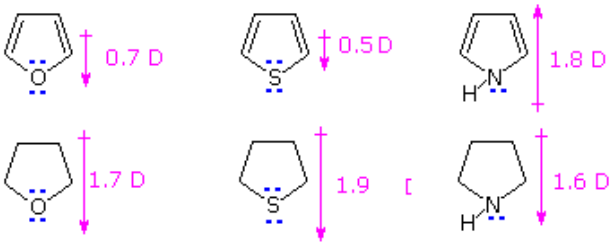
his process involves electrophilic aromatic substitution using a tethered cyclohexanol group using diphosphorus pentoxide, which closes the central ring onto an existing aromatic ring. Dehydrogenation using selenium converts the other rings into aromatic ones as well. The aromatization of six-membered rings by selenium is not clearly understood, but it does produce H_2Se. Phenanthrene can also be obtained photochemically from certain diarylethenes.

26. (a) Explain the aromaticity of the following compounds and give valuable reasons

i. 

ii. 
iii. 
iv. 
v. 
vi. 

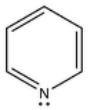




Stabilization Energies

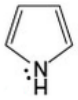
Benzene	Furan	Thiophene	Pyrrole
38	16	11	16

kcal/mole from heats of combustion



Pyridine

Lone pair is not part of the aromatic system



Pyrole

Lone pair is part of the aromatic system

Furan

1 Lone pair is part of the aromatic system

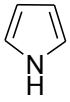
Thiphene

1 Lone pair is part of the aromatic system

Total number of pi electron in each case is 6

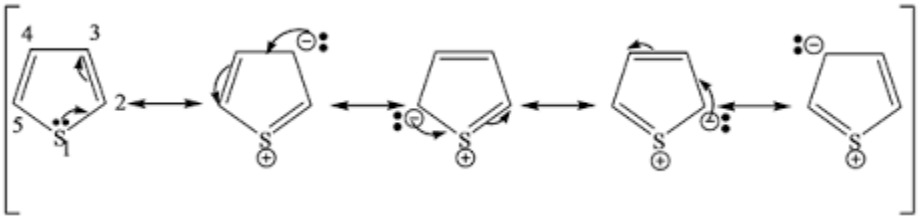
(b) Draw the resonance structure of the following compounds

i. 

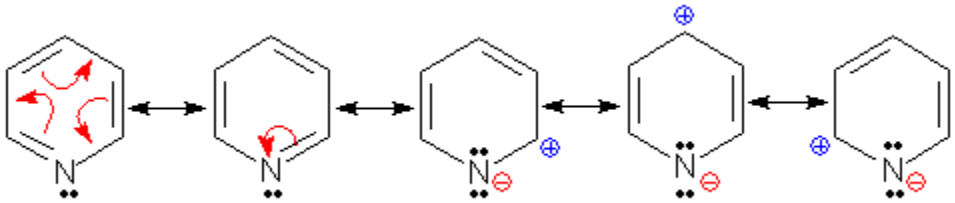
ii. 

iii. 

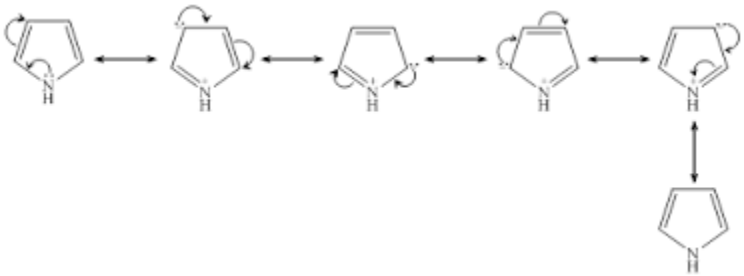
Thiophene



Pyridine



Pyrrole



Reg. No.: ---------- [17CHU303]

KARPAGAM ACADEMY OF HIGHER EDUCATION
Deemed to be University
(Established Under Section 3 of UGC Act 1956)
COIMBATORE-641 021

B.Sc., Degree Examination
(For the candidates admitted from 2017 & onwards)

II- B.Sc., Chemistry

Ist Internal Test

Organic Chemistry-III
(Nitrogen containing functional groups, Heterocyclic compounds and Natural Products)

Time: 2 Hours Maximum: 50 marks

Date: 14.7.2018

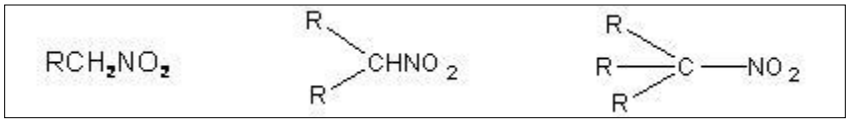
Section-A **20X1=20**

1. b. Nitro propane
2. a. Nitro compound
3. a. Primary amine
4. d. N-alkyl hydroxylamine
5. b. Nitrolic acid
6. a. Oxidation of oximes
7. b. Red colour solution
8. b. Nitrolic acid
9. b. Dimethyl amine
10. a. Isocyanides
11. a. Primary amine
12. a. An offensive smell
13. b. SP^2 hybridisation
14. a. 1-nitro naphthalene
15. a. 1-chloronaphthalene
16. b. 1:09
17. c. decalin
18. b. 2- naphthalene sulphonic acid
19. c. 1st or 2nd position
20. b. 61 K cal

Section B **3x2 = 6**

21. Define nitroalkanes?

Nitro alkanes are derivatives of alkanes. They are isomeric to nitrites (esters) classified as primary, secondary and tertiary depending on the nature of carbon atom to which nitro group is linked.



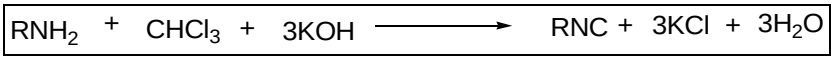
Primary nitro alkane, Secondary Nitro alkane, Tertiary nitro alkane —NO_2 group is an ambident group. If it attacks through nitrogen. It is called nitro and if it attacks through oxygen atom, it is called nitrite. Hence nitrites and nitro compounds are isomers.

22. Give any four physical properties of nitro alkanes?

- Aliphatic nitro alkanes are colourless and the aromatic nitro alkanes are yellow oily liquids.
- Pleasant and bitter almond odour
- Aliphatic compounds sparingly soluble and aromatic compounds are insoluble in water
- High boiling and melting points.

23. Write a note on carbylamines test?

The primary amine react with chloroform in the presence of alkali to form isonitriles which have offensive smell is known as carbylamines test. This reaction is used to distinguish the primary amine from secondary and tertiary amine.



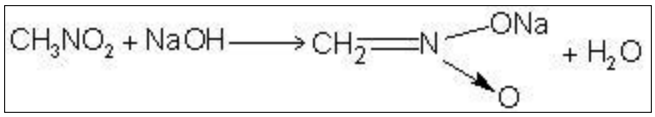
Section C **3x8 = 24**

24. (a) Write a note on chemical properties of Aromatic Nitroalkanes?

1. Nitroalkane on reduction with H_2/Ni produce 1^o amines while alkyl nitrites produce alcohols and NH_3

$$CH_3CH_2NO_2 \xrightarrow{[6H]} CH_3CH_2NH_2 + H_2O$$
$$1^o \text{ amine}$$

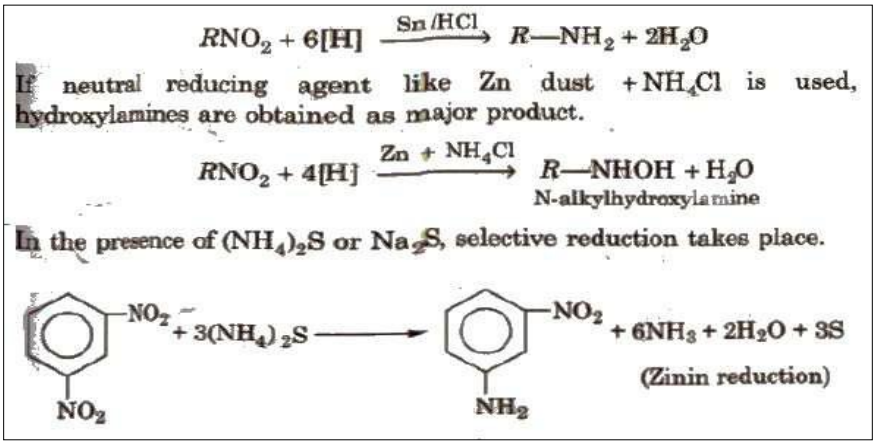
2. Nitroalkanes do not get hydrolysed in basic conditions while nitrites produce alcohols



$CH_3\ O - N = O + NaOH \longrightarrow CH_3OH + NaNO_2$

3. Reduction

With Sn/HCl or catalytic hydrogenation, nitroalkanes are reduced to amines.



Nitrobenzene gives different products with different reagents and in different mediums.

Medium	Reagent	Product
Acid	Sn/HCl	aniline
Neutral	Zn/NH_4Cl	N-phenyl hydroxylamine
	$Na_3AsO_3/NaOH$	azoxybenzene ($C_6H_5N{=}\overset{\overset{O}{\uparrow}}{N}C_6H_5$)
Alkaline	$Zn/NaOH, CH_3OH$	azobenzene
	$Zn/NaOH, C_2H_5OH$	hydrazobenzene
Metallic hydride	$LiAlH_4$	aniline
Electrolytic	dil H_2SO_4	*p*-aminophenol

(ii) Action of HNO_2

1° nitroalkane gives nitrolic acid which gives red colour with NaOH.

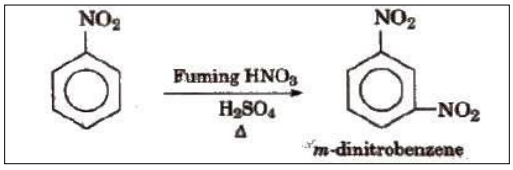
$$RCH_2NH_2 \xrightarrow[-H_2O]{HNO_2} \underset{\text{nitrolic acid}}{RC(NO_2){=}NOH} \xrightarrow{NaOH} \underset{\text{(red)}}{RC(NO_2){=}NONa}$$

2° nitroalkanes give pseudonitrol with HNO_2.

$$R_2CH(NO_2) \xrightarrow[-H_2O]{HNO_2} \underset{\substack{|\\ NO_2\\ \text{pseudonitrol}}}{R_2C{-}NO} \xrightarrow{NaOH} \text{Blue}$$

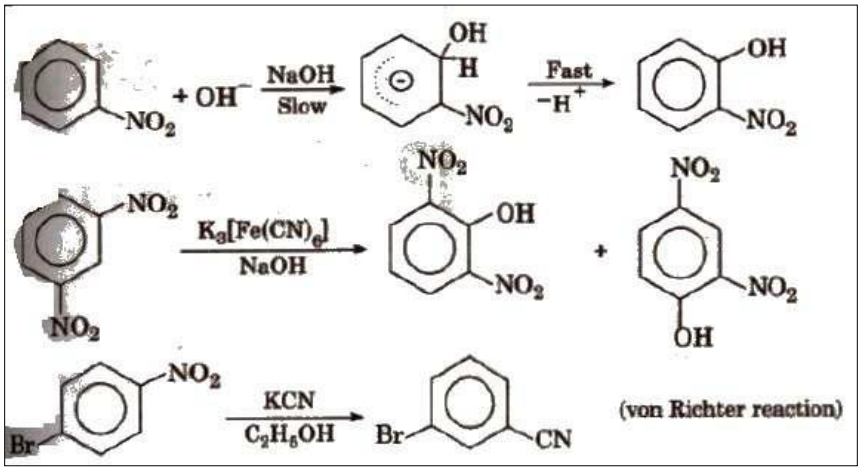
3° nitroalkanes does not react with HNO_2

4. **Electrophilic** substitution on nitration, nitrobenzene gives m-dinitrobenzene (as -NO_2 is a m-directing group and strongly deactivating).



It does not give Friedel-Craft's alkylation.

5. **Nucleophilic** substitution reaction -NO_2 group activates the ring towards nucleophilic substitution.



(or)

(b) <u>Explain the preparation and physical properties of aliphatic nitro compounds</u>?

(i) From alkyl halides:

Alkyl halides react with silver nitrite in ethanolic solution to give nitro compounds. Alkyl nitrite is formed in minor quantity. This reaction is used to prepare 1^o nitro compounds primarily while $2^o$and 3^o halides give major proportion of alkenes due to β – elimination. Contrary to this alkali nitrites give alkyl nitrites as major product. This is due to ionic nature of alkali nitrite.

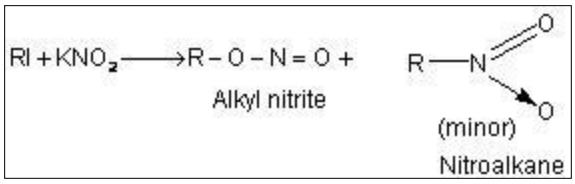
But if the reaction is carried out in solvents like DMF or DMSO, then even $NaNO_2$ or KNO_2 give good yield (about 60%) of nitro compound.

Reactions:

$$R—I + AgNO_2 \longrightarrow RNO_2 + AgI$$

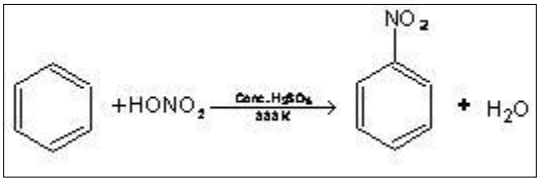
$$C_2H_5I + AgNO_2 \longrightarrow C_2H_5NO_2 + AgI$$

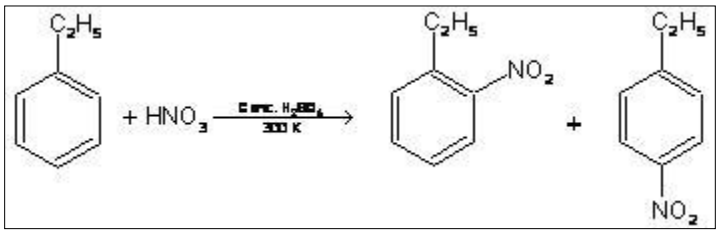
Nitroethane



(ii) Nitration:

Nitro derivatives of aromatic compounds like nitrobenzene are produced when benzene is allowed to react with nitrating mixture.(conc. HNO_3/conc.H_2SO_4).

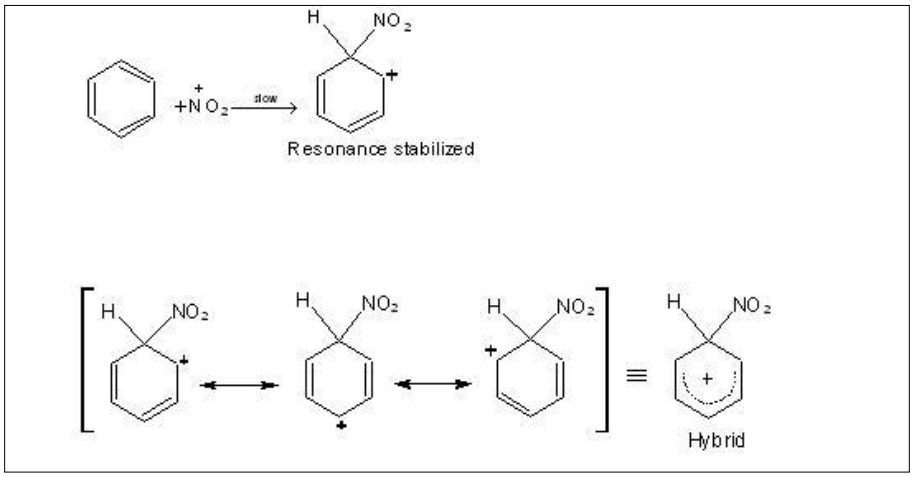




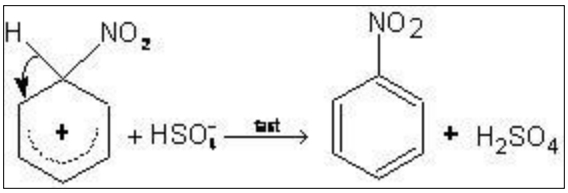
Mechanism:

Generation of nitronium ion

Attack of the nitronium ion NO_2^+ on benzene molecule



Loss of proton:



Nitrobenzene

Direct nitration of alkane involves vapour phase nitration at high temperature.

$$R — H + HONO_2 \xrightarrow[675\ K]{} R — NO_2 + H_2O$$

low yield

Problem faced in the method is that at such high temperature, a mixture of nitro alkanes is formed due to C – C cleavage.

e.g. $CH_3CH_2CH_3 + HNO_3 \longrightarrow CH_3CH_2CH_2NO_2 + CH_3CH_2NO_2 + CH_3NH_2$ + other products

(iii) From amines:

3^o nitroalkanes can be produced as follows:

$$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{\underset{|}{C}}}-NH_2 \longrightarrow CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{\underset{|}{C}}}-NO_2 + 2H_2O$$

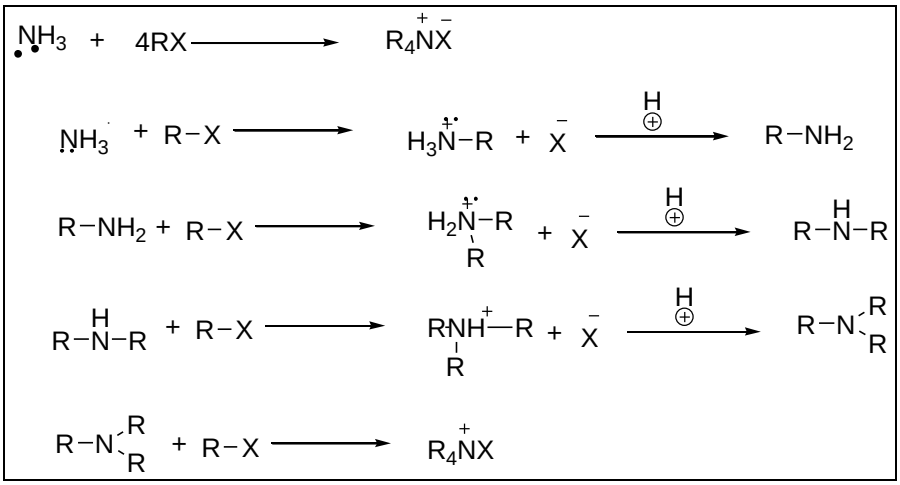
3^o butylamine (83% yield)

Physical Properties

- Aliphatic nitro alkanes are colourless.
- Pleasant odour
- Aliphatic compounds sparingly soluble because it has high density than H_2O.
- High boiling and melting points due strong internal interaction.

25. <u>(a) Give an account of Hofmann's degradation with mechanism?</u>

The ammonia react with Alkyl halides to form primary, secondary and tertiary amines to the corresponding steps. In each steps one of the H atom from ammonia replaced by alkyl® group. And finally reaction ends with formation of quatnary ammonium salt.



This is also applicable for $C_6H_5CH_2X$ type compounds. In this reaction alkyl halide reacts with ammonia to form primary amine as a nucleophile in the first step. Then the formed nucleophile reacts with another alkyl halide to form secondary amine. The secondary amine also act as nucleophile. Then it reacts with another RX to produce tertiary amine. Finally, this tertiary amine reacts with another RX to produce Quatnary ammonium salt.

(or)

(b) **How will you distinguish 1°,2° and 3° amines by using Nitrous acid and Hinsberg's method ?**

a. Hofmann's method:

Diethyloxalate is called Hofmann's reagent with which mixture of amines is treated.

- 1° amine forms solid dialkyl oxamide $(CONHR)_2$
- 2° amine forms liquid dialkyl oxamlc ester$(CONR_2\text{-}COOC_2H_5)$
- 3° amines do not react

b. **Hinsberg's method:**

Amines serve as nucleophiles in attacking the sulfonyl chloride electrophile, displacing chloride. The sulfonamides resulting from primary and secondary amines are poorly soluble and precipitate as solids from solution:

$$PhSO_2Cl + 2\ RR'NH \rightarrow PhSO_2NRR' + [RR'NH_2]Cl$$

For primary amines (R' = H), the initially formed sulfonamide is deprotonated by base to give water-soluble sulfonamide salt ($Na[PhSO_2NR]$):

$$PhSO_2N(H)R + NaOH \rightarrow Na^+[PhSO_2NR^-] + H_2O$$

Tertiary amines promote hydrolysis of the sulfonyl chloride functional group, which affords water-soluble sulfonate salts.

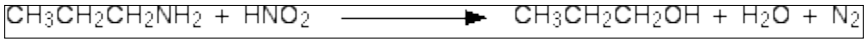
$$PhSO_2Cl+R_3N+H_2O\rightarrow R_3NH^+[PhSO^-_3]$$

c. **Nitrous acid method:**

Primary amines and nitrous acid

The main observation is a burst of colourless, odourless gas. Nitrogen is given off.

Amongst the products you get an alcohol where the $-NH_2$ group has been replaced by OH. (taking 1-aminopropane as an example for single step explanation):



$$CH_3CH_2CH_2NH_2 + HNO_2 \longrightarrow CH_3CH_2CH_2OH + H_2O + N_2$$

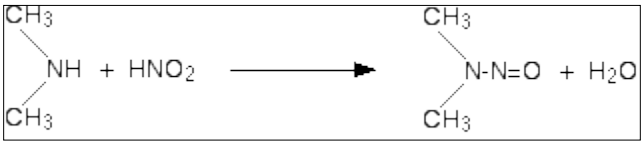
but the propan-1-ol will be only one product among many - including propan-2-ol, propene, 1-chloropropane, 2-chloropropane and others.

The nitrogen, however, is given off in quantities exactly as suggested by the equation. By measuring the amount of nitrogen produced, you could use this reaction to work out the amount of amine present in the solution.

Secondary amines and nitrous acid

This time there isn't any gas produced. Instead, you get a yellow oil called a nitrosamine. These compounds are powerful carcinogens.

For example:



$$(CH_3)_2NH + HNO_2 \longrightarrow (CH_3)_2N\text{-}N{=}O + H_2O$$

Tertiary amines and nitrous acid

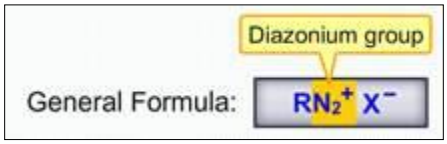
Again, a quite different result is occurrence of colourless solution.

All that has happened is that the amine has formed an ion by reacting with the acid present. With trimethylamine, for example, you would get a trimethylammonium ion, $(CH_3)_3NH^+$.

26. <u>(a) Briefly explain the structure, preparation and properties of benzene diazonium chloride?</u>

Benzene Diazonium Chloride ($C_6H_5N_2^+;Cl^-$)

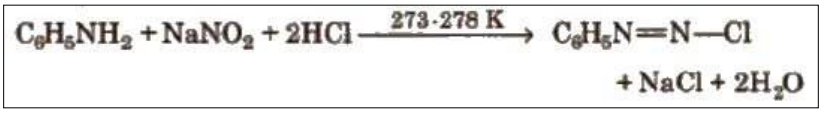
Diazonium salts have the general formula



Where X = Cl^-, Br^-, HSO^{4-}, BF^{4-}...etc

Preparation

Diazotisation reaction:



$$C_6H_5NH_2 + NaNO_2 + 2HCl \xrightarrow{273\text{-}278\ K} C_6H_5N{=}N{-}Cl + NaCl + 2H_2O$$

The excess acid in diazotisation reaction is necessary to maintain proper acidic medium for the reaction and to prevent combination of diazonium salt formed with the undiazotised amine. Diazonium salts are prepared and used in aqueous solutions because in solid state, they explode.

Properties

It is a colourless crystalline solid, soluble in water.

It has tendency to explode when dry.

Reactions Benzene diazonium chloride undergoes two main types of reaction

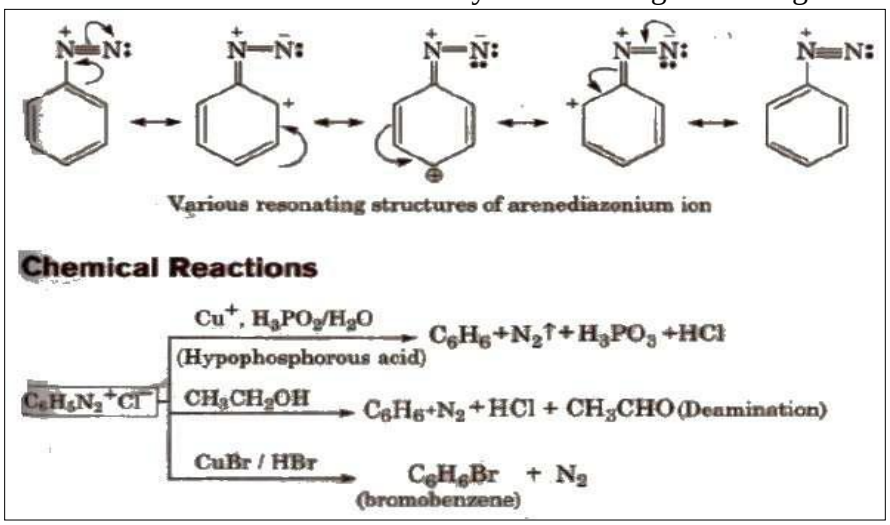
• **Substitution of the diazonium group** *nitrogen expelled*

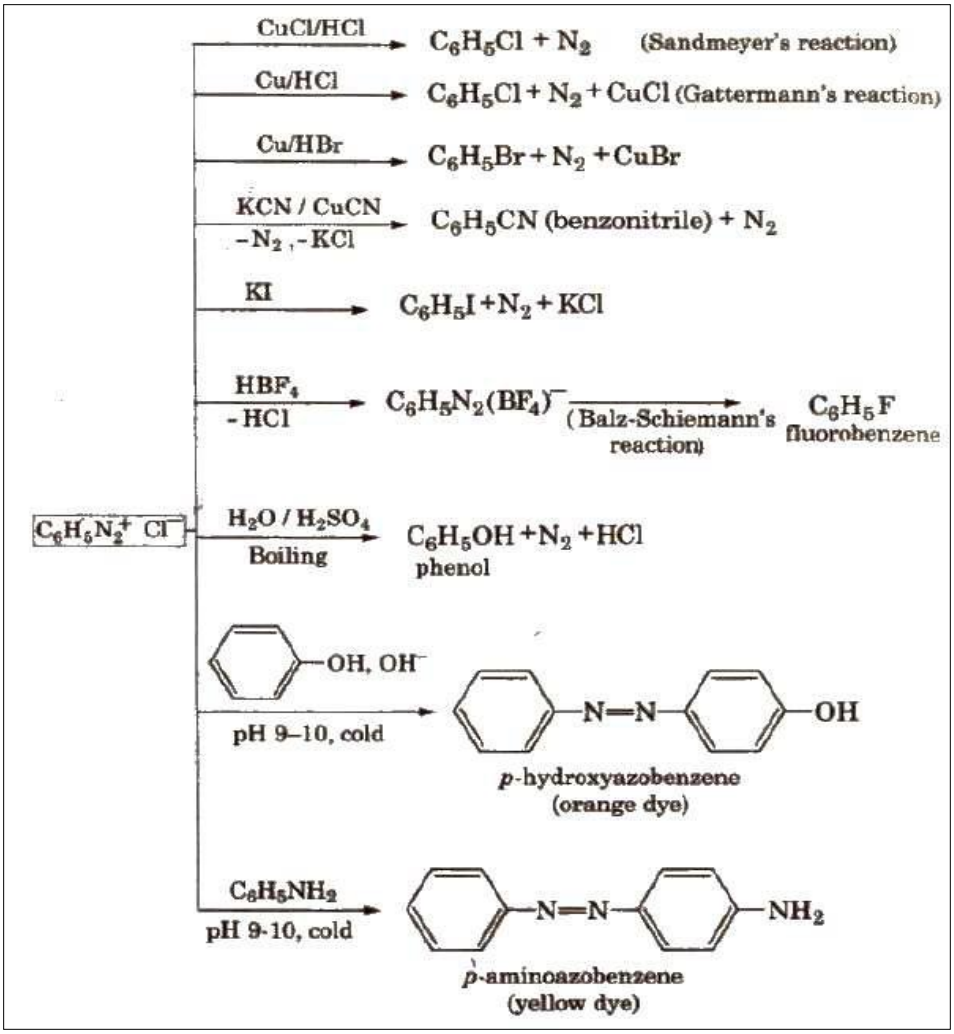
• **Coupling reactions** *the nitrogen atoms are retained*

Aryl diazonium salts are used as intermediates to synthesise a wide variety of organic compounds. Primary alkyl diazonium ions are not very stable. They decompose easily and tend to be explosive when dry. Aryl diazonium salts are stable only for short times at low temperatures. Resonance structures help to stabilise the ion by delocalising the positive charge around the aromatic ring.

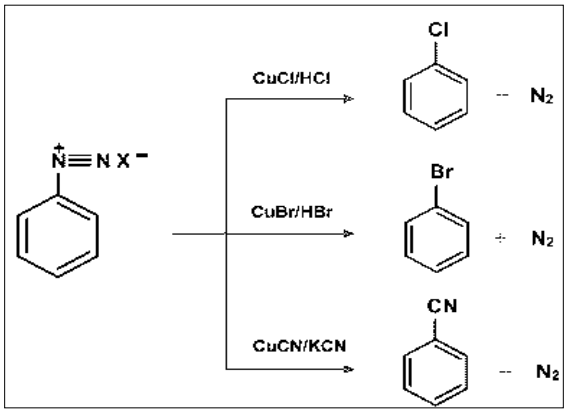
Stability of Arenediazonium salts

It is relatively more stable than the alkyldiazonium salt. The arene diazonium ion is resonance stabilised as is indicated by the following resonating structures:

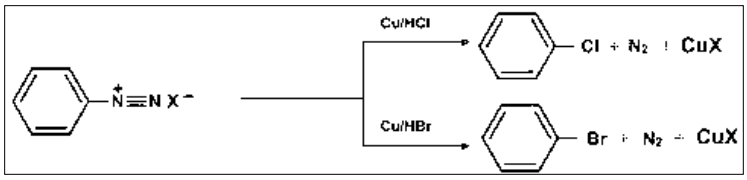




In the **Sandmeyer reactions**, diazonium groups are replaced by chloride, bromide or cyanide in the presence of copper (I) ions.



In the **Gatterman reactions**, diazonium groups are replaced with Chlorine (or) Bromine by treating the diazonium salt solution with haloacid in the presence of copper powder.



(or)

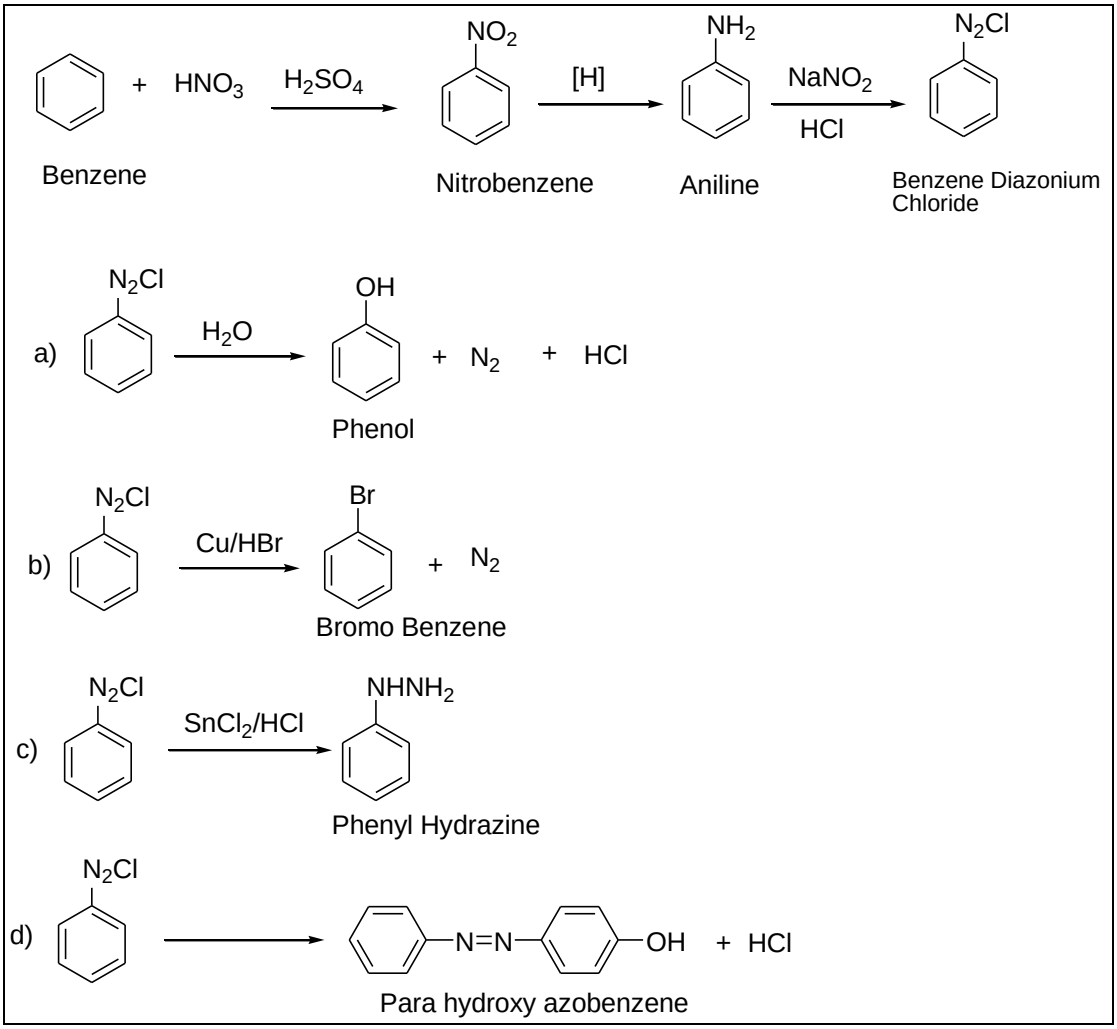
(b) Starting with benzene outline the synthesis of following compounds using diazonium salts as intermediates?

a. Phenol

b. Bromobenzene

c. Phenylhydrazine

d. Parahydroxyazobenzene



[17CHU303] **Reg. No……**

KARPAGAM ACADEMY OF HIGHER EDUCATION
COIMBATORE-641 021
(For the candidates admitted from 2016 & Onwards)

B.Sc., DEGREE INTERNAL EXAMINATION, SEP- 2018
CHEMISTRY
INTERNAL TEST-III
Organic Chemistry-III
(Nitrogen containing functional groups, heterocyclic compounds and Natural products)

Time: 2 Hours **Maximum: 50 marks**

Date: 9.10.2018

PART A **(20 x 1 =20)**

Answer all Questions

1. Fischer's synthesis is used to prepare
   a. Quinoline b. Isoquinoline c. Indole d. Pyran

2. To prepare 2-alkyl indole by the cyclodehydration of o-acyl amidotoluene is carried out with
   a. Sodium ethoxide b. Zinc chloride c. Potassium tertiary butoxide d. Tin and HCl

3. The starting material in Pomeranz Fritsch synthesis is
   a. Phenyl ethyl amine b. aminoaceta c. Aryl ethylamine and aldehydes d. aniline

4. Acetonyl acetone on dehydration with phosphorous pentoxide gives
   a. Furan b. pyrrole c. Thiophene d. pyran

5. The alternate name of indole is
   a. Quinoline b. Isoquinoline c. benzopyrroled. indole

6. In Lipps synthesis of indole the starting material is
   a. o-amino chlorostyrene b. o-hydroxy chlorostyrene c. o-nitro chlorostyrene
   d. o-chloro chlorostyrene

7. In the synthesis of quinoline o-amino benzaldehyde reacts with
   a. Acetaldehyde b. o-amino chlorostyrene c. o-hydroxy chlorostyrene
   d. Maleic anhydride

8. Ammonium mucate is distilled in the presence of glycerol gives
   a. Furan b. pyrrole c. thiophene d. pyridine

9. The catalyst used in the Fischer indole synthesis is
   a. Zinc chloride b. Vanadium pentoxide c. Chromium oxide d. Sulphuric acid

10. Alkaloids are
a. Weakly basic b. strongly basic c. weakly acidic d. strongly acidic

11. The reagent used in the Emde degradation is
a. sodium amalgam b. Sodium/ethanol c. Sodium nitrate d. Fe/HCl

12. Heroin is a
a. CNS drug- stimulants b. CNS drug- Depressan c. CNS drug- Hallucinogens
d. Psycho-active drug

13. Occur in the plant sources as the salt of acids, such as: oxalates, tannates
a. Alkaloids b. terpenes c. steroids d. carbohydrates

14. In Hoffmann exhaustive methylation, the Second step is
a. Formation of quarternary salt b. Conversion of quarternary salt in to hydroxide
c. Heating the quarternary hydroxide d. Elimination of alkene

15. Morphine is a
a. Pyrrolidine type alkaloids b. Quinoline alkaloid c. Tropane alkaloids
d. Isoquinoline alkaloid

16. The chief constituents of essential oils are
a. Monoterpenes and sesquiterpenes b. Diterpenes c. triterpenes d. tetraterpenes

17. Triterpenes consists of
a. 10 carbon atoms b. 20 carbon atoms c. 30 carbon atoms d. 15 carbon atoms

18. Terpenes are built up by condensation of isoprene units by either a 1-4 linkage (head to tail) is called
a. Hofmann rule b. Isoprene rule c. Zaysteff rule d. Flemings rule

19. Example for Tropane alkaloid
a. Hygrine b. Quinine c. Atropine d. Caffeine

20. Example for CNS drug- stimulants
a. Nicotine b. Benzodiazepines c. Psilocybin d. Cannabis

PART - B (3 x 2 =6)

Answer all Questions

21. How quinoline is prepared from Friedlander's synthesis.
22. How isoquinoline is prepared from cinnamaldehyde
23. What is meant by isoprene rule?

PART - C (3 x 8 =24)

Answer all Questions

24. a. How quinoline is prepared by (i) Skraup synthesis (ii) The Dobner-Miller synthesis

OR

b. Write note on Pictet-Spengler reaction and Pomeranz-Fritsch reaction

25. a. How indole is prepared by Fischer indole synthesis. Explain the mechanism

OR

b. a. Explain the structure elucidation and synthesis of nicotine

26. a. Explain the Occurrence, classification, rule in terpenes

OR

b. Explain with suitable examples (i) Hoffmann's exhaustive methylation, (ii) Emde's modification.

[17CHU303] **Reg. No……**

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B.Sc., DEGREE INTERNAL EXAMINATION, SEP- 2018
CHEMISTRY
INTERNAL TEST-III
Organic Chemistry-III
(Nitrogen containing functional groups, heterocyclic compounds and Natural products)

Time: 2 Hours **Answer Key** **Maximum: 50 marks**

PART A (20 x 1 =20)

Answer all Questions

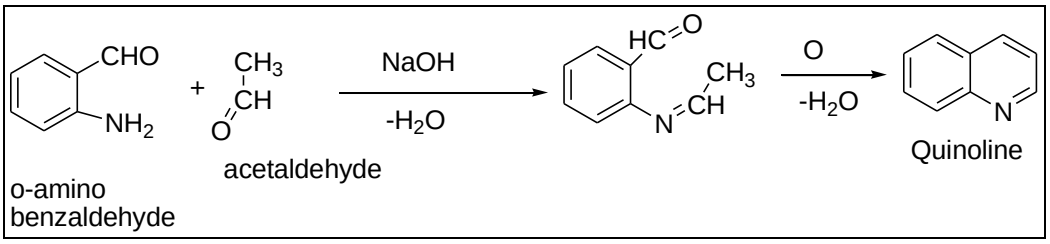
1. c. **Indole**
2. c. **Potassium tertiary butoxide**
3. c. **Aryl ethylamine and aldehydes**
4. **a. Furan**
5. c. **benzopyrrole**
6. **a. o-amino chlorostyrene**
7. **a. Acetaldehyde**
8. b. **pyrrole**
9. a. **Zinc chloride**
10. **a. Weakly basic**
11. a. **sodium amalgam**
12. b. **CNS drug- Depressan**
13. **a. Alkaloids**
14. b. **Conversion of quarternary salt in to hydroxide**
15. d. **Isoquinoline alkaloid**
16. **a. Monoterpenes and sesquiterpenes**
17. c. **30 carbon atoms**
18. b. **Isoprene rule**
19. c. **Atropine**
20. a. **Nicotine**

PART - B (3 x 2 =6)

Answer all Questions

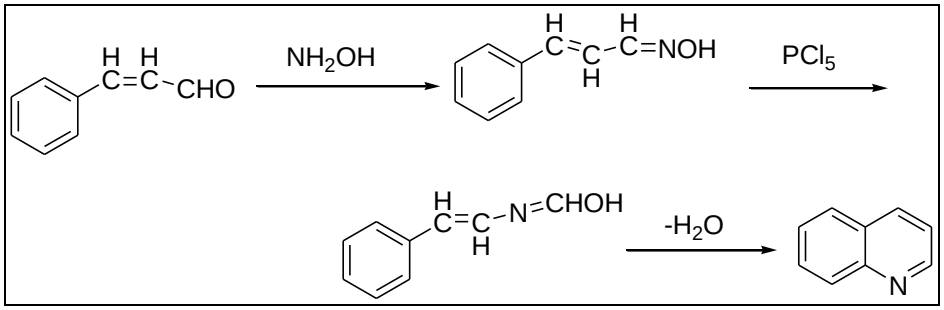
21. How quinoline is prepared from Friedlander's synthesis.

Quinoline is obtained by condensing the o-aminobenzaldehyde with acetaldehyde in the presence of sodium hydroxide solution.



22. How isoquinoline is prepared from cinnamaldehyde

Cinnamaldehyde reacts with hydroxyl amine to form its oxime it then reacts with PCl_5 to form isoquinoline.



23. What is meant by isoprene rule?

Isoprene Rule

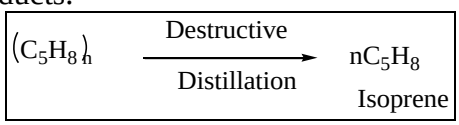
In 1887, Wallach enunciated the famous isoprene rule which may be stated as follows:-

"The skeleton structures of all naturally occurring terpenoids are built up of isoprene units".

From the above rule it follows that the divisibility into isoprene unit is regarded as a necessary condition to be satisfied by every naturally occurring terpenoid.

The isoprene rue has been deduced from the following facts:-

a) The empirical formula of almost all the naturally occurring terpenoids is C_5H_8.
b) The thermal decomposition of almost all terpenoids gives isoprene as one of the products.
   For example, rubber (polyterpenoid) on destructive distillation yields isoprene as one of the decomposition products.



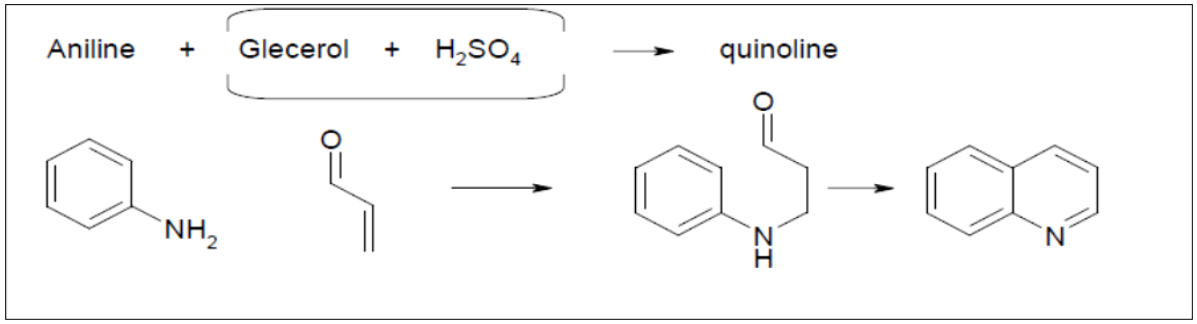
c) Isoprene rule has been confirmed by the fact that under special experimental conditions, isoprene undergoes polymerization to yield various terpenoids.

PART - C (3 x 8 =24)

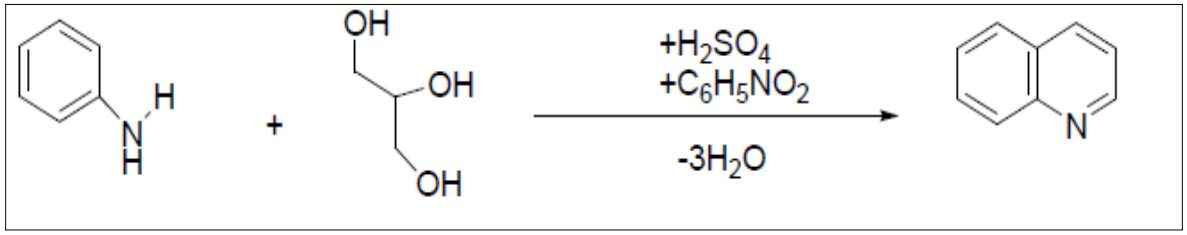
Answer all Questions

24. a. How quinoline is prepared by (i) Skraup synthesis (ii) The Dobner-Miller synthesis

i) Quinoline Skraup Synthesis

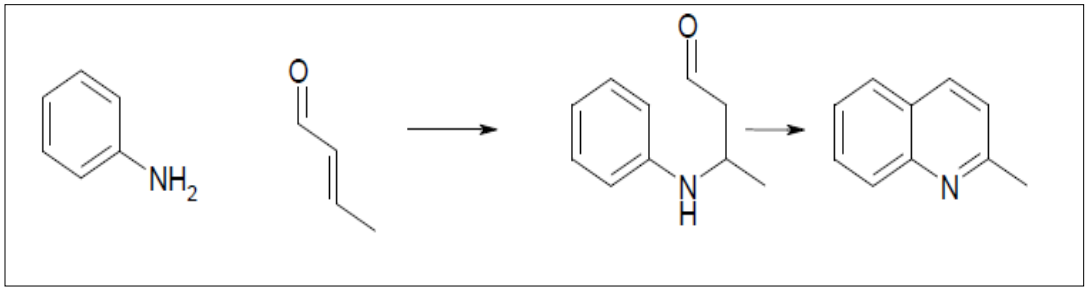


In the archetypal Skraup reaction, aniline is heated with sulfuric acid, glycerol, and an oxidizing agent such as nitrobenzene to yield quinoline.



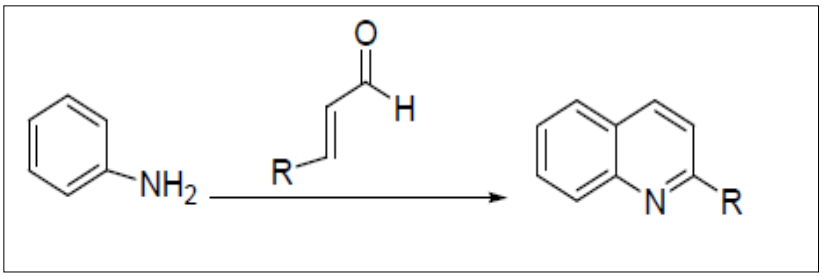
In this example, nitrobenzene serves as both the solvent and the oxidizing agent. The reaction, which otherwise has a reputation for being violent, is typically conducted in the presence of ferrous sulfate. Arsenic acid may be used instead of nitrobenzene and the former is better since the reaction is less violent.

ii) Doebner-von Millar



The **Doebner–Miller reaction** is the organic reaction of an aniline with α,β-unsaturated

carbonyl compounds to form quinolines.



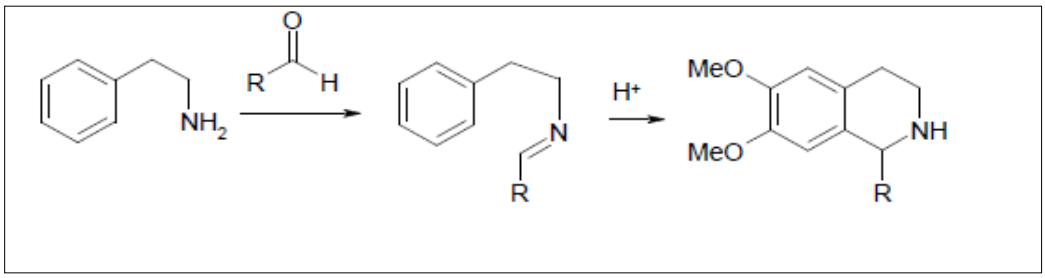
This reaction is also known as the **Skraup-Doebner-Von Miller quinoline synthesis**, and is named after the Czech chemist Zdenko Hans Skraup (1850–1910), and the Germans Oscar

Döbner (Doebner) (1850–1907) and Wilhelm von Miller (1848–1899). When the α,β-unsaturated carbonyl compound is prepared in situ from two carbonyl compounds (via an Aldol condensation), the reaction is known as the **Beyer method for quinolines**. The reaction is catalyzed by Lewis acids such as tin tetrachloride and scandium(III) triflate and Brønsted acids such as *p*-toluenesulfonic acid, perchloric acid, amberlite and iodine.

OR

b. Write note on Pictet-Spengler reaction and Pomeranz-Fritsch reaction

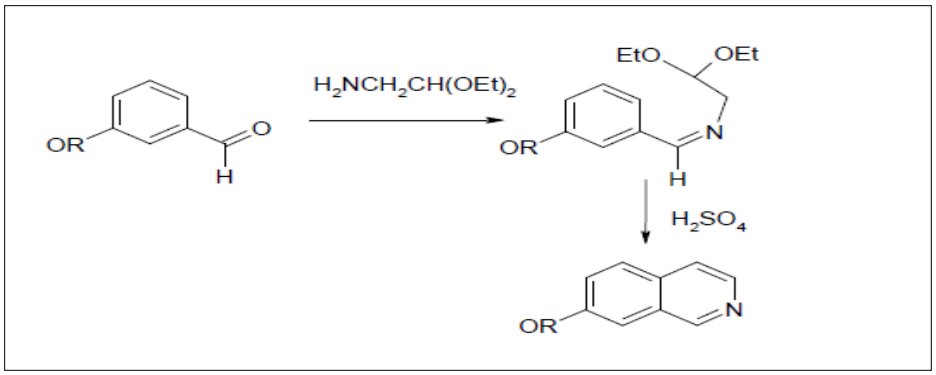
Pictet-Spengler Synthesis



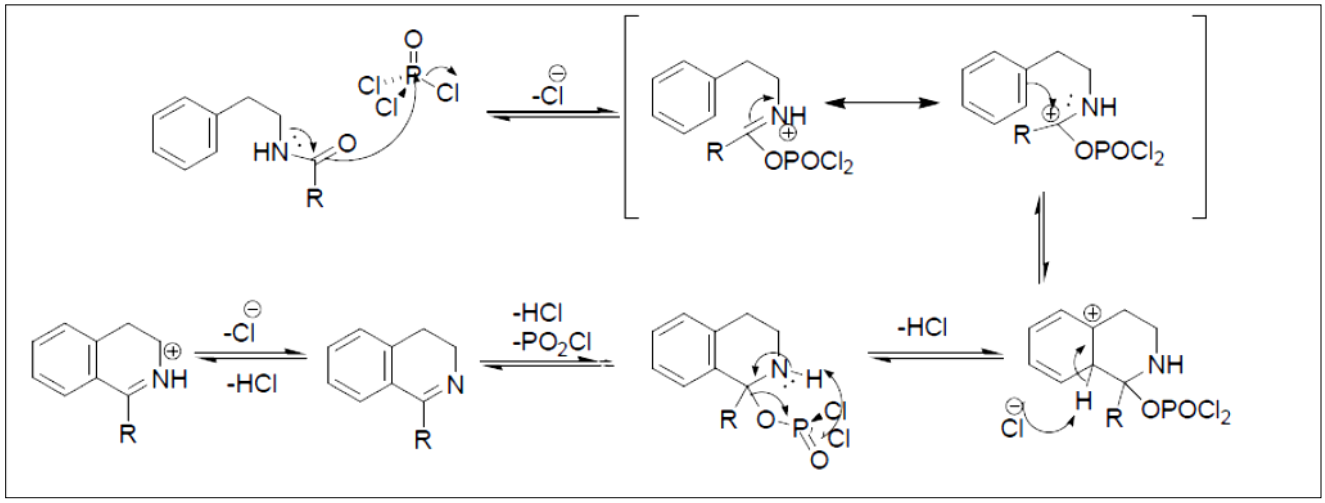
The Pictet-Spengler reaction is an organic reaction used to convert a β-arylenylamine and an aldehyde or ketone to a tetrahydroisoquinoline using an acid catalyst. The mechanism begins with protonation of the carbonyl oxygen by the acid which is subsequently attacked by the amine reagent. Proton transfer steps and the release of a water molecule results in a protonated imine intermediate, which then undergoes a 6-endo-trig cyclization reaction with loss of aromaticity of the aryl ring. A final deprotonation step restores the aromaticity and results in the tetrahydroisoquinoline product.

Pomeranz-Fritsch Synthysis

The aromatic aldehyde is condensed with an aminoacetal to form a Schiff base. The sulphuric acid act as catalyst to obtain isoquinoline

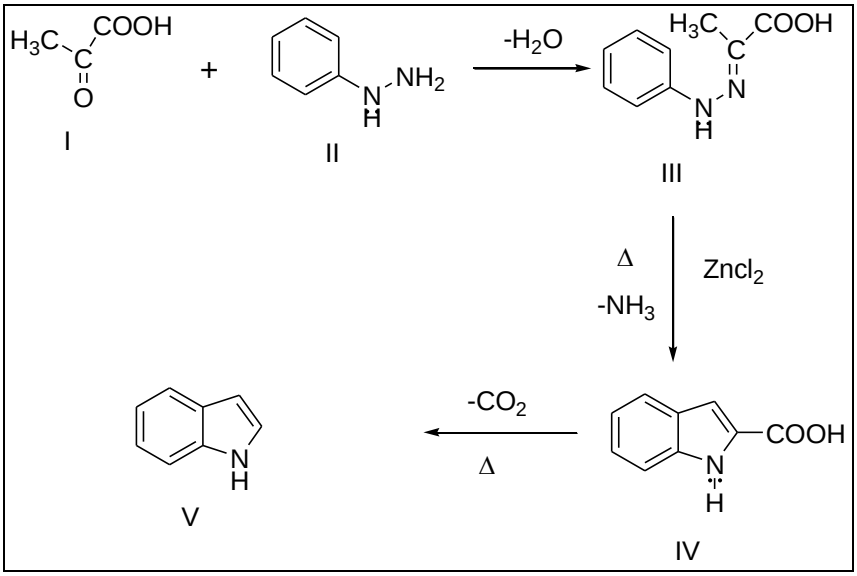


Mechanism



<u>25. a. How indole is prepared by Fischer indole synthesis. Explain the mechanism</u>

Pyruvic acid (I) is first treated with phenyl hydrazine (II). The corresponding phenyl hydrazone (III) is formed. The phenylhydrazone is heated with anhydrous zinc chloride or poly phosphoric acid. We get indole-2-carboxylic acid (IV) which on decarboxylation gives indole (V)



Properties

It is a crystalline solid.

Impure benzopyrrole has a strong unpleasant smell and pure one has a pleasant smell.

Pure one are used in perfumery for jasmine and orange blossom blends.

OR

b. Explain the structure elucidation and synthesis of nicotine

- Nicotine is the chief alkaloid of tobacco plant (nicotina tabacum)
- It accurs in the plant leaves as salts of malic acid and citric acid to the extent of 4 to 5%
- The alkaloid was named after the Frenchman Nicot who introduced tobacco in France in 1560

Isolation of nicotine

1. Waste parts of the tobacco plant are finely powdered and extracted with dilute acid. The water soluble salts of alkaloids are thus removed in solution, leaving the insoluble cellulose, chlorophyll etc behind.

2. The acid extract is then made basic with lime or NaOH and steam distilled.

Steam distillation separates the nicotine from water soluble non-volatile materials (sugars, inorganic salts& etc).

3. The distillate is acidified to about PH_3 with solid oxalic acid and concentrated to syrup.

On cooling, the crystalline salt of nicotine and oxalic acid separates. Other alkaloids not forming slightly soluble oxalates are left in the solution.

4. The crystalline nicotine oxalate is then transferred to a separating funnel and treated with excess of aqueous KOH. The nicotine thus set free rise to the surface as a brown oil and separated by extraction with ether.

5. The ethereal solution of the alkaloid is dried over solid anhydride KOH and the ether evaporated.

For further purification, the residue is fractionally distilled under vaccum.

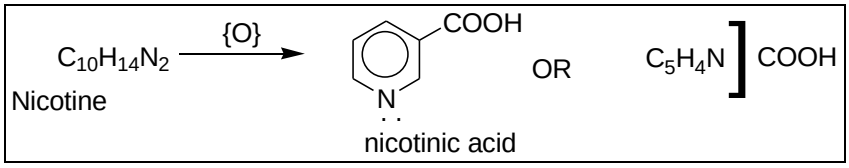
Properties:

1. Nicotine is one of the few alkaloids known to exist in a liquid form, colourless, boiling point 246^0 C.
2. It has to be tobacco –like smell and burning alkaline taste.
3. It is soluble in water and also in organic solvents such as ethanol, ether and benzene.
4. The natural alkaloids is Leavorotary $[\alpha]_D = -169^0$
5. It is deadly poison to animals and is used commercially as an insecticidal spray for plants and animals.
6. In small quantities, nicotine stimulates the nervous system for a while, which is followed by depression.

A low nicotine content tobacco is used for smoking purpose even though it is definitely injurious to health, causing diseases like asthma and lung cancer.

Structure:

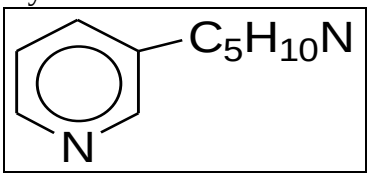
1. Elemental analysis and molecular weight determination leads to the molecular formula $C_{10}H_{14}N_2$ for nicotine.
2. It absorbs 2 molecules of CH_3I, suggesting the tertiary nature of both the nitrogen atoms.
3. On oxidation with chromic acid, nicotine yields nicotinic acid (pyridine-3-carboxylic acid).



This shows that the alkaloid contains a pyridine nucleus with a side chain at the 3-position.

That is the side chain has the composition ($C_{10}H_{14}N_2$-C_5H_4N) = $C_5H_{10}N$

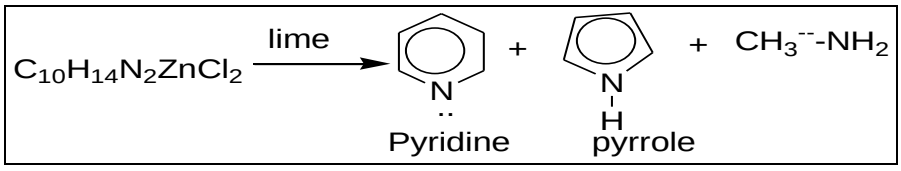
The formula for nicotine may be written as



From the above formula it is evident that the side chain must be saturated.

4. Nature and position of the side chain:

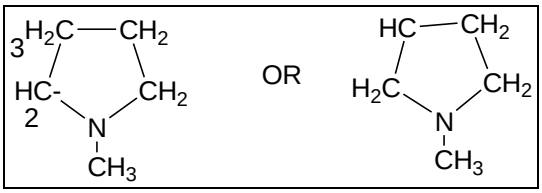
- The alkaloid forms an addition compound with Zinc chloride. $C_{10}H_{14}N_2ZnCl_2$, which when heated lime water yields pyridine, pyrrole and methylamine.



- This suggestion that the side chain, $C_5H_{10}N$ is a pyrrole derivative.

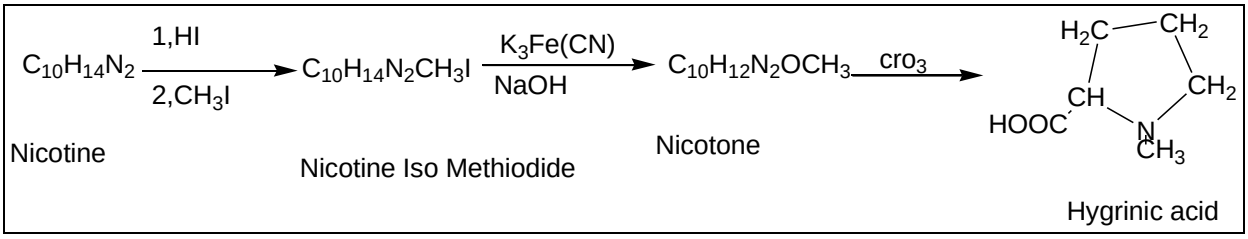
- When heated with concentrated hydriodic acid at 200-300^{0}C (Herzig and Meyer), Nicotine yields CH_3I, showing that methyl group is attached to N-atom.

  It appears that the side chain could be N-methyl pyrrolidine.



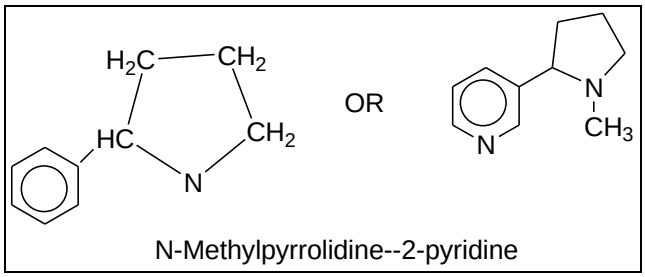
  However, the point of attachment of the side chain to the pyridine nucleus could be C_2 or C_3 as shown above

- Nicotine hydriodide when treated with CH_3I,forms nicotine isomethiodide which on oxidation with potassium ferriccyanide yields nicotine
- This on further oxidation with Cro_3 produces hygrinic acid



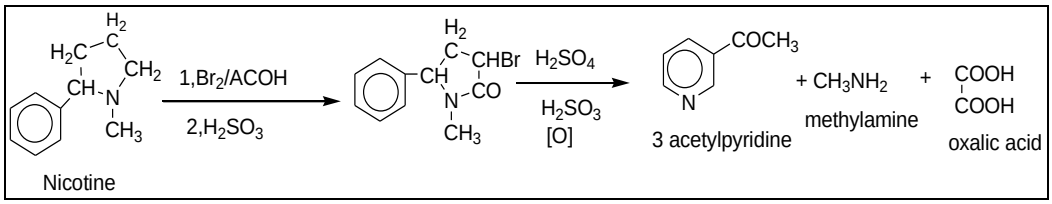
The formation of hygrinic acid as above proves beyond doubt that side chain ,N-methylpyrrolidine is attached to the pyridine rucles thorough C_2

5. From the foregoing considerations the structural formula of nicotine may be written

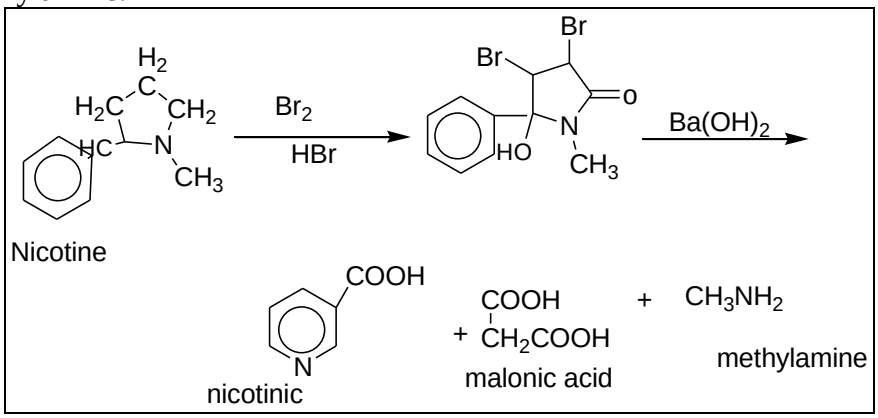


6. The above structure of nicotine is further confirmed us it explains the following reactions of the alkaloid admirably

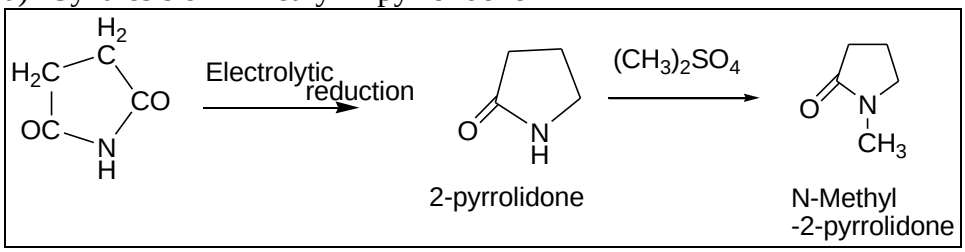
   - Nicotine when treated with bromine in acetic acid followed by aqueous sulphurous acid gives dibromonicotine, $C_{10}H_{10}ON_2Br_2$. This upon oxidation with mixture of sulphurous acid and sulphuric acid at 130 – 140^0 yields 3-aceetylphyridine ,oxalic acid and methylamide (pinner,1892)



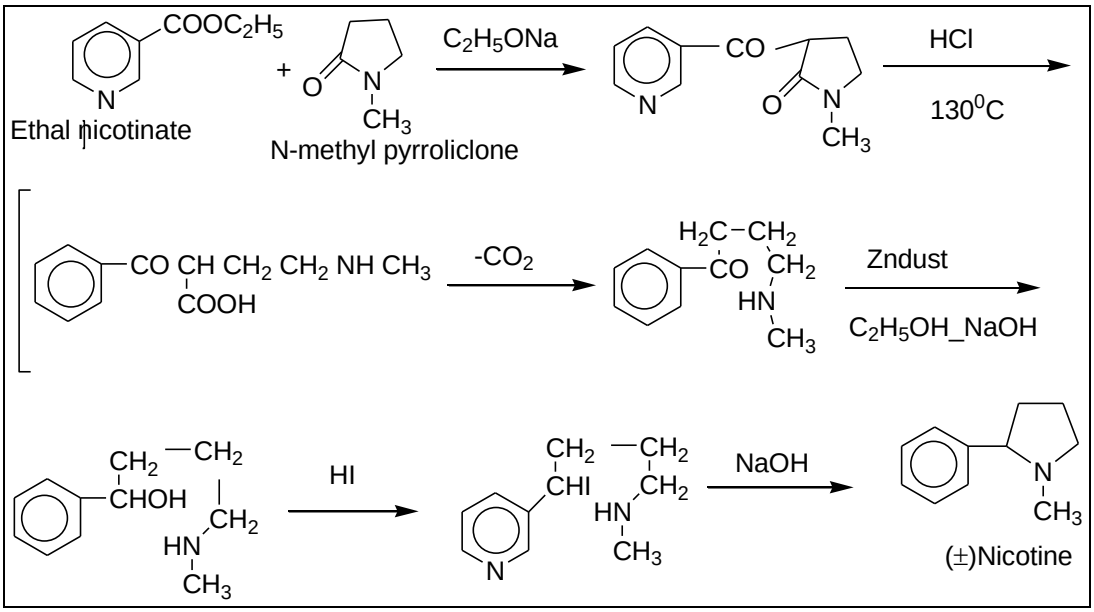
- Nicotine on reaction with bromine in hydrobromic acid gives which when heated with $Ba(OH)_2$ solution at 100^0C,yields nicotinic acid, malonic acid and methylamine.



7. Finally the structure of nicotine was confirmed by the following synthesis accomplished by spath (1928)
   a) Synthesis of N-methyl-2-pyrrolidone



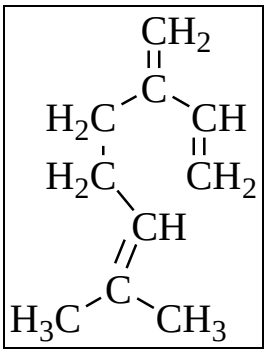
   b. Synthesis of nicotine
   - N-methyl-2-pyrrolidone produces as step(a) under goes reaction to yield nicotine

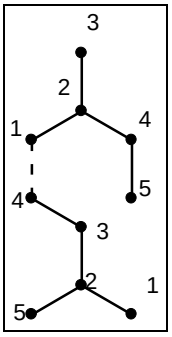


The dl-nicotine is resolved by means of (+)tartaric acid the synthetic (-)nicotine is identical with the natural compound.

26. a. Explain the Occurrence, classification, isoprene rule in terpenes

- Originally, the term "terpene" was employed to describe a mixture of isomeric hydrocarbons of the molecular formula $C_{10}H_{16}$ occurring in the terpentine and many essential oils which are obtained from the sap and tissues of certain plants and trees.
- The oxygenated derivatives like alcohols, aldehydes, ketones, etc. at the time were called camphor's.
- As more compounds relating to terpenes and camphor's were discovered with the pace of time, both the terms "terpenes" and "camphors" were amalgamated into a single term called "terpenoids".
- The *Modern definition* of this term is,
  It includes hydrocarbons of plant origin of the general formula $(C_5H_8)_n$ as well as their oxygenated, hydrogenated and dehydrogenated derivatives.
- As terpenoids are composed of isoprene units, these are sometimes called "isoterpenoids".
- Not only the carbon skeletons of terpenoids are divisible into isoprene units but the terpene hydrocarbons are usually exact multiplies of C_5H_8.
- An example is mycerene ($C_{10}H_{16}$) which has a carbon skeleton divisible into 2 isoprene units.





Importance

- In the recent part, biological activity of various substances has been related with terpenoids.
- Many sesquiterpenes have been found to be active against experimental tumours and the plant growth hormones like gibberellins and diterpenoids.
- As some terpenoids exhibit biological activity viz insecticidal anthelmintic or antiseptic activity. These are used in pharmacy.

Occurrence

- Terpenoids are most widespread, chemically interesting and provide structure of great diversity.
- Although the majority of terpenoids occur in plant kingdom, a few of them have also been obtained from other source.
- Most of the fragment components of plants are volatile with steam distillation, solvent extraction or other treatment of the plant. These components are called essential oils.
- These have been used in perfumery from the earliest times
- The simple mono and sesquiterpenoids are the chief constituents of the essential oils.
- However, the di, tri-terpenoids, which are not steam volatile are obtained from plant and resins.
- Unlike mono and sesquiterpenoids, these compounds donot possess any perfumery value.
- The tetraterpenoids constitute a group of compounds called carotenoids.

Isolation

Due to their wide occurrence in nature, all the terpenoids could not be isolated and separated by a general method.

However, mono and sesqui-terpenoids have a common source. ie, essential oils and therefore isolation has been generalized, this is carried out in 2 steps.

1. Isolation of essential oils.
2. Separation of terpenoids from essential oils.

Isoprene Rule

In 1887, Wallach enunciated the famous isoprene rule which may be stated as follows:-

"The skeleton structures of all naturally occurring terpenoids are built up of isoprene units".

From the above rule it follows that the divisibility into isoprene unit is regarded as a necessary condition to be satisfied by every naturally occurring terpenoid.

The isoprene rue has been deduced from the following facts:-

d) The empirical formula of almost all the naturally occurring terpenoids is C_5H_8.
e) The thermal decomposition of almost all terpenoids gives isoprene as one of the products.
   For example, rubber (polyterpenoid) on destructive distillation yields isoprene as one of the decomposition products.

$$(C_5H_8)_n \xrightarrow[\text{Distillation}]{\text{Destructive}} nC_5H_8$$
Isoprene

f) Isoprene rule has been confirmed by the fact that under special experimental conditions, isoprene undergoes polymerization to yield various terpenoids.
   For example,
   i) Isoprene, when heated to 280ºC get dimerised to yield a widely distributed terpenoid called dipentene.

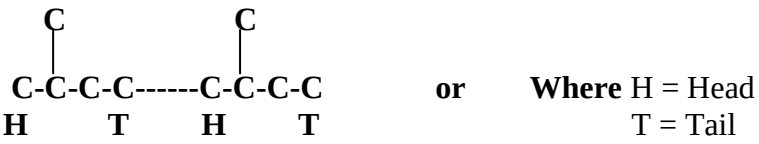
$$2\ C_5H_8 \xrightarrow{\text{Polymerization}} C_{10}H_{16}$$

   ii) Isoprene may be polymerized to yield a rubber like product.

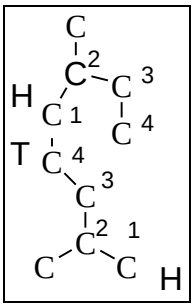
$$n\ C_5H_8 \xrightarrow{\text{Polymerization}} (C_5H_8)_n$$
Rubber (Polyterpenoid)

Special Isoprene Rule:-

- This rule proposed by ingold (1925), shows how the isoprene units in the terpenoid molecule are linked together.
- For this purpose, the branched end of the isoprene unit is considered as the head and the other end as the tail.
- According to the special isoprene rule, the isoprene units in terpenoids are linked in a head to tail fashion.
- Thus the basic carbon skeleton of a monoterpene according to the special isoprene rule will be as follows.



or **Where** H = Head
T = Tail



- It should be noted, however that this rule, which has proved very useful can only be used as a guiding principle and not as a fixed rule.
- Therefore, there are departures and violations of this rule in many compounds.

For example,

i) Certain terpenoids are known whose carbon content is not a multiple of five. For example,

Cryptone, a naturally occurring ketonic terpenoid contains nine carbon atoms and therefore, it cannot be divided into two isoprene units.

ii) Certain terpenoids are known whose carbon content is a multiple of five but cannot be divided in to two isoprene units.

iii) Certain terpenoids are also known in which the special isoprene rule is violated.
For example,

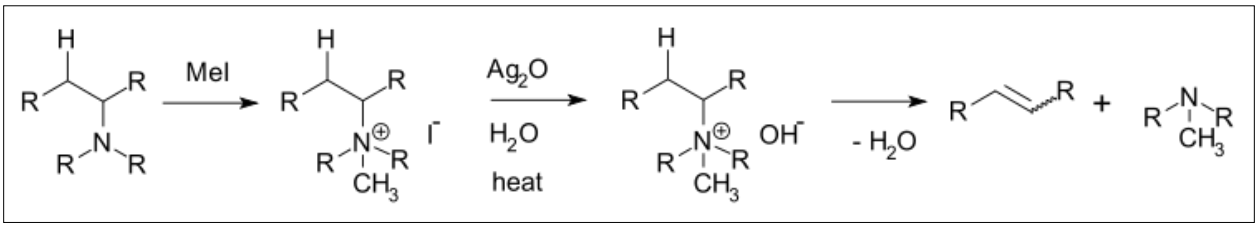
- Lavandulol is composed of two isoprene units of isoprene with the unusual linkage of tail to tail but not head to tail linkage.

OR

b. Explain with suitable examples (i) Hoffmann's exhaustive methylation, (ii) Emde's modification.

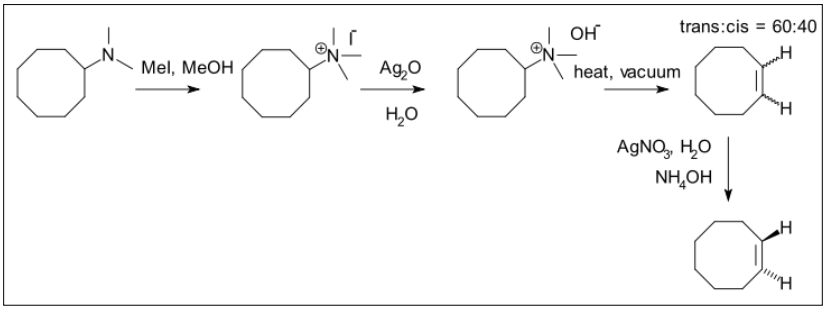
Hofmann's Exhaustive Methylation Method:

The principle of this method is that compounds, which contain the structural unit =CH=C–$N^+R_3OH^-$, eliminate a trialkylamine on pyrolysis at 200 °C or above to yield an olefin.
Hofmann elimination, also known as exhaustive methylation, is a process where a quaternary amine is reacted to create a Tertiary amine and an alkene by treatment with excess methyl iodide followed by treatment with silver oxide, water, and heat.



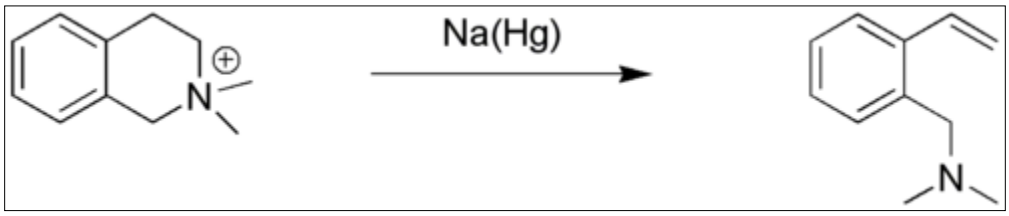
After the first step, a quaternary ammonium iodide salt is created. After replacement of iodine by an hydroxyl anion, an elimination reaction takes place to the alkene.

With asymmetrical amines, the major alkene product is the least substituted and generally the least stable, an observation known as the **Hofmann rule**. This is in direct contrast to normal elimination reactions where the more substituted, stable product is dominant (Zaitsev's rule).
The reaction is named after its discoverer, August Wilhelm von Hofmann.
An example is the synthesis of trans-cyclooctene:



In a related chemical test called **Herzig–Meyer alkimide group determination** a tertiary amine with at least one methyl group and lacking a beta-proton is allowed to react with hydrogen iodide to the quaternary ammonium salt which when heated degrades to iodomethane and the secondary amine

The **Emde degradation** (also called **Emde-reaction** or **Emde-reduction**) is a method for the reduction of a quaternary ammonium cation to a tertiary amine with sodium amalgam.



This organic reaction was first described in 1909 by the German chemist Hermann Emde and was for a long time of great importance in structure elucidation of many alkaloids, for example that of ephedrine. Alternative reducing agents exist for this reaction; for instance, lithium aluminium hydride.

Alkaloids are naturally-occurring organic compounds containing nitrogen moiety, and are usually heterocyclic in nature. They are nitrogen based organic compounds, with nitrogen enclosed in an heterocyclic ring. The alkyl amines are referred to as proalkaloids. Characteristics of alkaloids (1) They are basic in nature due to the presence of nitrogen in their ring. (2) They have complex structures. (3) They have bitter principles. (4) They are mostly obtained from plant materials. (5) They have high pharmacological and physiological activities. Examples of alkaloids are: (1) Quinine — an antimalarial drug isolated from a plant called Cinchonia officialis.

Reg. No.....

[16CHU303]

KARPAGAM UNIVERSITY

Karpagam Academy of Higher Education
(Established Under Section 3 of UGC Act 1956)
COIMBATORE – 641 021
(For the candidates admitted from 2016 onwards)

B.Sc., DEGREE EXAMINATION, NOVEMBER 2017

Third Semester

CHEMISTRY

ORGANIC CHEMISTRY III

(Nitrogen Containing Functional Groups, Heterocyclic Chemistry and Natural Products)

Time: 3 hours Maximum : 60 marks

PART – A (20 x 1 = 20 Marks) (30 Minutes)
(Question Nos. 1 to 20 Online Examinations)

PART B (5 x 2 = 10 Marks) (2 ½ Hours)
Answer ALL the Questions

21. Explain the Tautomerism present in aliphatic nitro compounds
22. Write short notes on Sandmeyer reaction
23. Write any one synthesis of furan
24. Explain with suitable examples what are five and six membered heterocycles
25. What is a terpene. Give an example

PART C (5 x 6 = 30 Marks)
Answer ALL the Questions

26. a. Discuss the action nitrous acid on primary, secondary and tertiary amines
OR
b. Write any three methods how nitro compounds are prepared

27. a. Starting from benzene diazonium chloride how to prepare
i) iodobenzene ii) Phenol iii) aminoazobenzene iv) Benzene
OR
b. What is diazotization? How toluene diazonium chloride is prepared in the laboratory. How phenol react with diazonium salts .

28. a. Explain Paal-Knorr synthesis to prepare furan and pyrrole
OR
b. How pyridine is prepared by Hantzsch synthesis

29. a. How indole is prepared by Fischer indole synthesis. Explain the mechanism
OR
b. How isoquinoline is prepared by Bischler Napieralski synthesis. Explain its mechanism

30. a. Explain how alkaloids are extracted from plant materials
OR
b. Explain the structure elucidation and synthesis of nicotine

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