AS PER PCI REGULATIONS

SECOND YEAR B. PHARM. | SEMESTER-IV

PHARMACEUTICAL ORGANIC CHEMISTRY-III

Dr. K. G. BOTHARA

NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

A Text Book of

PHARMACEUTICAL ORGANIC CHEMISTRY-III

As per PCI Regulations

Second Year B. Pharm.

Semester – IV

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Preface

Organic Chemistry deals with the name of composition of organic matter and more specifically the reasoning for the changes which it undergoes.

In the last three decades the ever growing volume and ever changing nature of our understanding about reaction mechanisms are witnessed. Author aims to describe the fundamental principles of organic chemistry with an emphasis on the characteristic reactions of various functional groups.

The text is divided into 5 units. Unit 1 and Unit 2 are devoted to isomerism and types of isomerism. Unit 3 and Unit 4 deals with the nomenclature, method of preparation, chemical reactions and uses of heterocyclic compounds. The last unit includes reactions of synthetic importance. However, the wide scope of the subject has necessitated restrictions to keep the size of the book within reasonable limits.

I wish to place on record my sincere thanks to the publisher, Shri. D. K. Furia and Shri. Jignesh Furia for their kind co-operation. I am also indebted to my colleagues for giving many valuable suggestions, of which I have been glad to take advantage.

Suggestions from all corners of the profession are welcome. Author is responsible for any deficiencies or errors that remain and would be grateful if readers would call them to his attention.

Author

Pune
1 January, 2019

Syllabus

UNIT-I **10 Hours**

Stereoisomerism

Optical isomerism – Optical activity, enantiomerism, diastereoisomerism, meso compounds, Elements of symmetry, chiral and achiral molecules.

DL system of nomenclature of optical isomers, sequence rules, RS system of nomenclature of optical isomers

Reactions of chiral molecules

Racemic modification and resolution of racemic mixture. Asymmetric synthesis: partial and absolute

UNIT-II **10 Hours**

Geometrical isomerism

Nomenclature of geometrical isomers (Cis Trans, EZ, Syn Anti systems)

Methods of determination of configuration of geometrical isomers. Conformational isomerism in Ethane, n-Butane and Cyclohexane.

Stereoisomerism in biphenyl compounds (Atropisomerism) and conditions for optical activity.

Stereospecific and stereoselective reactions

UNIT-III **10 Hours**

Heterocyclic Compounds

Nomenclature and classification

Synthesis, reactions and medicinal uses of following compounds/derivatives Pyrrole, Furan, and Thiophene – Relative aromaticity, and reactivity of pyrrole, furan and thiopene.

UNIT-IV **8 Hours**

Synthesis, reactions and medicinal uses of following compounds/derivatives: Pyrazole, Imidazole, Oxazole and Thiazole.

Pyridine, Quinoline, Isoquinoline, Acridine and Indole. Basicity of pyridine, Synthesis and medicinal uses of Pyrimidine, Purine, azepines and their derivatives.

UNIT-V **7 Hours**

Reactions of Synthetic Importance

Metal hydride reduction ($NaBH_4$ and $LiAlH_4$), Clemmensen reduction, Birch reduction, Wolff Kishner reduction.

Oppenauer-oxidation and Dakin reaction.

Beckmanns rearrangement and Schmidt rearrangement.

Claisen-Schmidt condensation.

❖❖❖

Contents

Unit...I

STEREOISOMERISM

♦ **SYNOPSIS** ♦

1.1 INTRODUCTION

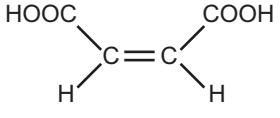
Stereochemistry helps to define the structure of a molecule and orientation of the atoms and functional groups present, in three dimensions. Stereoisomers possess the same molecular and structural formulae and the same functional groups but differ in the three-dimensional spatial orientation of these atoms or groups within the molecule. Due to the difference in orientation of the functional group and geometry of the molecule, stereoisomers differ in their physical, chemical, physicochemical and biochemical properties. Based on symmetry and energy criteria, stereoisomers are divided into three classes.

(a) Geometrical isomers

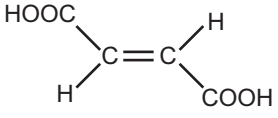
(b) Optical isomers

(c) Conformational isomers.

(a) Geometrical isomers (cis-trans isomerism): Maleic acid (m.p. 130°C) and fumaric acid (m.p. 287°C) have the same molecular formula but differ in the arrangement of functional groups around double bond. They have different physical and, to some extent, chemical properties. This type of isomerism is known as **geometrical isomerism**.



Maleic acid
(cis-butenedioic acid)

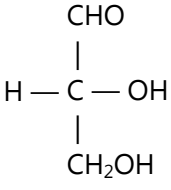


Fumaric acid
(trans-butenedioic acid)

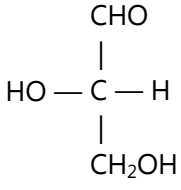
The presence of a carbon-carbon double bond restricts the freedom of rotation about double bond. The designation cis (Latin word: same side), is used to denote the presence of like atoms or groups on the same side and trans (Latin word, across) is used when they are on opposite sides. Isomerism seen in non-cyclic, open-chain compound due to the presence of a double bond, is called as **π diastereoisomerism** while when it occurs in a cyclic skeleton lacking a double bond, it is termed as **σ diastereoisomerism**.

(b) Optical Isomerism (enantiomerism): In 1815, Biot found that a number of organic and inorganic compounds in the solution form, have the ability to rotate the plane of polarized light in opposite directions but in identical amplitude, passing through them. Optical isomerism is seen in compounds that can rotate plane polarised light. A carbon atom connected to four chemically different functional groups is known as asymmetric or chiral carbon and the presence of at least one asymmetric carbon atom in the structure is the pre-requirement for a molecule to show optical isomerism.

If there is one asymmetric carbon then two optically active isomers are possible. Isomer rotating plane of polarized light to the right is said to be dextrorotatory (Latin, dexter : right) while isomer showing rotation to the left is known as laevorotatory (Latin, laevus : left). Both isomers are mirror images of each other yet are not superimposable. They are called as enantiomers and the pair of enantiomers is called as enantiomorph. An enantiomer does not possess a plane or center of symmetry. For example,



D-glyceraldehyde



L-glyceraldehyde

When the enantiomers are present together in equal concentration, the rotation of plane polarized light caused by laevo isomer will be neutralized by a dextro rotating isomer and the mixture will be optically inactive. Such mixtures are called as racemic mixtures. The conversion of an enantiomer into a racemic form is called as racemization. While the separation of racemic mixture into individual enantiomers is called as resolution. The maximum number of optically active isomers possible for a molecule having more than one asymmetric carbon atoms may be given by the formula

$$N = 2n$$

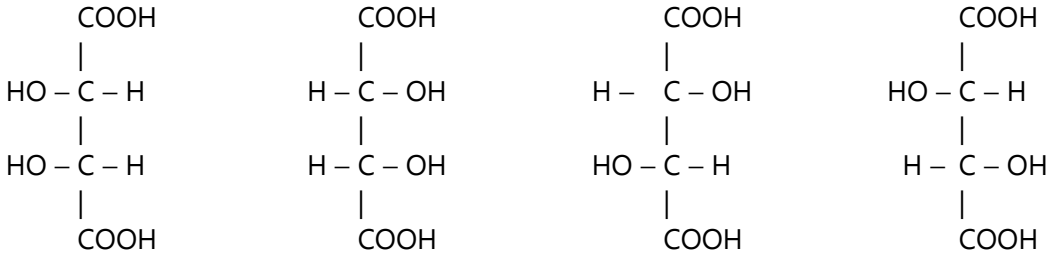
where,

N = Number of optically active isomers, and

n = Number of asymmetric carbon atoms.

With the exception of rotation of plane-polarised light, enantiomers have identical physical and chemical properties like boiling point, melting point, solubility. Their chemical properties are same towards achiral reagents, solvents and conditions. Towards chiral reagents, solvents and catalysts, enantiomers react at different rates.

As per the rule given above, tartaric acid will have four optically active forms because of the presence of two asymmetric carbon atoms.



(I) (II) (III) (IV)

Forms (I) and (II) are identical and symmetrical. In these forms, the upper half is the mirror image of the lower half. This makes the molecule optically inactive through internal compensation. Such identical and symmetrical stereoisomers are called as meso-isomers.

Forms (III) and (IV) are mirror images of each other but are not superimposable. They are enantiomeric forms.

While if you compare (III) with (I) or (IV) with (I), these are not enantiomeric pairs. They are neither mirror images nor superimposable. Only one of the two halves of their molecules are identical while the remaining halves are mirror images. Such stereoisomers which are not mirror images and are non-superimposable are called as diastereomers. They have different physical and chemical properties, with both achiral and chiral reagents. The rates are different and the product may be different.

1.2 IMPORTANCE OF OPTICAL ISOMERISM

Nearly all naturally occurring substances having asymmetric carbon atoms are in either the d or the *l* form rather than as racemic mixtures. In drugs and pharmaceuticals, most of the adverse effects and low potency may be related to the utilization of the drug in the form of its racemic mixture. Since, enantiomer in its pure form, is more active and selective, there is now an increasing interest to present the drug in the market in its active enantiomeric form instead of its racemic form. Optical isomerism has also been successfully utilized in elucidating the mechanism of many chemical reactions.

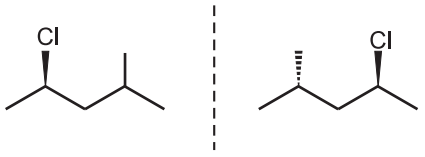
The enantiomer that rotates a beam of polarised light in the clockwise direction is indicated by the prefix (+), formerly d (+) or dextro (–), the other enantiomer rotates light in a counter clockwise direction and is indicated by the prefix (–), formerly *l*(–) or levo.

They have identical chemical and physical properties in an achiral environment but form different products when reacted with other chiral molecules and exhibit optical activity.

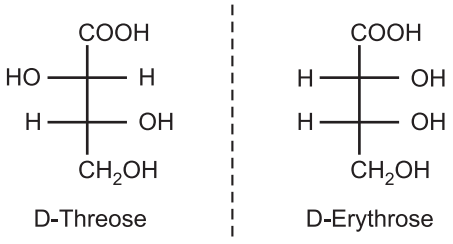
1.3 DIASTERIOISOMERISM

Stereoisomers with two or more asymmetric or chiral carbons (stereocenter) will show diasterioisomerism. The stereoisomers that are neither mirror images of one another nor are superimposable, are known as diasterioisomers.

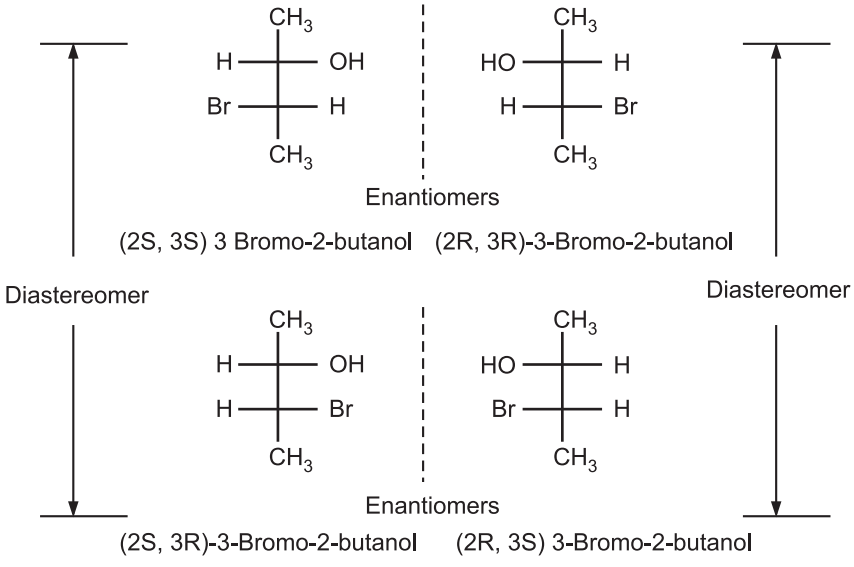
For example:



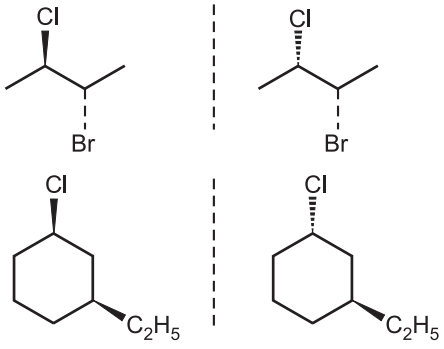
Each stereocenter gives to two different configurations. It means if a molecule contains two asymmetric carbons, there are upto four possible conformations. When two diastereoisomers differ from each other at only one stereocenter they are known as epimers. e.g., D-threose and D-erythrose are epimers of each other. Unlike enantiomers, diastereoisomers have different physical and chemical properties.



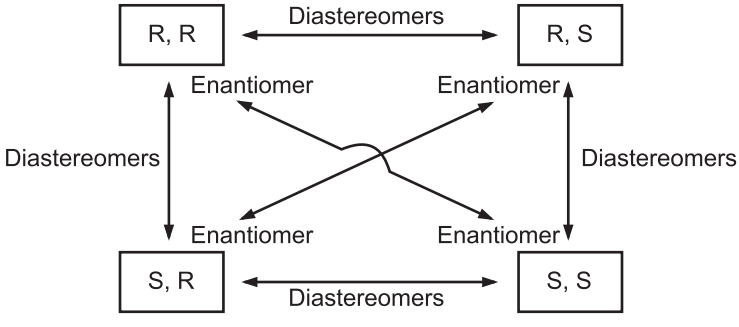
In case of 3-bromo-2-butanol, we have four possible combinations as SS, RR, SR and RS. Out of these, two molecules SS and RR are enantiomers of each other while the configurations RS and SR are diastereomers of SS and RR configurations.



Thus in diastereoisomers, the chemical formula and atom connectivity remain the same but the three dimensional orientation or shape of the molecule is different e.g., 2-bromo-3-chloro ethane.



The molecules are different in the configuration of chlorine atoms but same with the bromine atoms hence they are diastereomers. Similarly in cyclic compound 3-ethyl-1-chlorocyclohexane, ethyl groups have same configuration but the chlorine atoms have opposite configuration. Hence, these molecules are diastereomers. Configurations differ at some stereocenters but not at others can not create mirror images. So they are not enantiomers, but are diastereomers.

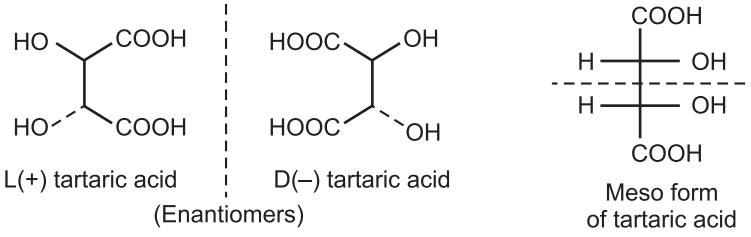


The dihydrotestosterone molecule contains seven stereocenters. Applying 2^N rule, gives 128 possible configurations. Out of these, only one is enantiomeric pair while rest are diastereomers.

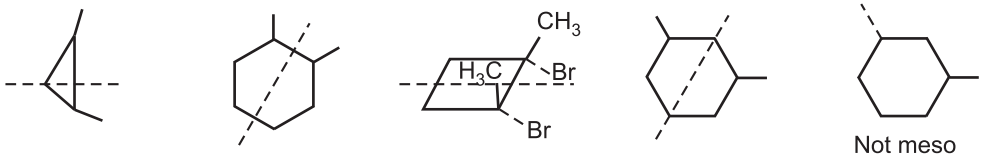
1.4 MESO COMPOUNDS

When multiple stereocenters present in a molecule create an internal plane of symmetry, it leads to meso compounds. Tartaric acid contains two asymmetric centers which give rise to four configurations. But there are really only three stereoisomers of tartaric acid: a pair of chiral molecules (enantionmers of each other) and the achiral meso compound. In meso compound, we have internal mirror plane that splits the molecule into two symmetrical sides, the stereochemistry of both left and right side should be opposite to each other. This leads to auto cancellation of stereo activity of each other resulting into optical inactivity. Hence, meso compounds can not be assigned with either dextrorotatory (+) or levorotatory (–) designation. The internal mirror plane is simply a line of symmetry that bisects the molecule. Each half is a mirror image of the other half. Each half must contain a stereocenter in order to be a meso compound. These stereocenters must also have different absolute

configurations. Due to internal symmetry, they meso molecule is achiral. Hence, this configuration is not optically active. The meso form is also a type of diastereomer. The remaining two isomers are enantiomeric pair (D-and L-form).



The melting point of both enantiomers of tartaric acid is about 170°C while the meso-tartaric acid has the melting point of 145°C. A meso compound is 'superimposable' on its mirror image. Examples in cyclic meso compounds include.



In summary a meso compound should have two or more stereocenters, an internal symmetry plane and the stereochemistry should be R and S.

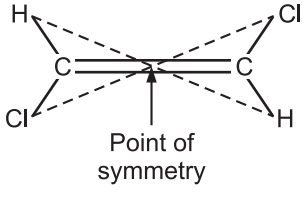
Table 1.1: Difference between enantiomer and diasteromers

Sr. No.	Parameter	Enantiomer	Diastereomer
1.	Number of stereocenters	One	Two or more
2.	Mirror images	Yes	No
3.	Superimposition	No	No
4.	Physical properties	Same	Different
5.	Chemical properties	Same	Different

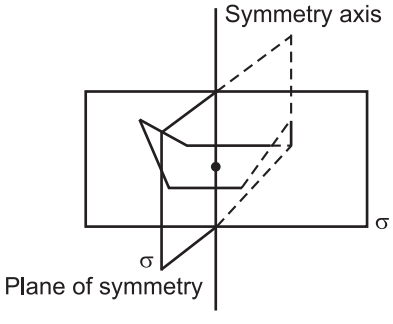
1.5 ELEMENTS OF SYMMETRY

A chiral object is not identical (i.e. non-superimposable) in all respects. An achiral object is identical (hence superimposable) with its mirror image. Chiral objects have a "handedness". Like gloves or shoes, chiral objects come in pairs, a right and a left. Achiral objects do not have a handedness just like a plain round ball. Thus, chirality of an object is related to its symmetry. Certain symmetry elements like a point, a line or a plane may be useful to check the symmetry of the molecule. The rotation or reflection around the symmetry element leaves the object in an orientation indistinguishable from the original. Reflection means the coincidence of atoms on one side of the plane with corresponding atoms on the other side, as though reflected in a mirror.

(i) Point of symmetry: In a chiral molecule, (E)-1,2,-dichloroethene, two lines drawn passing through point of symmetry ensure the same structural features at the opposite lines. Similarly the boat conformation of cyclohexane has two intersecting planes of symmetry (σ). A plane of symmetry divides the object in such a way that the points on one side of the plane are equivalent to the points on the other sides by reflection through the plane.



(a)



(b)

The existence of a reflective symmetry (a point or plane of symmetry) indirectly proves the molecule is achiral. Chiral molecules however may have rotational symmetry axes and do not have any reflective symmetry elements.

Table 1.2: Examples of rotational axis (360°/n) in the molecules

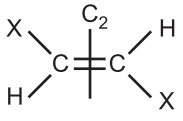
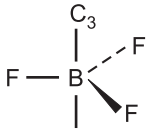
Type	n	Angle Rotation	Example	
C_2	2	180°	E isomers	
C_3	3	120°	Boron trifluoride	
C_4	4	90°	Cyclobutane	
C_5	5	72°	Cyclopentane	
C_6	6	60°	Benzene	
C_∞	∞	0-360°	Linear molecules e.g. CO_2, Acetylene	O = C = C HC ≡ CH

Table 1.3: Terms commonly used

Sr. No.	Terms	Symbol
1.	Plane of symmetry	δ
2.	Center or point of symmetry	i
3.	Rotational axis where the degrees of rotation that restore the object is 360/n (C_2 = 180° rotation; C_3 = 120° rotation; C_4 = 90° rotation; C_5 = 72° rotation; At C_1 = (i.e. 360° rotation), the molecule returns to its original orientation	C_n
4.	Only a single plane of symmetry	C_s
5.	Only a single point of symmetry	C_i
6.	Vertical plan Horizontal plan Diagonal plane	v h d

Examples:

(1) Methane: It is an example of a high symmetry molecule having 4 C_3 axes, 3 C_2 axes and 6 σ (planes). It belongs to the tetrahedral point group Td. It is achiral.

(2) Cis-1,2-dichloroethane: This structure has two orthogonal planes of symmetry and C_2 axis at their intersection. It is achiral.

(3) Trans-1,2-dichloroethane: This structure has a plane of symmetry, an orthogonal C_2 axis and a point of symmetry at their intersection. It is achiral.

(4) Trans-1,2-dimethylcyclopropane: This structure has only a single C_2 axis. It is a dissymmetric and chiral.

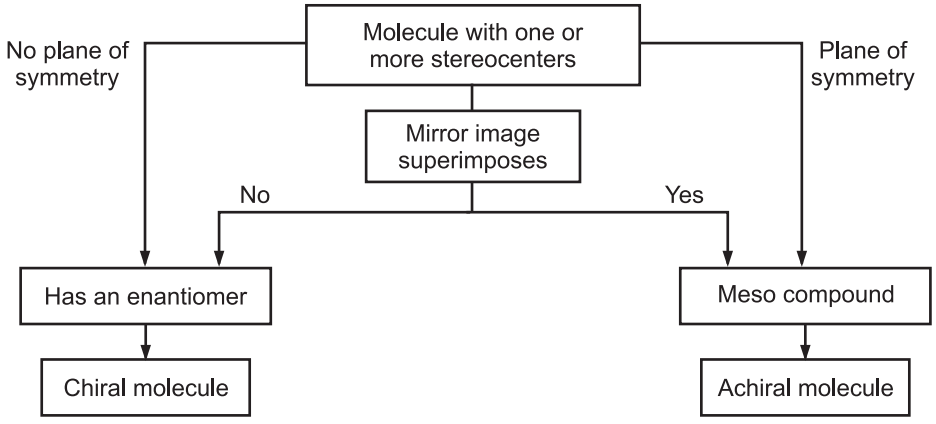
(5) Cyclohexane (boat conformation): It has a C_2 axis and two planes of symmetry. It is achiral.

(6) Cyclohexane (chair conformation): It has planes, axes and a point of symmetry. The principle axis is C_3.

(ii) Plane of symmetry:

A molecule with a zero strereocenters is always achiral. A molecule with odd number of stereoisomers (1, 3, 5 etc.) will always be chiral. A molecule with even number of sterocenters may be chiral or achiral due to meso compounds. Beside this planes of symmetry and inversion centers are the parameter to determine chirality of a molecule. Planes of symmetry are usually easier to identify than inversion centers.

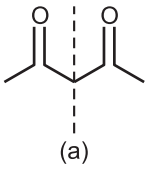
Plane that cuts the molecule in half to get same things on both sides is known as **plane of symmetry.** It can be either perpendicular to the plane or within the plane. A molecule having a plane of symmetry in any conformation is usually achiral.



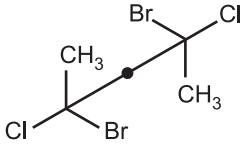
(iii) Inversion center:

The molecule (a) has a plane of symmetry through the central carbon. This is a mirror plane where one half of the molecule is a perfect reflection of the other half of the molecule. This molecule is achiral.

The molecule (b) has a center of symmetry or an inversion center. An inversion center is a point in the molecule (may or may not be an atom) through which all other atoms can converted through 180° into another identical part. The molecule is achiral because of inversion center.



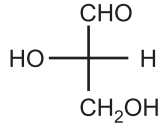
(a)



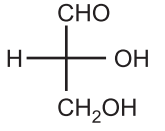
(b)

1.6 NOMENCLATURE OF OPTICAL ISOMERS

The d/*l* system was developed by Fischer and Rosanoff in around 1900. Totally arbitrarily, (+) glyceraldehyde was defined as being D because the OH group attached to the C_2 is on the right hand side of the molecule. While (–) glyceraldehyde was defined as L because the OH group is on the left hand side.



L-Glyceraldehyde



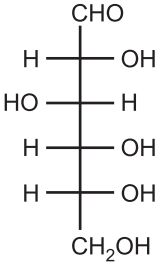
D-Glyceraldehyde

(1) The d/*l* system (named after Latin dexter and laevus, right and left) names the molecule by relating them to the molecule glyceraldehyde. This system of nomenclature represents an older system for distinguishing enantiomers of amino acids and carbohydrates. This arbitrary type of configuration (d/*l* system) is known as Relative Configuration.

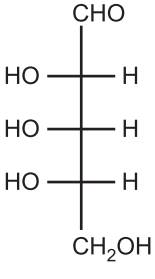
(a) To name complex amino acids and carbohydrates in Fischer projection, take carbonyl group (aldehyde, ketone or carboxylic acid) on the top and CH_2OH on the bottom.

(b) The D descriptor is used when the –OH or $–NH_2$ on the 2^{nd} carbon (from bottom) points to the right and L is used when the –OH or $–NH_2$ points to the left. Thus, from stereochemistry of only one stereocenter (i.e. 2^{nd} carbon from bottom) the stereochemistry of all other stereocenters in the molecule is defined.

(c) The d/*l* nomenclature does not indicate which enantiomer is dextrorotatory and which is levoratatory. It just says that the compound's stereochemistry is related to that of dextro - or levo - enantiomer of glyceraldehyde. For example, d-fructose is levorotatory. Hence, it is stated that all natural amino acids are L while natural carbohydrates are D. Thus, (+) glucose has the D-configuration and (+) ribose has the L-configuration.



D(+)-glucose



D(+)-ribose

1.6.1 The Cahn Ingold Prelog (CIP) Sequence Rule

An absolute configuration refers to the spatial arrangement of the atoms of the chiral molecules and its stereochemical description using terms (R) or (S). Cahn, Ingold and Prelog introduce Sequence Rules to assign an order of priority to the atoms or the groups directly attached to a stereocenter. The absolute configuration of a given stereocenter is defined as either (R) or (S) by applying these rules.

Rule 1: Atom of higher atomic number is given priority over those of lower atomic number e.g.,

I > Br > Cl > F >O > N > C > H.

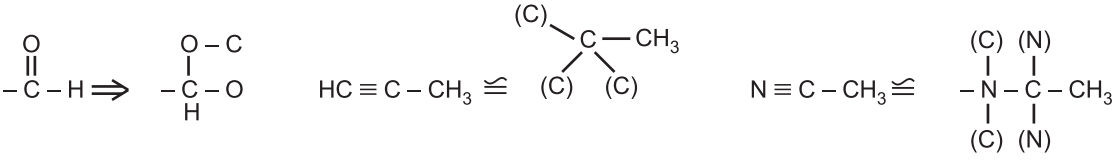
Rule 2: Isotope of higher atomic weight takes precedence. e.g.,

^3H (tritium) > ^2H (deuterium) > ^1H (hydrogen)

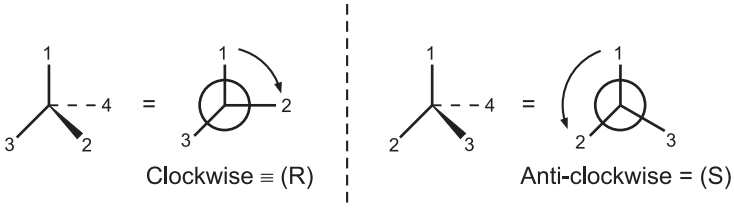
Rule 3: When two or more atoms directly attached to a stereocenter are same, the order of priority depends on the next atom along the chain. e.g.,

$–CO_2CH_3 > –CO_2H > CONH_2 > COCH_3 > CHO > CH_2OH$

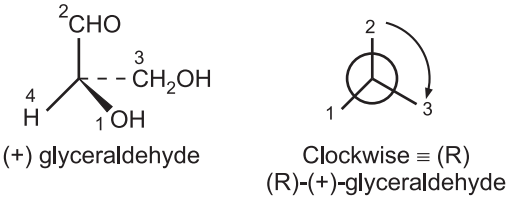
Rule 4: If an atom is double bonded to another atom, treat it as if it were singly bonded to two of those atoms. If an atom is triply bonded to another atom, treat it as if it were singly bonded to three of these atoms. Convert the unsaturated group directly attached to the stereocenter into saturated group to decide order of priority e.g.,



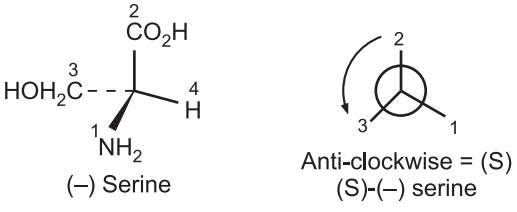
Applying above sequence rules, assign the numbers to the functional groups as per order of priority. Draw a generic tetrahedral center and view the molecule so that the atom/group with lowest priority should project maximum away in space. A clockwise decreasing order is assigned the (R) - configuration while an anti-clockwise decreasing order is assigned the (S)-configuration.



Examples:

1. 

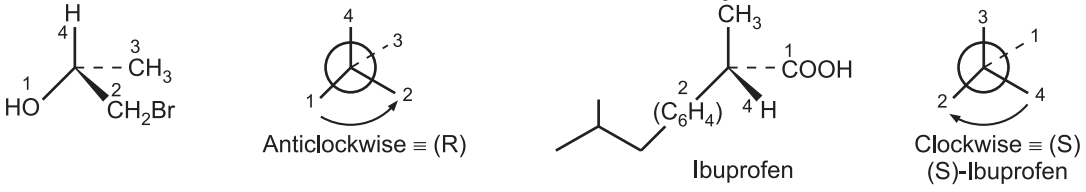
As per sequence rule, the order of priority of the groups is
OH > CHO > CH_2OH > H

2. 

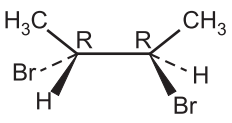
As per sequence rule, the order of priority of the groups is
NH_2 > CO_2H > CH_2OH > H

Rule 5: A longer group may not necessarily have a higher priority over another smaller group. e.g. $–CH_2Cl$ has a higher priority than $–CH_2CH_2CH_2CH_3$.

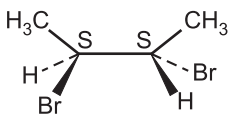
Rule 6: If a lowest priority group is in the front of the plane of the molecule then the assignment is reversed. i.e., clockwise is S and anticlockwise is R.



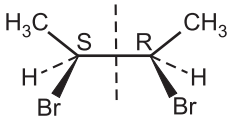
Rule 7: If there are multiple chiral carbons in a molecule, the configuration of entire molecule can be defined by using number that specifies the location of the stereocenter preceding configuration e.g., (1R, 4S). e.g.,



(2R, 3R)-2,3-dibromobutane



(2S, 3S)-2,3-dibromobutane

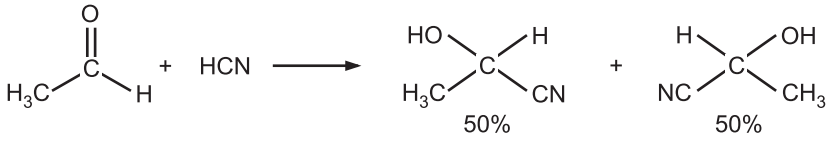


meso-2,3-dibromobutane

1.7 RACEMIC MODIFICATION

A racemic modification or racemate is a 1 : 1 mixture of (+) and (–) enantiomers. When enantiomers are mixed together in equal amount, the rotation caused by a molecule of one isomer is exactly cancelled by an equal and opposite rotation caused by a molecule of its enantiomer. Hence, the overall optical rotation of racemate is zero. A racemic modification is thus optically inactive. The prefix (±) is used to denote the racemic nature of the sample. e.g., (±)-2-methyl-1-butanol.

When one of the starting material is chiral, the product of the reaction will always be formed as a racemate in the absence of chiral catalyst.



However, biologically active pure enantiomer can be synthesized in the presence of chiral catalysts or agents.

1.7.1 Methods of Racemic Modification

(a) Mixing: A racemic modification may be achieved by an intimate mixing of exactly equal amounts of dextro (+) and levo (–) isomers.

(b) Chemical synthesis: When one of the starting material is chiral the product of reaction will always be formed as a racemate in the absence of chiral catalyst. e.g., when hydrogen cyanide reacts with acetaldehyde (chiral), equal number of mole of two enantiomeric forms of lactonitrile, $CH_3CHOHCN$ results.

(c) Thermal recemization: Racemization may occur when an optically active material is heated. It leads to temporarily breaking one of the 4 bonds to a stereocenter. The atom/group separated exchanges the position and joins back to stereocenter to form another enantiomer e.g., the distillation of optically active enantiomer of α-phenethyl chloride leads to its racemization.

(d) Walden inversion: The racemization of 2-iodooctane by potassium iodide in refluxing acetone involves a process known as Walden inversion.

(e) Epimerization: It is the change in the configuration at one asymmetric carbon atom in a compound having more than one stereocenters. It thus leads to interconversion of diastereomers.

(f) Mutarotation: It is a spontaneous change with time, in the rotation of freshly prepared solutions of optically active substance till it reaches an equilibrium. Mutarotation is the result of either epimerization or a spontaneous structural change. The rate of mutarotation depends on temperature, solvent and catalyst. For example, the mutarotation of glucose is known to be acid-base catalysed.

1.7.2 Resolution of Racemic Mixture

The process of separating a racemate into pure enantiomers is known as resolution. Enantiomers have identical physical properties (b.p., m.p., solubility) and hence it is difficult to separate enantiomers using conventional methods. If a pair of enantiomers is converted into a pair of diastereomers, the diastereomers can be separated easily utilizing the difference in their physical properties. Once separated, the pure enantiomer may be regenerated back from its respective diastereomer.

For example,

(i) A racemic mixture of enantiomers of an acid can be converted to a salt using a chiral base having D-configuration. The salt obtained contains a mixture of two diastereomers: (D acid, D base) and (L acid, D base). Due to difference in their physical properties, the diastereomeric salts are fully separated. Dissociation of separated diastereomeric salt leads to regeneration of D-acid and L-acid respectively.

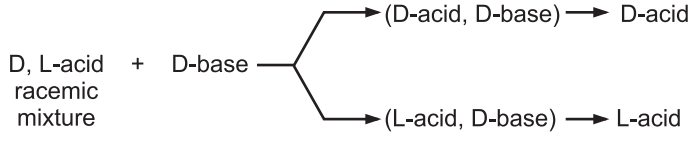
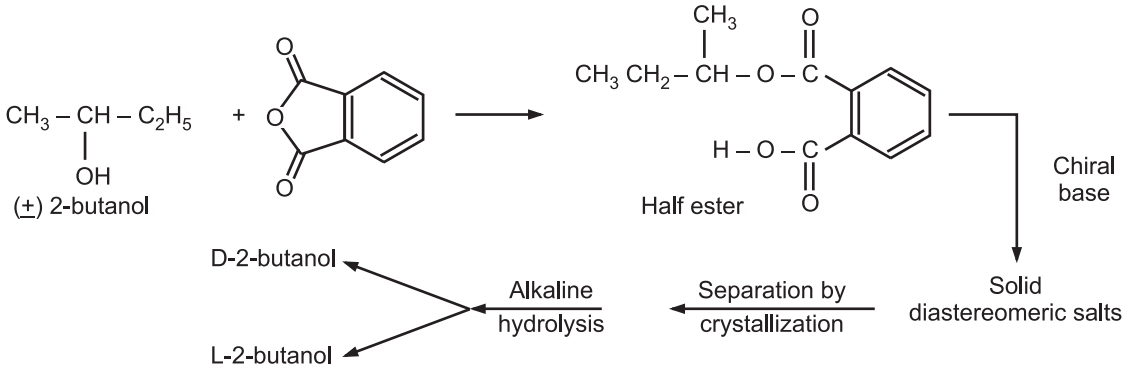


Fig. 1.1: Resolution of racemic mixture

Racemic acids may be resolved using commercially available chiral bases like brucine, strychnine, *l*-phenyl ethanamine. Similarly racemic bases may be resolved using chiral acids such as (+) tartaric acid, (–) malic acid, (–) mandelic acid and (+) camphoric acid.

A racemic alcohol may be resolved by converting the racemate into a mixture of diastereomeric esters using a chiral acid. The separation of these diastereomeric ester becomes difficult if they are liquid. In such cases, instead of full ester, half ester is synthesized containing one free carboxylic group. A chiral base, brucine then forms solid diastereomeric salts which can be later separated by crystallization. The pure enantiomer of 2-butanol is regenerated through hydrolysis of respective diastereomeric salt.



(ii) Resolution by biochemical means: Certain mold, bacteria or fungi selectively destroy one enantiomer at a faster rate than the other enantiomer. For example, the mold *Pencillium glaucum* if allowed to grow with racemic mixture, it selectively destroys the dextro isomer leaving pure levo isomer behind.

Table 1.4: Pharmacological effects of Racemic drug mixtures

Drug	Biological response	Enantiomer
Terbutaline	Trachea relaxation	(–)
Propranolol	β-blockade	(S)
Amosulalol	α-blockade	(+)
	β-blockade	(–)
Warfarin	Anticoagulation	(S)
Verapamil	Negative chronotropic	(–)
Atenolol	β-blocker	(S)
Nitrendipine	Ca^{++} channel blocker	(S)
Zopiclone	Sedation	(R)
Terfenadine	Antihistaminic	(S)
Albuterol	Antiasthmatic	(S)
Flurbiprofen	Anti-inflammatory	(S)
Ketoprofen	Anti-inflammatory	(S)
Thalidomide	Immunosuppresive	(S)
Tetramisole	Anthelmintic	(S)-form (levamisole)
Propoxyphene	Analgesic	Dextro form
	Antitussive	Laevo form
Tranylcypromine	Antidepressant	(–)
	Improvement in performance	(+)
Sotalol	Antihypertensive	(–)
	Antiarrhythmic	(+)

Advantages of Resolution:

(i) To avoid side effects of unwanted enantiomer leading to improved therapeutic profile and less chances of drug interaction.

(ii) Reduction in the therapeutic dose and hence the cost of treatment.

(iii) Lesser metabolic, renal and hepatic load of a drug on the body as the dose (for a pure enantiomer) reduces to the half of racemic mixture.

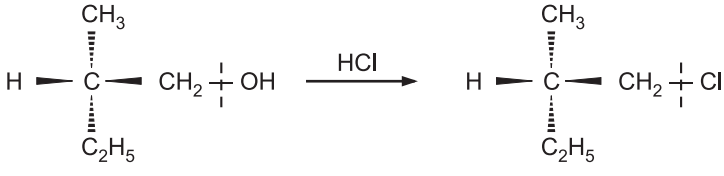
1.8 REACTIONS OF CHIRAL MOLECULES

Chiral molecules react with the reagents in variety of ways and accordingly reactions are classified as follows:

1. Reactions where bonds with the chiral center are not broken.
2. Reactions leading to generation of chiral center.
3. Reactions of chiral compounds with optically active reagents.
4. Reactions where bonds with the chiral center are broken.

1. Reactions where bonds with the chiral center are not broken.

These reactions can be used to relate configuration of one compound to that of another. Configuration is retained when reaction does not involve breaking of a bond to a chiral center.



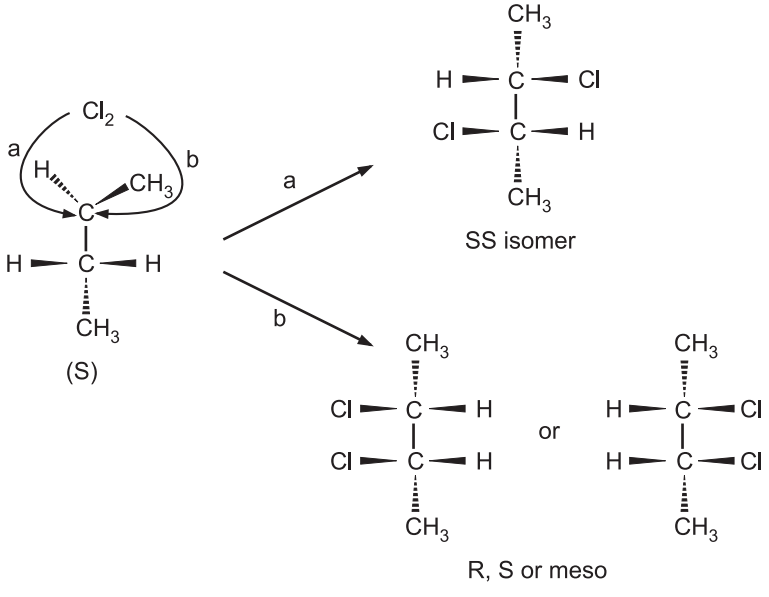
(S)(–) 2-methyl-1-butanol (S)(+) 1-chloro-2-methyl butane

Here as the bond to the chiral center is not broken 'S' configuration is retained, because '–CH_2–Cl' occupies same relative position as that was occupied by –CH_2OH in the reactant. This retention of configuration can be utilized to determine configurational relationship between two optically active compounds by converting them into each other by reactions that do not involve breaking of a bond to a chiral center. Only relative configuration can be assigned than absolute configuration.

Such reactions are used to get specific rotations of optically pure compounds. e.g. 2-methyl-1-butanol from fusel oil has specific rotation of –5.90° and is optically pure. Upon treatment with hydrogen chloride, 1-chloro 2-methyl butane has specific rotation of +1.67°. So if a sample has rotation equal to this value, compound is said to be pure. If rotation is about + 0.8°, compound is said to be only 50% optically pure.

2. Reactions leading to generation of chiral center:

Generation of first chiral center in a compound usually yields equal amounts of enantiomers (Racemic mixture) but reactions that form second/new chiral center yields unequal amounts of diastereomers depending on the side of attack.



Retention of configuration(s) occurs as there is no bond breaking to the chiral center. For new chiral center, depending on side of attack from the same or opposite side, diastereomers are formed but in unequal amounts. This is because the intermediate 3-chloro-2-butyl radical contains a chiral center and it lacks symmetry. So two faces of the molecule for attack are not equal to each other. Here S isomer would yield the SS and meso compound in ratio of 29 : 71.

In some reactions both configurations may not be actually generated but probability exists. Similarly R isomer would yield RR and meso compound in ratio of 29 : 71. If the reactant is optically inactive, it yields optically inactive products.

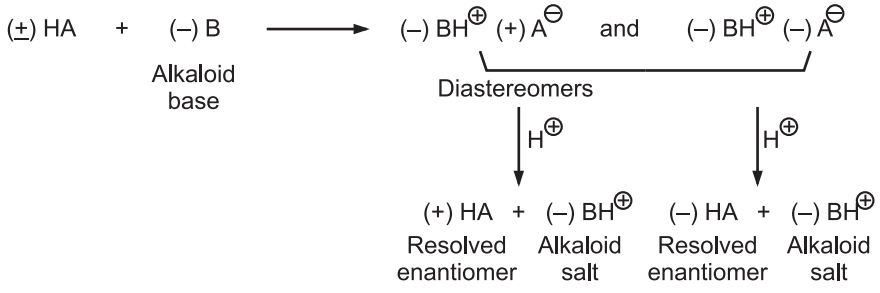
3. Reactions of chiral compounds with optically active reagents

Such reactions are commonly used in resolution or separation of a racemic mixture/modification into individual enantiomers. Because enantiomers have similar physical properties (except optical rotation) they are not separated by usual methods of fractional distillation or crystallization.

So to obtain pure enantiomers from racemic modification, use of optically active reagents is made. Such optically active reagent is easily obtained from natural sources or generated from naturally available reagents.

Common reactions are reactions of organic acids and bases to form salts.

e.g. Reaction of racemic acid (±) HA with alkaloid reagent (–) B.



Formed diastereomers have different physical properties and can be easily separated by fractional distillation or crystallization. Further by addition of mineral acid resolved enantiomers can be recovered from the solution.

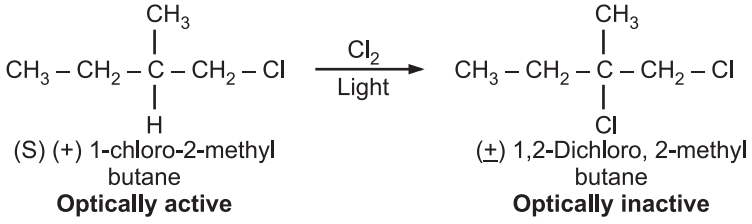
Alkaloid bases commonly used are (–) brucine, (–) quinine, (–) strychnine etc.

Similarly, racemic bases can be separated with acid reagents e.g. (–) malic acid. Compounds other than acids, bases can also be resolved. Alcohols are weakly ionized and are not appreciably acidic or basic so their resolution is facilitated by attaching them with acidic handle which can be removed later.

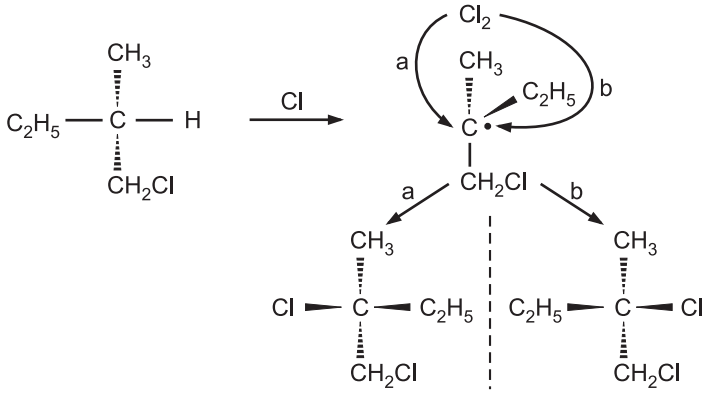
4. Reactions where bonds with chiral center are broken

Stereochemistry of such reactions depend on the mechanism of the reaction. Hence, stereochemistry can be helpful to give evidence of a particular mechanism.

e.g.



As the product is optically inactive and a racemic mixture, it implies second chlorine can be attached from either face of the intermediate, which can be a free alkyl radical with loss of chirality.



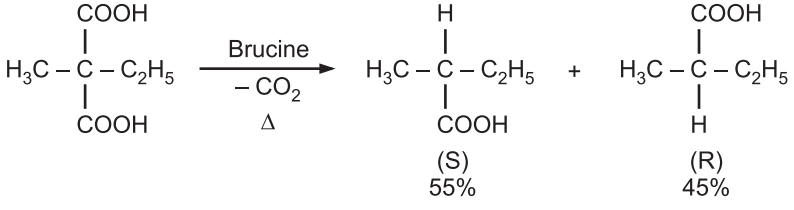
If there is simultaneous attack of chlorine while displacement of hydrogen, only the product from backside attack of chlorine would have been obtained instead of optically inactive product, so mechanism involving free alkyl radicals is correct.

- A reaction is stereospecific when reactants exist as steroisomers and each isomeric reactant gives a different stereoisomeric product.
- A reaction is stereoselective when reactant irrespective of any stereoisomerism produces predominantly or exclusively one stereoisomeric form of the product than other possible forms.

1.9 ASYMMETRIC SYNTHESIS (PARTIAL AND ABSOLUTE)

De novo synthesis of a chiral substance from an achiral precursor such that one enantiomer predominates over the other is called as asymmetric synthesis. For reactions where molecules already contain chiral element and synthesis introduces a new chiral element, synthesis is referred as 'stereoselective or enantioselective' synthesis or diastereoselective synthesis.

- Decarboxylation of ethyl methyl malonic acid to give α methylbutyric acid is one of the first recorded asymmetric synthesis.



- Generally chiral reagents are used to carry out the reaction, if they are not available, chirality is acquired upon chelation, solvation etc.
- Reactants are adsorbed onto chiral surfaces or within chiral crystals.
- Chiral adjuvant or chiral auxiliary is temporarily attached to the achiral substrate which is cleaved after the synthesis by hydrolysis to recycle the adjuvant.
- When a new stereogenic center is created in achiral molecule we get a racemic mixture while in diastereoselective synthesis, formation of any one of the desired diastereomer is preferred over the other.

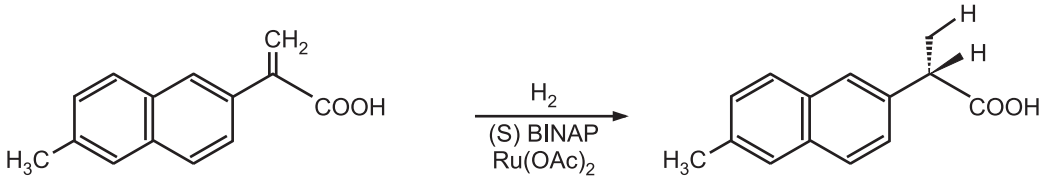
Typical asymmetric syntheses include

- Asymmetric hydrogenation
- Asymmetric epoxidation
- Asymmetric dihydroxylation

Partial term was used when optically active compounds are prepared from achiral compounds by intermediate use of optically active compounds as reagent without necessity of resolution, contrary to the 'absolute' asymmetric synthesis where physical reagent like circularly polarised light was used.

1. Asymmetric Hydrogenation (Reduction):

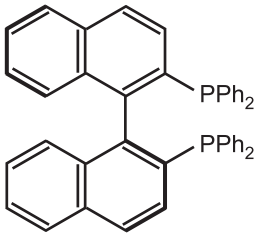
It is used for asymmetric synthesis of analgesic drug Naproxen.



S Naproxen

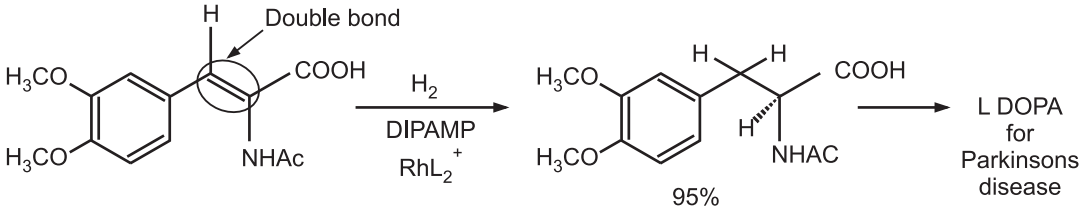
Reaction is carried out in presence of chiral catalyst to hydrogenate double bond. The catalyst selects a single enantiotopic face of the double bond and adds hydrogens across it.

BINAP is a chelating diphosphine. Chirality is due to restricted rotation of the bond joining two naphthalene ring systems. Along with Ruthenium it acts as excellent catalyst for hydrogenation.

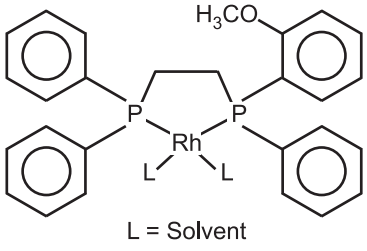


S-BINAP

For double bonds bearing amino group, better catalysts are based on rhodium.



The catalyst is a cationic complex of rhodium with another diphosphine DI PAMP.

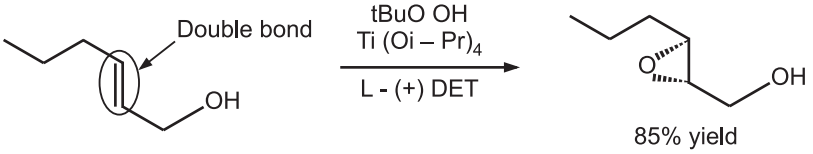


L = Solvent

- Important application of asymmetric hydrogenation is in synthesis of L menthol from (R) citronellal.

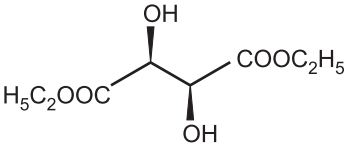
2. Asymmetric epoxidation:

Oxidation of alkenes by asymmetric epoxidation is one of the popular sharpless reaction.



85% yield

Catalyst is a transition metal, Titanium tetraisopropoxide with tertiary butyl hydroperoxide. The ligand is diethyl tartarate which is chiral and imparts selectivity to the reaction.



L (+) Diethyl Tartrate (DET)

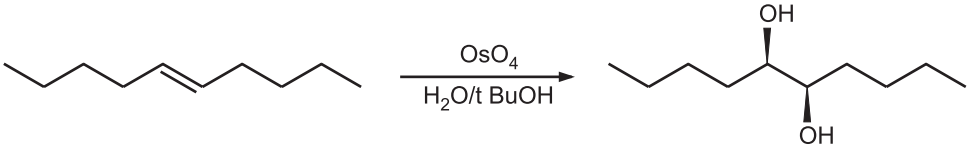
Such metal catalysed epoxidation works only on allylic alcohols. Initially active complex is formed from two titanium atoms bridged by two tartrate ligands. Each titanium atom retains two of its isopropoxide ligands and is co-oridinated to one of the carbonyl group of the tartrate ligand. When oxidizing agent tBuOOH is added, it displaces one of the remaining isopropoxide ligands and one of the tartrate carbonyl groups. Further allylic alcohol is co-ordinated with the titanium displacing another isopropoxide ligand.

Because of the shape of the complex of the reactive oxygen atom of the bound hydroperoixde has to be delivered to the lower face of alkene and epoxide is formed in high enantiomeric excess.

Epoxides easily react with many nucleophiles to give 1,2, disubstituted products and thus used in synthesis of drugs e.g. Propranolol- used as β blocker.

3. Asymmetric dihydroxylation:

Dihydroxylation of alkenes by osmium tetroxide in catalytic amount is carried out.



97% enantiomeric excess

- Osmium (VIII) act as oxidizing agent and $K_3Fe(CN)_6$ is commonly used to reoxidize the osmium after each catalytic reaction.
- To increase rate of reaction K_2CO_3 and methanesulfonamide are added.
- Chiral ligands are usually alkaloids dihydroquinidine and dihydroquinine based which must be attached to aromatic ring e.g. Phthalazine.

- Trans alkenes dihydroxylates more selectively than other alkenes because of alignement of ligand and catalyst.
- Reaction has been successfully used for synthesis of antibiotic chloramphenicol in few steps.

Energy Profile diagrams for asymmetric synthesis

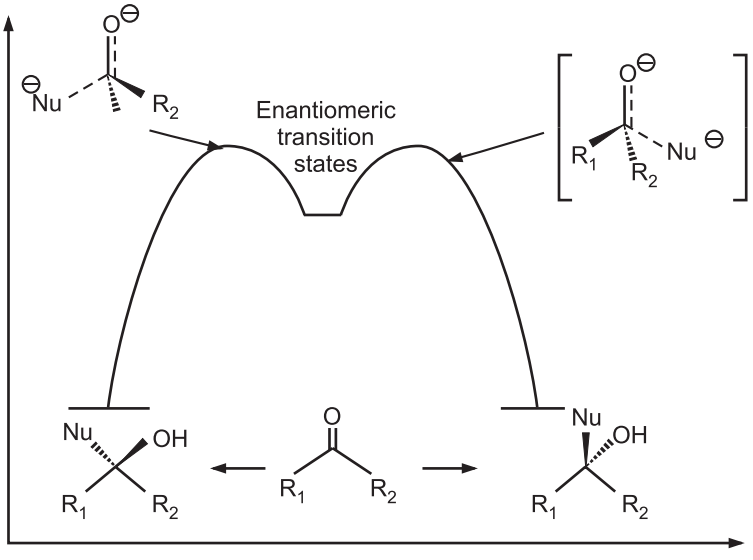


Fig. 1.2: Nucleophilic attack on ketone in achiral environment where enantiomeric products are produced in exactly equal amounts

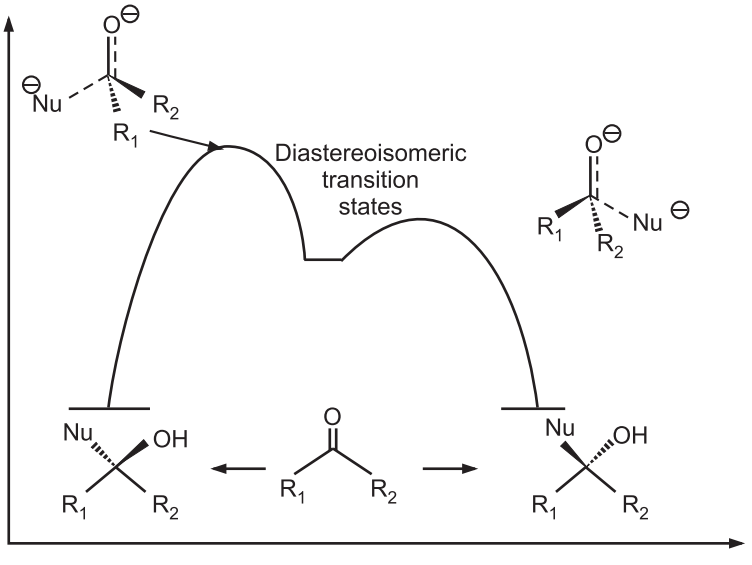
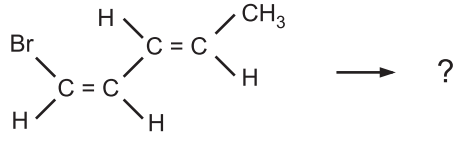
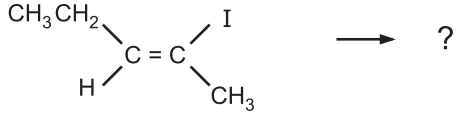


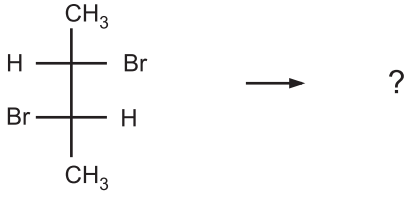
Fig. 1.3: Nucleophilic attack on a ketone in chiral environment where enantiomeric products are produced in unequal amounts.

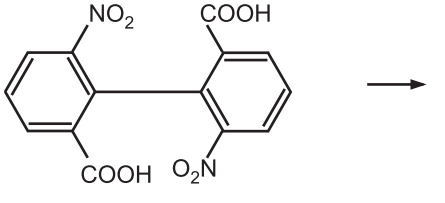
QUESTIONS

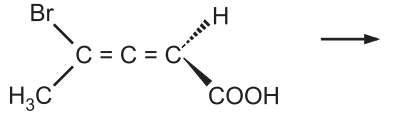
1. What are diastereomers? Explain with suitable example?
2. What is conformational isomer? Explain with suitable example?
3. Assign R/S configuration of following:

(a) 

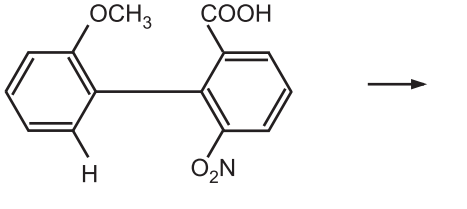
(b) 

(c) 

(d) 

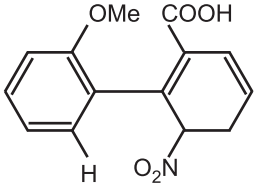
(e) 

4. Exaplain resolution of raecemic mixture.
5. Define enantiomer and mesocompound with structure.
6. Comment on resolution of racemic modification.
7. Define chirality and optical isomerism.
8. Explain significance of stereochemistry in biological activity.
9. Assign R and S configuration.



10. What is resolution ? Give in brief any two methods?
11. Differentiate between enantiomers and diastereomers.
12. Explain various ways to represent chiral centre with example.
13. Write short note on methods of resolution of racemic mixture.
14. Draw and specify R or S
    a. 3-Chloro-2,2,5,trimethylhexane
    b. 3-bromohexane
    c. 1,3-dichloropentane
15. Explain with example stagged and eclipsed.
16. Give advantage of Z/E nomenclature over cis - trans with example.
17. Assign R and S nomenclature for following.

(i)



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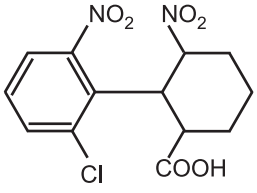
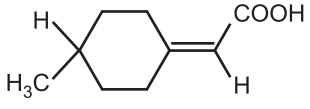
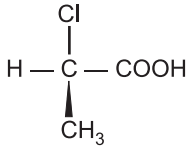


(iii)



18. Differentiate between:
    a. Enantiomers and diastereomers
    b. Mesoform and racemic mixture
19. Write rules of R.S configuration.
20. Explain optical isomerism with examples.
21. What is racemic resolution ? Explain with suitable examples, various methods used.
22. Assign R and S

(i)



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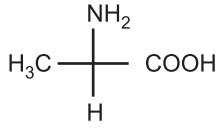

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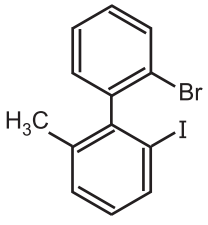
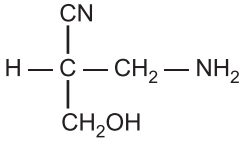


(iv)



23. Define configuration, conformation. Give example of each.
24. Write note on chirality in detail.
25. Optical isomerism is not exhibited by meso compounds, why ?
26. Define recemic mixture and give its examples.
27. What is Dihedral angle in stereoisomer?
28. Differentiate and give detail account on geometrical and optical isomerism.

❖❖❖

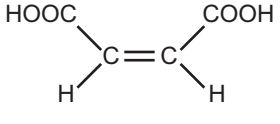
Unit...II

GEOMETRICAL ISOMERISM

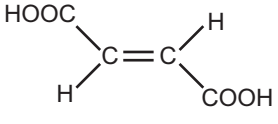
♦ **SYNOPSIS** ♦

2.1 INTRODUCTION

Maleic acid (m.p. 130°C) and fumaric acid (m.p. 287°C) have the same molecular formula but differ in the arrangement of functional groups around double bond. They have different physical and, to some extent, chemical properties. This type of isomerism is known as **Geometrical isomerism**.



Maleic acid
(cis-butenedioic acid)



Fumaric acid
(trans-butenedioic acid)

2.2 NOMENCLATURE OF GEOMETRICAL ISOMERS

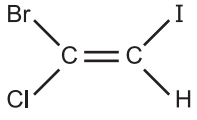
(i) Cis-trans Nomenclature: The presence of a carbon-carbon double bond restricts the freedom of rotation about double bond. The designation cis (Latin word : same side), is used to denote the presence of like atoms or groups on the same side and trans (Latin word, across) is used when they are on opposite sides. Isomerism seen in non-cyclic, open-chain compound due to the presence of a double bond, is called as **π diastereoisomerism** while when it occurs in a cyclic skeleton lacking a double bond, it is termed as **σ diastereoisomerism**.

(ii) E/Z System of Nomenclature: The simple convention of denoting the geometrical isomers by cis/trans is not possible when there are more than two different substituents on a double bond. Hence a new system of nomenclature known as the E/Z notation method is to be adopted.

Except for very simple alkenes, the nomenclature for alkene officially uses E/Z notation. In cyclic alkanes, cis and trans terminology is retained. The E/Z notation is not used in cyclic alkanes.

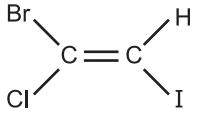
The group of highest priority on double bonded carbon atoms is first choosen according to Cahn-Ingold-Prelog (CIP) priority sequence rule.

For example, in the following structure,



Z-form

Here, the priority of functional groups attached to both double bonded carbon atoms is Br > Cl and I > H. It means the highest priority functional groups are on the same side of the double bond (i.e., cis-isomer). Hence, it is named as Z-form (from German word, Zussamen meaning together). If the highest priority functional groups are on the opposite sides of the double bond (i.e., trans-isomer), it is named as E-form (from the German word, Entagagen meaning opposite). Thus, E stands for opposite side and Z for the same side. Generally cis-isomer is said to be Z-form and trans-isomer is said to be E-form with few exceptions.

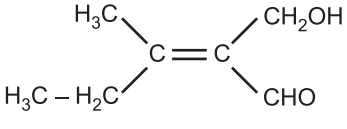


E-form

CIP Rules for determining priorities:

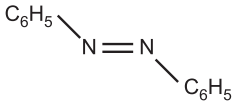
(a) The atom which has the highest atomic number is given the higher priority, in the case of simple structure, and

(b) In the most complicated molecule where group of atoms constitute the functional groups attached to the carbons of double bond, the priority depends on atomic weights of other atoms present in the group. For example, the priority in the given molecules is CH_3CH_2 – > CH_3 and CHO > CH_2OH. In case of CHO, oxygen is counted twice because of carbon oxygen double bond. Hence, the given structure has Z-form. If an atom is triply bonded to another atom, treat it as if it were singly bonded to three of those atoms.

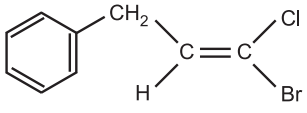


Z-form

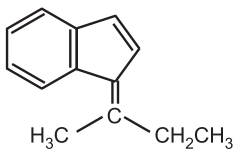
(c) For molecules with multiple double bonds, it is necessary to indicate the alkene location for each E or Z symbol. For example, the prefix (2E, 4E, 6Z, 8E) used in IUPAC name of alitretinoin indicates that the alkenes starting at positions 2,4,8 are E while the alkene at position 6 is Z.



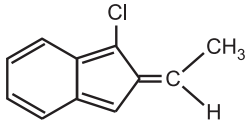
E-Azobenzene



E-form

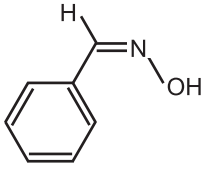


E-form

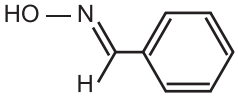


Z-form

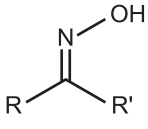
(iii) Syn/Anti system of Nomenclature: The cis-trans isomerism in some classes (such as oximes, diazoates and azo) containing one or more carbon to nitrogen or nitrogen to nitrogen double bonds is designated by syn/anti-isomerism. Syn/anti nomenclature is based upon two substituents in an acyclic molecule. For example, in sterioisomeric oxime, configuration of oximes is usually denoted by prefixes "syn" and "anti" instead of cis and trans.



Anti-isomer
(H and OH is trans)



Syn-isomer
(H and OH is cis-)



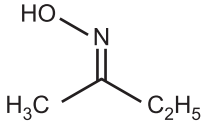
An oxime

The oximes may be of two types.

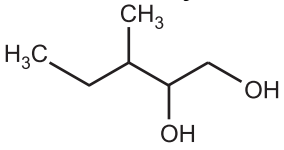
(a) Aldoximes: These are derived when aldehydes are treated with hydroxyl amine. (either R or R' is hydrogen), and

(b) Ketoximes: These are derived when ketones are treated with hydroxyl amine (both R or R' are alkyl/aryl groups).

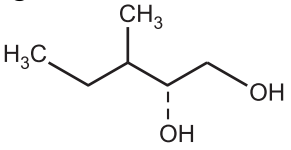
The geometrical isomerism in oximes occurs due to restricted rotation of C = N bond. In syn-aldoximes, both the hydrogen and the hydroxyl group are on the same side of the C = N and in anti-form, they are on the opposite side. However, in case of ketoxime, the syn and anti descriptors indicate the spatial relationship between the group (whose name appears first in the name of compound) and the hydroxyl group. For example, the ketoxime of butanone may be named as either syn methyl ethyl ketoxime (methyl and OH are syn) or anti-ethyl methyl ketoxime (ethyl and OH are anti). As per E-Z notation, the syn acetaldoxime is named as E-acetaldoxime whereas the anti form is named as Z-acetaldoxime.



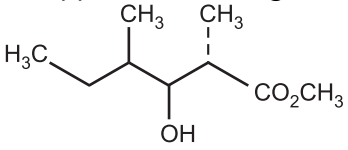
Similarly, Syn/Anti nomenclature is also used for octahedral complex fused rings. The syn-isomer has adjacent fused rings whereas the anti-isomer has opposite fused rings.



Syn



Anti



2,3-anti; 3,4-syn; 2,4-anti

2.3 DETERMINATION OF CONFIGURATION OF GEOMETRICAL ISOMERISM

The methods of determination of configuration are classified as:

(I) Chemical methods and (II) Physical methods

2.3.1 Chemical Methods

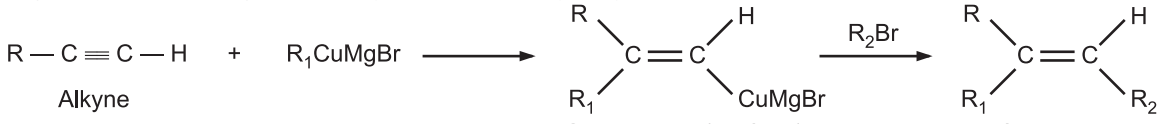
These methods include:

(a) Absolute method: This method is based on the following observations.

(i) Functional groups in cyclic compound located cis to each other can be converted into cyclic lactones, anhydrides or amides. e.g., maleic acid containing two –COOH groups cis to each other forms anhydride easily. Hence, it can be identified as cis-(maleic acid). Similarly in fumaric acid the two –COOH groups are on the opposite side, it can not form anhydride easily. Hence, it can be identified as trans-form.

(ii) Cis-isomers can be synthesized from the small rings but trans isomers can not be synthesized from small rings.

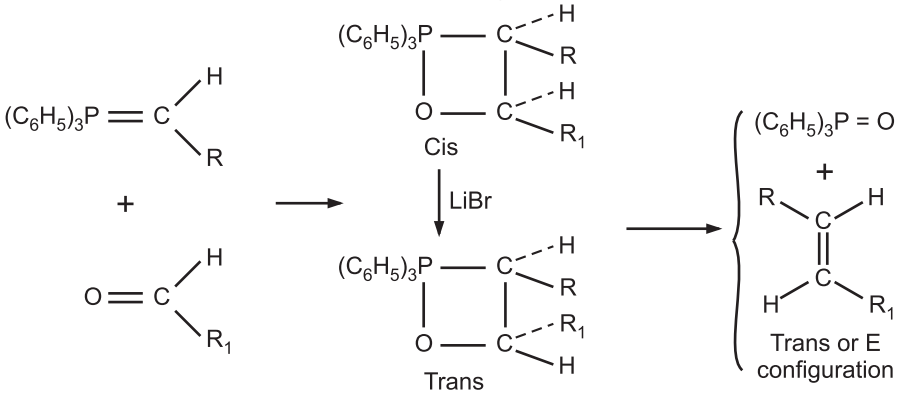
(b) Through chemical reaction not affecting the configuration of the double bond: The synthesis of trisubstituted alkene of known configuration is possible by syn addition of organo-copper reagent to alkyne followed by alkylation.



Alkyne — Syn addition (cis-form) — Cis-isomer

(c) If we synthesize a product from a starting material of known configuration, then the configuration of the product remains same as that of starting material.

(d) The stereoselective reaction helps to predict the configuration of the resulting product. One such stereoselective reaction is Wittig reaction.



2.3.2 Physical Methods

The geometrical isomers differ from each other in their physical properties which include:

(a) Boiling point, melting point, density, refractive index and dipole moment

(b) Acid strength

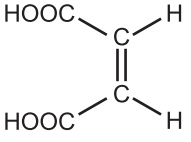
(c) UV-visible spectra

(d) Vibrational (IR-Raman) spectra

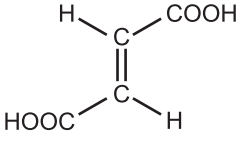
(e) NMR (1H, 13C both)

(f) X-ray, microwave spectra and electron diffraction methods.

(a) The parameters like boiling point, melting point, density and refractive index are not very reliable for prediction of configuration of the isomers. Dipole moment is variable for cis and trans isomer, sometimes higher for trans and at times for cis isomer. Similarly, trans isomer has greater symmetry than the cis. Therefore, trans has usually a higher melting point. e.g.,

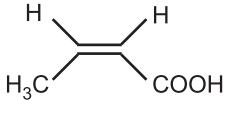


Maleic acid
m.p. = 130ºC

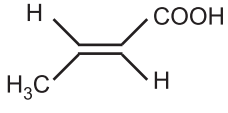


Fumaric acid
m.p. = 300ºC

(b) Acid Strength: The acid strength is strongly dependent on the configuration of the compound e.g. pKa of cis and trans isomers of crotonic acid are.

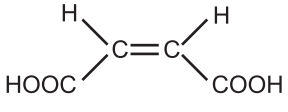


Cis-crotonic acid
(pKa = 4.44)

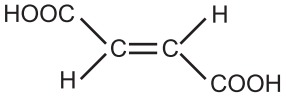


Trans-crotonic acid
(pKa = 4.70)

The cis form (maleic acid) is more acidic in its first dissociation than trans form (fumaric acid) but the acidity of second proton is reversed. This is because of intramolecular H-bonding formed within the conjugate anion of maleic acid. It is stabilized to a greater extent than fumaric after first dissociation of proton. In the second dissociation, in cis-two negative anion species close to each other is not favourable as in fumaric, the trans form (the negative species further away). Hence, the trans form is more acidic than cis in second dissociation.

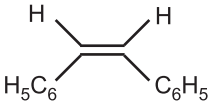


Cis form
(Maleic acid)

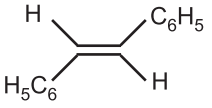


Trans form
(Fumaric acid)

(c) UV-visible Spectra: Cis isomer has two bulky groups on the same side. Hence, internally the molecule is extremely crowded and thus has less resonance energy and less stable than trans isomer. The cis-isomer suffers distortion and is forced to be non-coplanar and thus has absorption maxima at slightly shorter wavelength than the trans isomer.



Cis-stilbene



Trans-stilbene
(Z_{max} = 295.5 mμ)

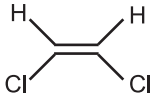
(d) Infrared and Raman Spectra: The difference in the IR spectra of two isomers may be pointed out in the following regions.

1650 cm^{-1} (C = C), and

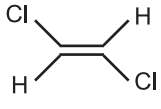
970 – 690 cm^{-1} (= C – H out of plane vibration).

Similar for trans 1,2-dichloroethylene, dipole moment is zero, due to its symmetrical nature.

Cis-isomer shows no IR absorption but shows Raman absorption at 1577 cm^{-1}. While trans-isomer shows strong IR absorption at 1590 cm^{-1} but shows no Raman absorption.



Cis-isomer



Trans-isomer

(e) NMR Spectra: Not only it gives you information regarding which functional groups are present, but NMR spectra are also capable of giving information about the position and configuration of atoms (environment) in the molecule. NMR spectra can differentiate chemcally unlike protons. In a disubstituted ethylene, RHC = CHR′, where R and R′ differ significantly in the way they influence the magnetic environment of the olefinic protons, thereby these protons experience a resonance condition at differnt field strengths. These olefinic protons are typically found in low field of the NMR spectrum and the hydrogens are said to be deshielded.

Trans isomer is strongly coupled and hence has a coupling constant of 17-18 c.p.s. (cycles per second). While the coupling constant of cis-isomer ranges from 8-11 c.p.s. Similarly the difference in chemical shifts of cis- and trans- isomers may be used to identify the configuration of the isomer.

(f) X-ray and Electron Diffraction: Single crystal X-ray diffraction is the most powerful tool for detailed structural characterization of crystalline compounds. It reveals the spatial atomic arrangement providing an image of the internal structure of the crystal. Single crystal

X-ray diffraction is the main source of information on the geometrical structure of the molecules including bond distances, bond angles, conformations of flexible molecules as well as intermolecular contacts.

2.4 CONFORMATIONAL ISOMERISM

These are the isomers generated due to rotation around single bonds present in the molecule. They may be rapidly interconverted to each other again through further rotation around single bonds. There exists a rotational energy barrier that needs to be overcome to convert one conformer to another.

Some important examples of conformational isomerism include:

(i) Open chain alkane conformations: Staggered, eclipsed and gauche conformers.

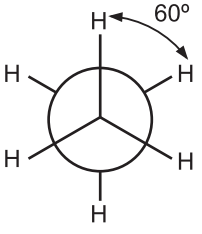
(ii) Ring conformation: Chair and boat conformers.

(iii) Atropisomerism: A molecule can become chiral due to restricted rotation about a bond.

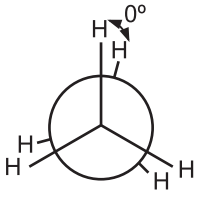
(iv) Folding of molecule.

2.4.1 Conformations of Ethane

Out of infinite conformations possible, most important conformers of ethane are: (i) Staggered conformation and (ii) Eclipsed conformation.



(i) Staggered conformation



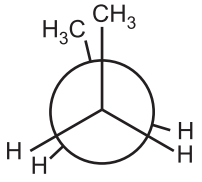
(i) Eclipsed conformation

Since the angle between the C – H bonds of 1st and 2nd carbons is 60º, the staggered conformation is the most stable conformation of ethane. In eclipsed form, the angle is 0º between two C – H bonds leading to repulsion in their electron cloud which raises the energy and decreases the stability of the molecule. The eclipsed conformation of ethane is less stable than the staggered conformation by 3 kcal/mol.

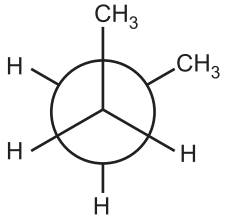
In eclipsed conformation, the bulky substituents of the molecule are brought closer leading to repulsion amongst them. This hindrance causes resistance to rotation (torsional strain i.e., force that opposes rotation due to the repulsion of bonding electrons.) It is not possible to isolate either of ethane conformations due to their rapid interconversion at room temperature.

2.4.2 Conformations of n-Butane

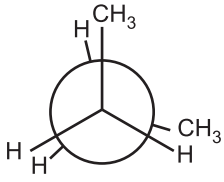
Various conformations of n-Butane include,



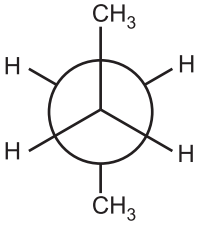
Syn (Eclipsed) (E_2)
Dihedral angle = 0° and 360°
Maximum energy



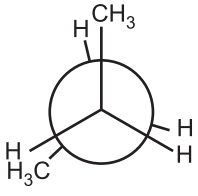
Gauche (Staggered)
Dihedral angle = 60°
Energy = 0.88 kcal/mol.



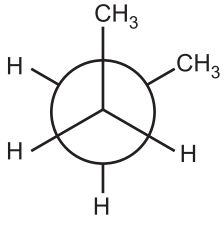
Eclipsed (E_1)
Dihedral angle = 120°
Lower energy



Anti (staggered)
Dihedral angle = 180°
Least energy



Eclipsed
Dihedral angle = 240°
Lower energy



Gauche (staggered)
Dihedral angle = 300°
Energy = 0.88 kcal/mol.

Dihedral angle: It is the angle created by two intersecting planes.

Table 2.1: Types of interactions in conformers of n-butane

Sr. No.	Interaction	Cause	Energy cost kcal/mol.
1.	H ⟷ H eclipsed	Torsional strain	1.0
2.	H ⟷ CH_3 eclipsed	Torsional strain	1.4
3.	CH_3 ⟷ CH_3 eclipsed	Torsional and steric strain	2.6
4.	CH_3 ⟷ CH_3 gauche	Steric strain	0.9

Table 2.2: Various strains contributing to rotational energy barrier

Sr. No.	Name	Cause
1.	Angle strain	Expansion or compression of bond angles from the tetrahedral value of 109.5°.
2.	Torsional strain	Eclipsing of bonds on neighbouring atoms.
3.	Steric strain	Repulsive interactions between non-bonded atoms in close proximity.
4.	Ring strain	Combination of angle strain and torsional strain.

The gauche butane is less stable than antibutane by 3.8 kJ/mol. because of steric interference between H-atoms on the two methyl groups.

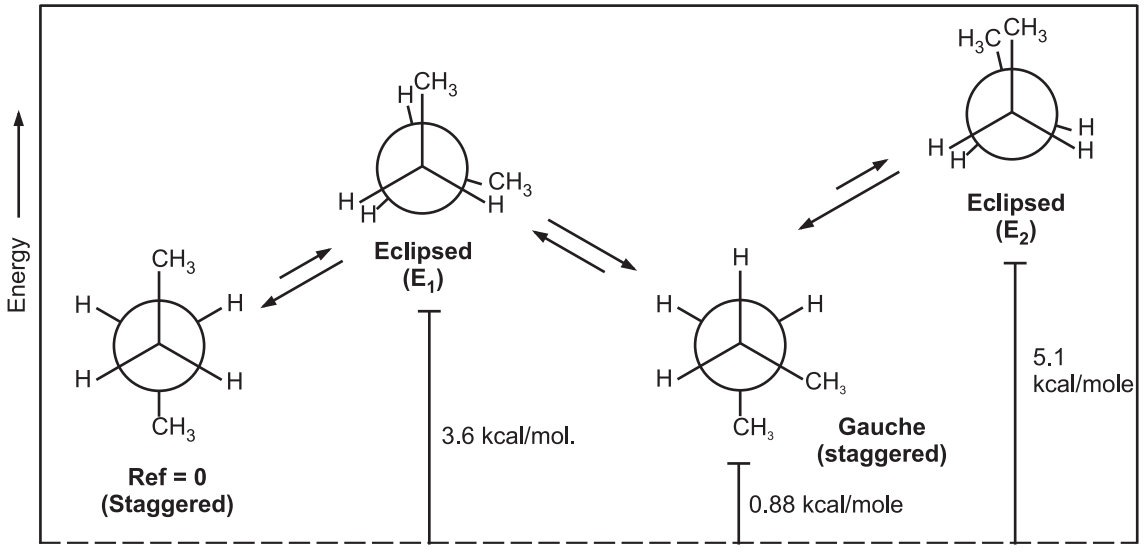


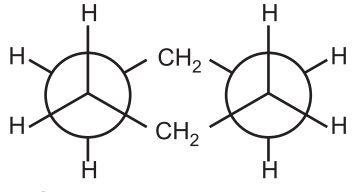
Fig. 2.1: n-Butane torsional energy profile

2.4.3 Conformations of Cyclohexane

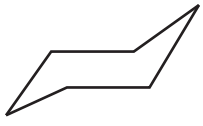
In cyclohexane all carbon atoms are sp^3 hybridized with a bond angle of 109°. This leads to two types of conformations.

(i) Chair conformation: It is the most stable form having tetrahedron bond angle of 109°. It adopts staggered arrangement having least torsional strain.

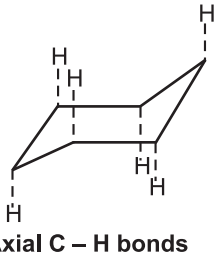
Chair cyclohexane has six axial hydrogens perpendicular to the ring (parallel to the ring axis) and six equatorial hydrogens near the plane of the ring.



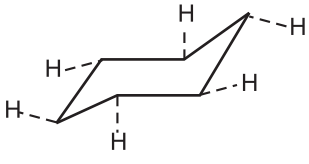
Staggered arrangement of bonds in chair conformation



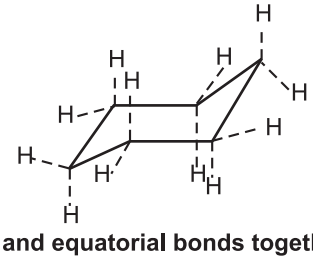
Chair conformation



Axial C – H bonds



Equatorial C – H bonds



Axial and equatorial bonds together

Six membered rings are almost free of strain in a chair conformation.

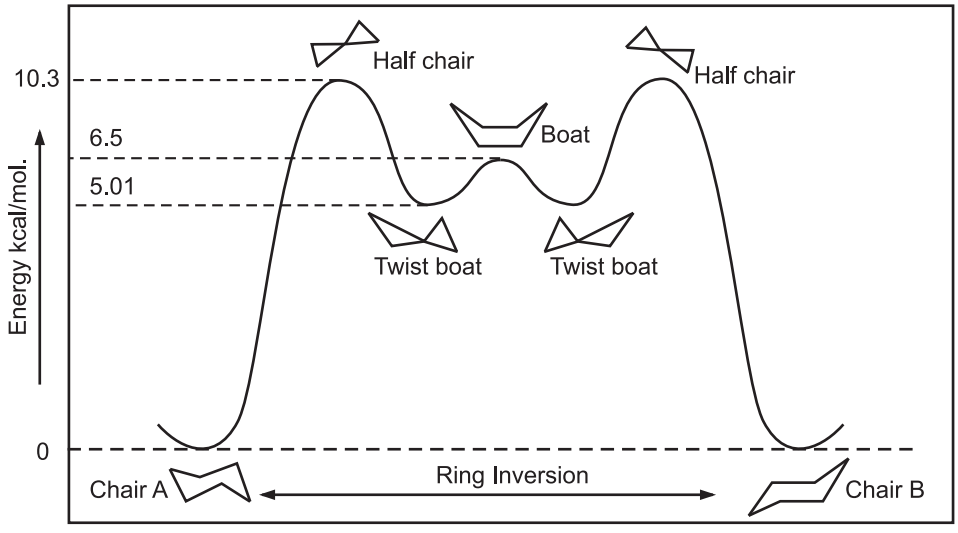


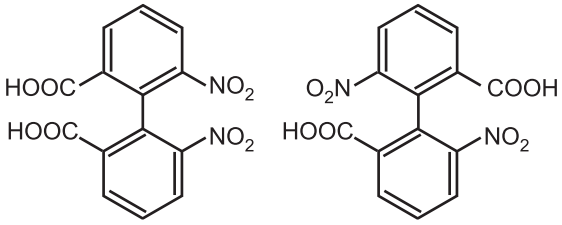
Fig. 2.2: Cyclohexane torsional energy profile

Boat form can be obtained from chair conformation by bending of the bonds. This transformation of chair to boat form occurs through intermittant – half chair and twist boat form. In boat conformation, carbon 1 and 4 are bent towards each other while all hydrogens in the chair conformation are staggered, four hydrogens are eclipsed in the boat conformation. Hence, the boat conformation is less stable than a chair conformation by 6.5 kcal/mol.

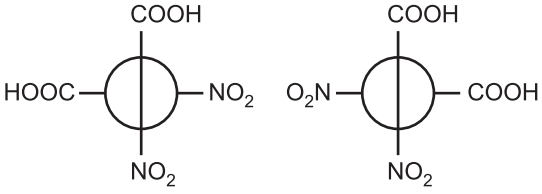
As a result of simultaneous rotation about all C – C bonds, chair conformations readily get interconverted, resulting in the exchange of axial and equatorial positions. It is known as ring inversion or ring flip. In this process, equatorial bonds become axial and axial becomes equatorial.

Atropisomerism: Atropisomerism is stereochemistry arising from restricted bond rotation that creates a chiral axis. Atropisomers are stereoisomers resulting from hindered rotation about one or more single bonds between two planar moieties where the energy barrier to rotation is high enough to allow for isolation of individual conformers. The conformers are detectable by NMR if half lives of conformers exceed 10^{-2} sec. and can be isolated if their half lives are above 1000 sec.

The name atropisomerism (from Greek, a = not and tropos = turn) was introduced by Kuhn in 1933 but it was first detected in 6,6-dinitro -2, 2′-diphenic acid by Christie in 1922. The bulkier groups on ortho position of the biphenyl ring restrict the rotation through C–C bond gives two enantiomers and resolvable at room temperature.



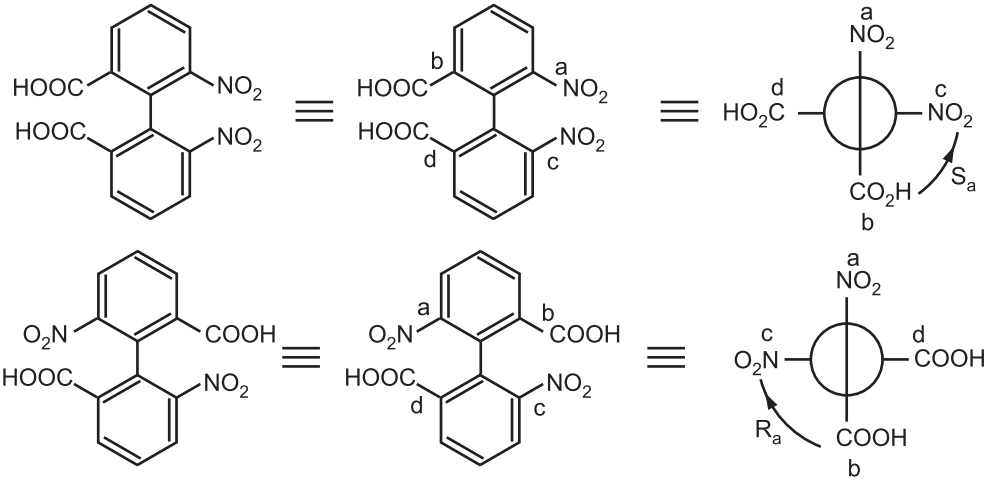
Atropisomers



Newman projections

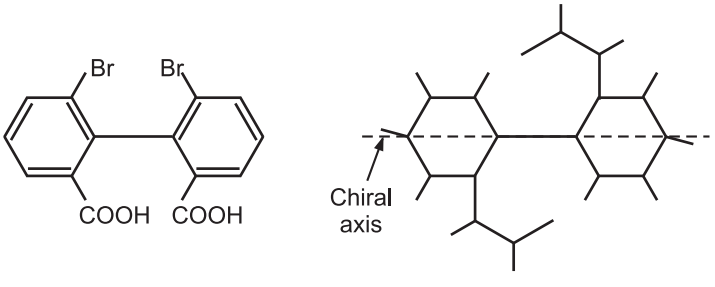
Atropisomerism induces time dependent inversion of chirality via bond rotation generating atropisomers having different pharmacokinetic, biological and toxicological profiles.

Nomenclature: The Cahn-Ingold-Prelog system suggested assigning stereo chemical descriptors (R, S descriptors) to molecules with axial chirality. All four groups are ranked with overall priority given to the groups on the front atom of the Newman projection. The two configurations are termed as R_a and S_a in analogy to the conventional R/S.



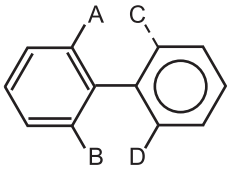
In yet another nomenclature, if the sequence a-b-c-d of the substituents is clockwise, the configuration is called P or Δ. If it is counter clockwise, the configuration is called M or ^.

Atropisomerism is also called as axial chirality. The chirality is not simply a centre or a plane but an axis. The simple symmetric biphenyl is achiral. Only biphenyl having different substitutents at ortho position contains a chiral axis. The biphenyl rings turn perpendicular to each other in order to minimize steric clashes the biphenyl bond restricted. For example,



2.5 CONDITIONS FOR OPTICAL ACTIVITY

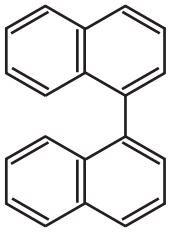
(i) The planes of the two aryl groups must be non-planar. It is achieved by placing bulky groups in the ortho positions.

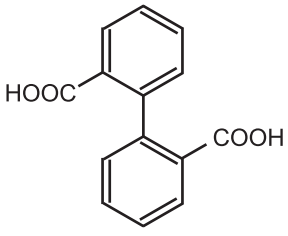


(ii) In most of the cases, the enantiomers can be resolved.

(iii) Ortho substitutents increase the restricted rotation by their steric repulsion.

(iv) Mono ortho substituted biaryl compounds do not show atropisomerism at room temperature. e.g.





(v) In addition to the substitutents at ortho position, the bulky groups adjacent to the ortho substitutents increase stability and isolatability of atropisomers.

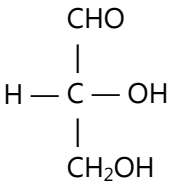
(vi) Heteroaromatic system provides chirality even though their ortho substituents are same.

2.6 OPTICAL AND GEOMETRICAL ISOMERISM

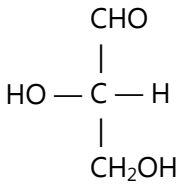
Optical Isomerism (enantiomerism): In 1815, Biot found that a number of organic and inorganic compounds in the solution form, have the ability to rotate the plane of polarized light in opposite directions but in identical amplitude, passing through them. Optical isomerism is seen in compounds that can rotate plane polarised light. A carbon atom connected to four chemically different functional groups is known as asymmetric or chiral carbon and the presence of at least one asymmetric carbon atom in the structure is the pre-requirement for a molecule to show optical isomerism.

If there is one asymmetric carbon then two optically active isomers are possible. Isomer rotating plane of polarized light to the right is said to be dextrorotatory (Latin, dexter : right) while isomer showing rotation to the left is known as laevorotatory (Latin, laevus : left). Both isomers are mirror images of each other yet are not superimposable. They are called as enantiomers and the pair of enantiomers is called as enantiomorph. An enantiomer does not possess a plane or center of symmetry.

For example,



D-glyceraldehyde



L-glyceraldehyde

When the enantiomers are present together in equal concentration, the rotation of plane polarized light caused by laevo isomer will be neutralized by a dextro rotating isomer and the mixture will be optically inactive. Such mixtures are called as racemic mixtures. The conversion of an enantiomer into a racemic form is called as racemization. While the separation of racemic mixture into individual enantiomers is called as resolution. The maximum number of optically active isomers possible for a molecule having more than one asymmetric carbon atoms may be given by the formula

$$N = 2n$$

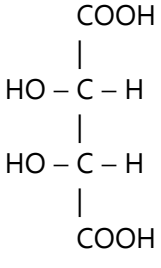
where,

N = Number of optically active isomers, and

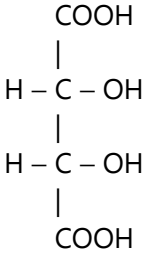
n = Number of asymmetric carbon atoms.

With the exception of rotation of plane-polarised light, enantiomers have identical physical and chemical properties like boiling point, melting point, solubility. Their chemical properties are same towards achiral reagents, solvents and conditions. Towards chiral reagents, solvents and catalysts, enantiomers react at different rates.

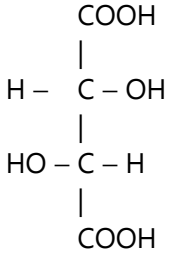
As per the rule given above, tartaric acid will have four optically active forms because of the presence of two asymmetric carbon atoms.



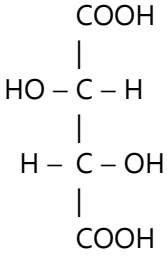
(I)



(II)



(III)



(IV)

Forms (I) and (II) are identical and symmetrical. In these forms, the upper half is the mirror image of the lower half. This makes the molecule optically inactive through internal compensation. Such identical and symmetrical stereoisomers are called as meso-isomers.

Forms (III) and (IV) are mirror images of each other but are not superimposable. They are enantiomeric forms.

While if you compare (III) with (I) or (IV) with (I), these are not enantiomeric pairs. They are neither mirror images nor superimposable. Only one of the two halves of their molecules

are identical while the remaining halves are mirror images. Such stereoisomers which are not mirror images and are non-superimposable are called as diastereomers. They have different physical and chemical properties, with both achiral and chiral reagents. The rates are different and the product may be different.

A molecule is called as chiral if it is not superimposable to its mirror image. Many drugs bear one or more asymmetric carbon atoms on their skeleton. Due to non-identical 3D structures, the interaction of these chiral molecules with the target sites may differ.

The resulting enantiomers have different pharmacokinetic profile and may elicit differentiated biological responses. The biological response induced by a pair of enantiomers can differ in potency or in nature. One enantiomer may act at one receptor site whereas another enantiomer is recognized by other target sites and possesses altogether different activity and toxicity profile.

2.6.1 Optical Isomers and Biological Activity

Stereochemistry, enantiomers, symmetry, asymmetry and chirality are important concepts that help us to understand the therapeutic and toxic effects of drugs. The word 'chiral' is derived from the Greek word *cheir* which means 'hand'. A chiral drug consists atleast one asymmetric carbon atom and has two enantiomers. Although each enantiomer has identical chemical and physical properties, individually they may interact differently with receptors, enzymes and proteins in the body. A number of mechanisms (e.g. metabolism, protein binding, clearance) in the body can be stereoselective which may account for pharmacokinetic differences among enantiomers.

Formulation factors such as the rate of dissolution, melting point, powder flow characteristics and solubility are all different for the racemate and to be taken into account to ensure bioequivalence of the formulations.

Because the isomers have different three dimensional structures, they have different affinities for receptors and enzymes which are also three dimensional. This explains the reason for the different therapeutic and toxicological properties exhibited by different enantiomers.

Generally one enantiomer is more potent than the other in exhibiting pharmacological response. The more potent enantiomer is called as eutomer and less potent enantiomer is termed as distomer. The ratio of activities of eutomer and distomer is called as 'eudismic ratio' which is a useful parameter to assess the relative potency of the enantiomers. This ratio is normally different at different receptor sites. The logarithm of this ratio is termed as eudismic index (EI).

If two enantiomers of disopyramide are administered independently, they have the same pharmacodynamic and pharmacokinetic profile. If administered together, they have dramatically different pharmacokinetic profiles. This is the result of difference in protein binding.

Table 2.3: Plasma-protein binding of enantiomers

Drugs	% unbound	
Acidic Drugs:		
Indactinone	R (–) 0.90	S (+) 0.30
Methobarbital	R (–) 2.29	S (+) 0.13
Moxalactam	R (+) 47.00	S (–) 32.00
Pentobarbital	R (+) 36.60	S (–) 26.50
Phenprocoumon	R (+) 1.07	S (–) 0.72
Warfarin	R (+) 1.20	S (–) 0.90
Basic Drugs:		
Amphetamine	(+) 84	(–) 84
Chloroquine	(+) 33	(–) 51
Disopyramide	(+) 27	(–) 39
Fenfluramine	(+) 2.8	(–) 2.9
Methadone	(+) 9.2	(–) 12.2
Propoxyphene	(+) 1.8	(–) 1.8
Propranolol	(+) 12	(–) 11
Tocainide	(+) 86-91	(–) 83-89
Verapamil	(+) 6.4	(–) 11

Similarly, the stereoselective clearance affects the plasma half-life of the drug. Upon administration of leucovorin calcium enantiomers, *l*-leucovorin is rapidly cleared from the body and has a plasma half-life of 32 minutes, whereas d-leucovorin is slowly cleared and has a plasma half-life of 45 minutes.

S (–) Timolol is one of the few adrenoceptor blockers marketed as the pure enantiomer used clinically to treat systemic hypertension, angina pectoris and glaucoma. When this form is used topically in eyes for treating glaucoma, severe bronchoconstriction is noticed. In contrast R (+) timolol lowers intraoccular tension without causing significant bronchospasm. R (+) form is therefore safer for treating glaucoma than S (–) form. Similarly humans preferentially metabolise (+) fenfluramine while rats favour the (–) enantiomer.

Table 2.4: Worldwide sales of single-enantiomer drugs

	Total market ($)		Single enantiomer drugs ($)	
$ Billions	**1999**	**2000**	**1999**	**2000**
Analgesic	21.5	23.0	1.0	1.3
Antibiotics/Antifungals	29.3	31.7	23.9	23.9
Antiviral	17.7	19.1	6.2	6.5
Anticancer	13.7	15.6	9.4	10.4

Contd...

Cardiovascular	42.7	46.6	24.8	26.9
Central nervous system	47.7	53.9	8.6	9.0
Dermatological	17.9	18.4	1.3	1.2
Gastrointestinal	43.9	47.2	3.0	3.5
Hematology	16.5	15.4	8.6	9.1
Hormones	20.0	22.0	13.8	14.6
Ophthalmic	7.1	7.4	1.8	2.0
Respiratory	36.5	40.5	5.1	6.1
Vaccines	6.5	7.3	2.0	3.0
Others	39.0	41.9	5.5	5.6
Total	**360.0**	**390.0**	**115.0**	**123.3**

Table 2.5: Pharmacological effects of Racemic drug mixtures

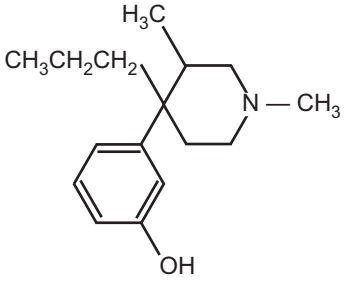
Drug	Biological response	Enantiomer
Terbutaline	Trachea relaxation	(–)
Propranolol	β-blockade	(S)
Amosulalol	α-blockade	(+)
	β-blockade	(–)
Warfarin	Anticoagulation	(S)
Verapamil	Negative chronotropic	(–)
Atenolol	β-blocker	(S)
Nitrendipine	Ca^{++} channel blocker	(S)
Zopiclone	Sedation	(R)
Terfenadine	Antihistaminic	(S)
Albuterol	Antiasthmatic	(S)
Flurbiprofen	Anti-inflammatory	(S)
Ketoprofen	Anti-inflammatory	(S)
Thalidomide	Immunosuppresive	(S)
Tetramisole	Anthelmintic	(S)-form (levamisole)
Propoxyphene	Analgesic	Dextro form
	Antitussive	Laevo form
Tranylcypromine	Antidepressant	(–)
	Improvement in performance	(+)
Sotalol	Antihypertensive	(–)
	Antiarrhythmic	(+)

(1) Dexchlorpheniramine is highly stereoselective; the (S) - (+) - isomer is about 200 times more potent than the (R) - (–) - isomer.

(2) d-Ketamine is a hypnotic and analgesic agent; the *l*-isomer is responsible for the undesired side-effects. In the case of local anaesthetic prilocaine, although both isomers are active, only one isomer contributes to the toxicity.

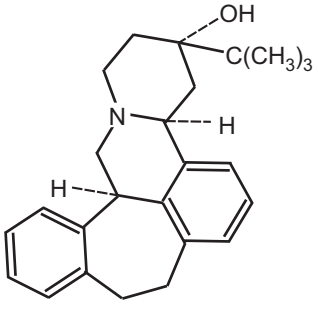
(3) Both isomers of bupivacaine are local anaesthetics, but only the *l*-isomer shows vasoconstrictive activity. Indacrinone has a uric acid retention side-effect. The d-isomer is responsible for both the diuretic activity and the side-effect while the *l*-isomer acts as a uricosuric agent.

(4) It also, is possible for the enantiomers to have opposite effects. The *l*-isomers of some barbiturates exhibit depressant activity and the d-isomers have convulsant activity. Similarly the d-isomer of the narcotic analgesic picenadol, is an opiate agonist, the *l*-isomer is a narcotic antagonist and the racemate is a partial agonist.



Picenadol

(5) (+) - Butaclamol is a potent antipsychotic, but the (–) isomer is essentially inactive. The eudismic ratio (+/–) is 1250 for D_2-dopaminergic receptor. (–) Baclofen is a muscle relaxant that binds GABA B receptors. The eudismic ratio (–/+) is 800.



Butaclamol

(6) The eudismic ratio (*l*/d) for propranolol is about 100. However, propranolol also exhibits local anaesthetic activity for which the eudismic ratio is 1.0. Labetalol, as a result of two asymmetric carbon atoms, exists in four stereoisomeric forms, having the stereochemistries (RR), (SS), (RS) and (SR). This drug has α- and β-adrenergic blocking properties. The (RR) - isomer is predominantly the β-blocker and the (SR) - isomer is mostly the α-blocker. While other 50% of the isomers, the (SS) - and (RS)-isomers, are almost inactive.

(7) If you consider two enantiomers, such as R (–) and (S) (+) epinephrine, interacting with a receptor that has only two binding sites (Fig. 2.3), it becomes apparent that the receptor cannot distinguish between them. However, if there are at least three binding sites, the receptor easily can differentiate them. The R - (–) - isomer has three points of interaction and is held in the conformation shown to maximise molecular complementarity. The (S) - (+) - isomer can have only two sites of interaction (the hydroxyl group cannot interact with the hydroxyl binding site, and may even have an adverse steric interaction); consequently it has a lower binding energy.

The chiral interactions help us to discover which parts of the molecule are involved in primary receptor interaction. Chirality may also be used to distinguish different states of activation of ion channel receptors.

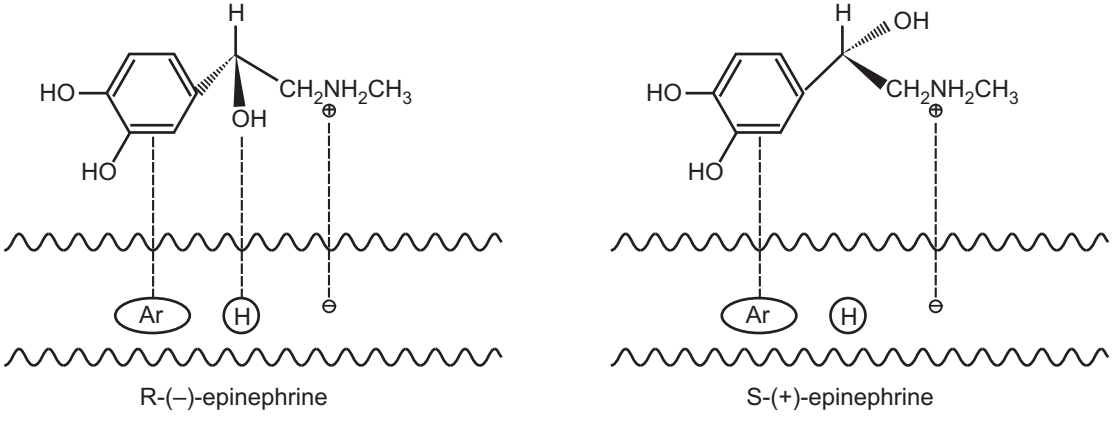


Fig. 2.3: Effect of stereochemical features on the biological activity

Generally in a recemic mixture, one enantiomer is bioactive while other remains either inactive or possesses different activities. Hence in case of drug containing one asymmetric carbon, administration of a racemic form permits the delivery of 50% active compound. At present only about 12% of synthetic chiral drugs are available in pure chiral form in the market while remaining 88% are sold as racemates.

An effort to make the drug commercially available in pure chiral form, add to the cost of the synthesis. Various options like, to reduce the number of asymmetric centers, replacing asymmetric carbon with nitrogen, adding symmetry to the molecule, are hence used to save this added cost.

When a drug exists in stereoisomeric forms, the rate and routes of metabolism may differ between the enantiomers. The rate of metabolism of two enantiomers would be expected to differ where they form diastereomeric complexes with the metabolizing enzyme. Extra complications may arise because of ability of metabolic processes to interconvert chiral centers.

Conformational Factors:

Various conformations are possible for a flexible drug structure. Besides drug, the receptor sites also exhibit flexible nature and can acquire conformation in adaptation to the mutual effect of drug. However, suitable steric features need to be present in a drug molecule if it is to have significant affinity and intrinsic activity at receptor site. The X-ray crystallographic spectrophotometry is routinely used to determine conformation of a drug molecule while NMR spectra provides information for geometric isomers when the compound is in liquid state.

Optical isomers, particularly diastereoisomers (i.e. compounds with two or more asymmetric centres), exhibit similar chemical reactions but different physical properties. Since the physical properties are important in drug distribution, metabolism and interaction with the receptor, the biological properties of such isomers may also be different.

We may expect from the definition of optical enantiomers (that compounds having identical physical and chemical properties except for their ability to rotate the plane of polarised light) that they may have the same biological activity. However, this is not the case with many of the enantiomers.

Table 2.6: Stereoisomeric Drugs

Cardiovascular Agents:		
Acebutolol	Alprenolol	Atenolol
Betaxolol	Bisoprolol	Bopindolol
Bucumolol	Butefolol	Bufuralol
Bunitrolol	Bupranolol	Butofilolol
Carazolol	Carvedilol	Curteolol
Disopyramide	Dobutamine	Indenolol
Mepindolol	Metipranolol	Metroprolol
Nadolol	Oxpranolol	Pindolol
Propranolol	Quinidine	Sotalol
Toliprotol	Verapamil	Xibenolol
Central Nervous System:		
Butaclomol	Butorphanol	Buprenorphine
Codeine	Dihydroergotoxine	Dobutamine
Fluoxetine	Ketamine	Lorazepam
Meclizine	Nalbuphine	Nalfename
Naloxone	Naltrexone	Oxaprotiline
Oxymorphone	Phenylpropanol amine	Physostigmine
Chloramphetamine	Thioridazine	Toloxaton
Tomoxetin	Vasopressin	Viloxazin

Contd...

Anti-inflammatory and Analgesics:		
Beclomethasone	Betamethasone	Cicloprofen
Corticosteroid	Dihydroxy thebane	Fenbuphen
Fenoprofen	Flurbiprofen	Ibuprofen
Ketoprofen	Indoprofen	Minoxiprofen
Norlevorphanol	Oxycodone	Pirpofen
Stanozolon	Steroids	Suprofen
Triamcinolon		
Anticancer:		
Bleomycin	Cytarabine	Doxorubicin
Methotrexate	Mitomycin C	
Antibiotics, Anti-infectives, Antiviral:		
Ciprofloxacin	Norfloxacin	Ofloxacin
Genitourinary Hormones:		
Benzyl glutamate	Bromocriptine	Butoconazole
Calcitonin	Estradiol	Flurogesterone
Gonadorelin	Ketodesogestrel	
Norgestrel	Prednisolone	
Progesterone	Testosterone	

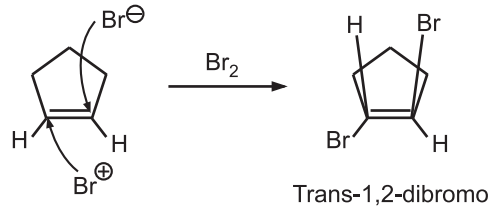
Table 2.7: Geometrical Isomerism

Sr. No.	Drug Name	Biologically active form	Therapeutic activity
1.	Diaminodichloroplatinum	cis-platin	Anticancer drug in testicular and ovarian cancers.
2.	Diethylstilbestrol (DES)	trans-DES	Estrogenic activity
3.	Thiothixene	cis-thiothixene	Antipsychotic acitivity
4.	Vitamin K_2	trans form	
5.	3-methylfentanyl (Mefentanyl)	cis-mefentanyl	Analgesic
6.	Resveratrol	trans form	Anticancer drug
7.	Retinal	11-cis isomer	Vision

2.7 STEREOSPECIFIC AND STEROSELECTIVE REACTIONS

(a) Stereospecific Reactions:

Stereospecific reaction is a reaction where the stereochemistry of the starting material governs the stereochemistry of the product. Only a single stereoisomer is produced in a given reaction rather than a mixture. For example, bromination of cyclopentene occurs through stereospecific anti addition to give trans-1, 2-dibromocyclopentane only.

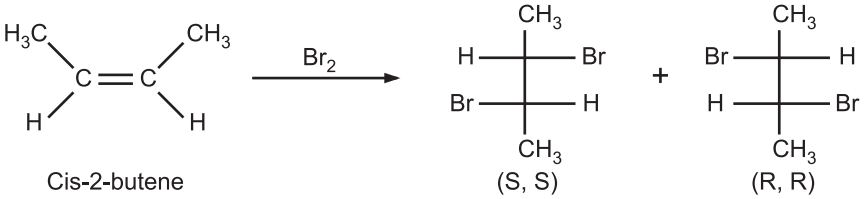


Cyclopentene — Trans-1,2-dibromo cyclopentane

During the addition of dichlorocarbene to 2-pentene, the cis-2-pentene gives only one product, substituted cis-cyclopropane while the trans-2-pentene gives only one product, substituted trans-cyclopropane.

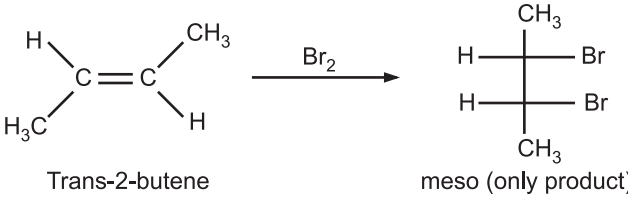
In yet another bromination reaction of 2-butene, two geometric isomers (cis and trans) of 2-butene gives three stereoisomeric products where cis-2-butene gives (S, S) and (R, R) 2,3-dibromobutane while trans-2-butene gives meso-2,3-dibromo butane.

(i)



Cis-2-butene — (S, S) — (R, R)

(ii)



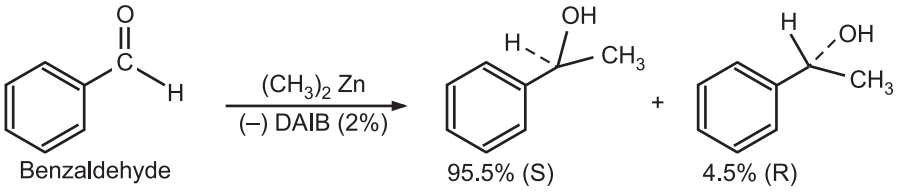
Trans-2-butene — meso (only product)

In above case, bromination of cis-2-butene, the stereochemistry of products is governed by cis-2-butene. Here it is stereospecific reaction. While bromination of trans-2-butene leads to formation of only one product (meso). Hence, it is stereoselective reaction.

(b) Stereoselective Reactions:

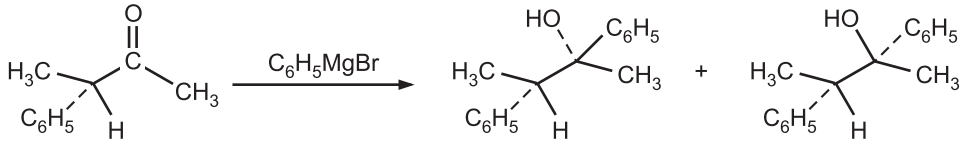
Stereoselective reaction is a reaction where one stereoisomer of a product is formed preferentially over another. If enantiomers of a chiral product are formed in unequal amounts, it is called as an enantioselective reaction.

(i) Enantioselective reaction:



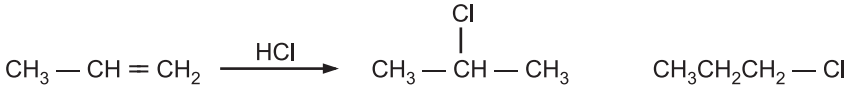
Benzaldehyde 95.5% (S) 4.5% (R)

(ii) Diastereoselective reaction:



91.5% 8.5%

Similarly when diastereoisomers are produced in unequal amounts, the reaction is called diastereoselective reaction. In this reaction two dia-stereoisomers could be formed but one is favoured. All stereospecific reactions are stereoselective but stereoselective reactions are not necessarily stereospecific. For example, the reaction of HCl with propene gives 1-chloropropane and 2-chloropropane.

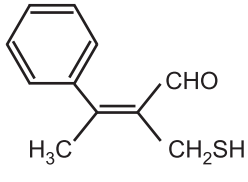


Propane 2-chloro propane (Major) 1-chloro propane (Minor)

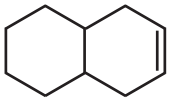
Since, one product is favoured over another, this reaction is said to be stereoselective. If above reaction yields only 2-chloropropane, then the reaction is called stereospecific.

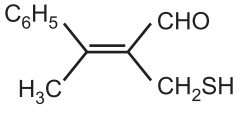
QUESTIONS

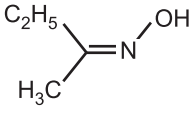
1. What is conformational isomer? Explain with suitable example.
2. Discuss chair, boat and twist boat conformation of cyclohexane molecule.
3. Give conformational isomerism in ethane.
4. Draw Fischer projection for
   i) 2-chlorobutane ii) (R)-2-Butanol
5. Why chair conformation is more stable than boat conformation ? Explain.
6. Define and classify stereoisomerism. Explain different types of representation of structure.
7. Assign Z and E form

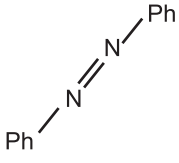


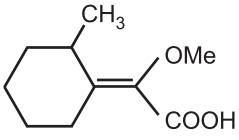
8. Explain conformation of n-butane.
9. Explain chair conformation is more stable than boat by using cyclohexane example.
10. Why trans-decalin is more stable than cis-decalin, explain with structure?
11. Explain any two stereospecific reactions and any two stereoselective reactions.
12. Explain stereochemistry of monosubstituted cyclohexane.
13. What is Atropisomerism ? Explain with respect to Biphenyls.
14. Draw Sawhorse projection of following
    a. Meso 2,3-dibromo butane
    b. 2-chlorobutane
    c. 2R, 3S 2-chloro butanol
15. Trans 1,2 dimethyl cyclohexane is more stable than its cis isomer. Why ?
16. What is isomerism involved in Allenes?
17. Write note on stereospecificity and write three examples.
18. Assign E and Z nomenclature for following:

(i) 

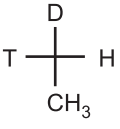
(ii) 

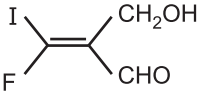
(iii) 

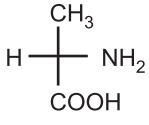
(iv) 

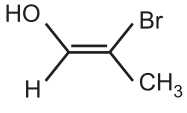
(v) 

19. Give configuration of following isomers:

(i) 

(ii) 

(iii) 

(iv) 

20. Define stereoisomer. Explain how you will calculate number of stereoisomers by taking any one example.
21. Describe confirmation isomerism of n-butane with energy profile diagram.
22. Explain confirmation of decalin.
23. Explain conformation isomerism of dialkyl cyclohexane.
24. What is meant by geometric isomerism? What are conditions to be fulfilled by compound to exhibit geometric isomerism.
25. Explain the terms "enantiomers" and discuss Newmann and Sawhorse representation of ethane.
26. Enumerate few advantages of Z/E nomenclature over cis/trans nomenclature.

❖❖❖

Unit...III

HETEROCYCLIC COMPOUNDS

♦ **SYNOPSIS** ♦

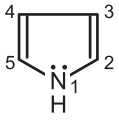
3.1 INTRODUCTION

Heterocycles are cyclic compounds in which one or more atoms of the ring are hetero atoms like O, N, S, P, etc. They are present in many biologically important molecules such as alkaloids, essential amino acids, vitamins, haemoglobin, nucleic acids and hormones. Heterocyclics are also present in large number of synthetic drugs like caffeine, acyclovir (antiviral), clopidogrel (anti-platelet), diazepam, carbamazepine (anti-epileptic), nicotine, etc.

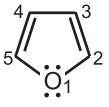
3.1.1 Classification

These heterocycles may be classified on the basis of number of atoms present in the ring. For example,

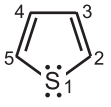
(a) Five membered heterocyclic ring containing one heteroatom:



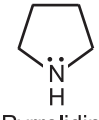
Pyrrole



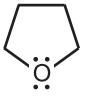
Furan



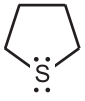
Thiophene



Pyrrolidine

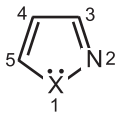


Tetrahydro-furan (THF)



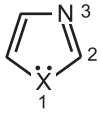
Thiolane

(b) Five membered heterocyclic ring containing two heteroatoms (1, 2 – azoles):



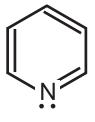
(i) Pyrazole: X = N – H
(ii) Isoxazole: X = O
(iii) Isothiazole: X = S

(c) Five membered heterocyclic ring containing two heteroatoms (1, 3 – azoles):

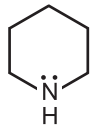


(i) Imidazole: X = N – H (Azole)
(ii) Oxazole: X = O (Oxa)
(iii) Thiazole: X = S (Thia)

(d) Six membered heterocyclic ring containing one heteroatom:

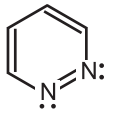


Pyridine

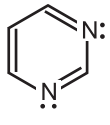


Piperidine

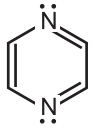
(e) Six membered hetero cyclic ring containing two heteroatoms:



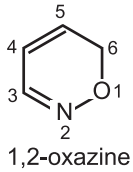
Pyridazine



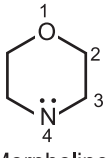
Pyrimidine



Pyrazine

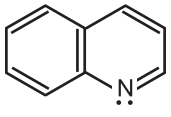


1,2-oxazine

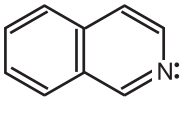


Morpholine

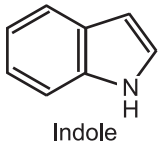
(f) Polyclic heterocyclic rings:



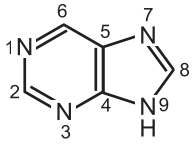
Quinoline



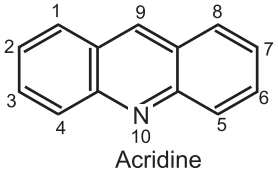
Isoquinoline



Indole



Purine



Acridine

3.1.2 Nomenclature

The IUPAC rules for nomenclature of heterocyclic rings are as follows:

(i) The type of heteroatom is indicated by a prefix as shown below:

Sr. No.	Heteroatom	Prefix	Order of Priority
01	Nitrogen	Aza	3
02	Oxygen	Oxa	1
03	Sulfur	Thia	2
04	Phosphorus	Phospha	4

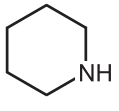
(ii) The ring size is indicated by a suffix as shown below:

Ring size	Suffix
3	ir (from tri)
4	et (from tetra)
5	ol
6	in
7	ep
8	oc
9	on
10	ec

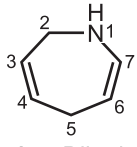
(iii) Unsaturation in the ring may be denoted by prefix such as "dihydro" or "tetrahydro". e.g.,

Oxa + irane
= Oxirane

Thia + Olane
= Thiolane

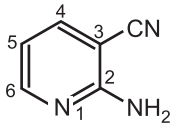


Aza + inane
= Azinane

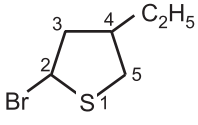


2, 5-Dihydro
azepine

(iv) The heteroatom is designated as number 1 and the substituents around the ring are numbered so as to have lowest number for the substituents. e.g.,

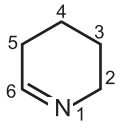


2-Amino-3-cyano azine
(2-Amino-3-cyano pyridine)

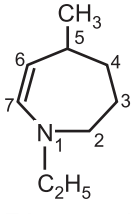


2-Bromo-4-ethyl
thiolane

(v) While numbering, give priority to saturated atoms. e.g.,



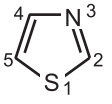
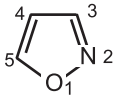
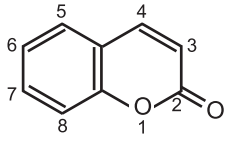
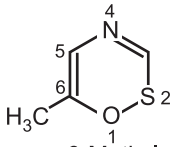
2,4,5,6-Tetrahydro
azine



1-Ethyl-5-methyl
-2,3,4,5-tetrahydro azepine

(vi) In case of ring containing more than one heteroatom, the order of preference for numbering is O, S and N. The ring is numbered from the heteroatom of preference

in such a way so as to give the smallest possible number to the other heteroatoms in the ring. e.g.,

6-Methyl
1,2,4-oxathiazine

(vii) A positively charged ring is denoted by suffix "- ium". While groups such as C = S and C = NH present in the ring are denoted by the suffixes "- thione" and "-imine".

Aromaticity and Basicity: Heterocyclic rings are aromatic if they obey Huckel's rules of aromaticity. The aromaticity is present if,

(i) The ring is planar

(ii) Continuous conjugated system is present (i.e., all atoms of the ring are sp^2 hybridized), and

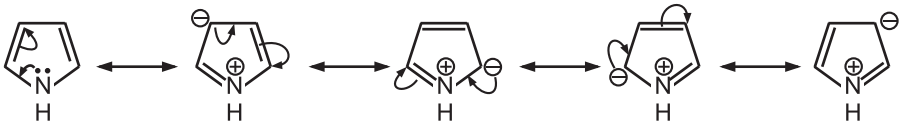
(iii) The number of π electrons is equal to 4n + 2, where n = 0, 1, 2, 3, etc.

According to these rules, pyrrole, furan, thiophene, imidiazole, pyridine, pyrimidine, are aromatic heteocycles. The aromaticity order in these heterocycles depends on the electro negativity of the heteroatom: O > N > S. Hence, aromaticity follows the order as:

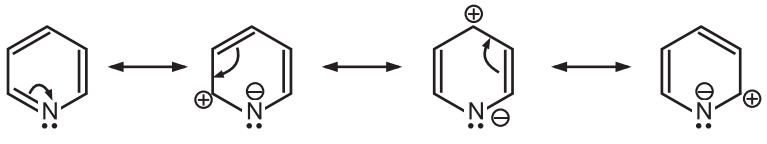
Thiophene > Pyrrole > Furan

These heterocycles are non-basic because the lone pair of electrons available with N-atom, becomes the part of the aromatic system and is not available for N-protonation.

The presence of a nitrogen atom in these heterocyclic aromatic rings, affects the electron density of other atoms in the ring. If the nitrogen atom acts as an electron donar, there is a net gain in electron density in the ring and the ring is called π - excessive. (i.e., all other atoms carry excess of electron density, δ -ve charge). For example pyrrole

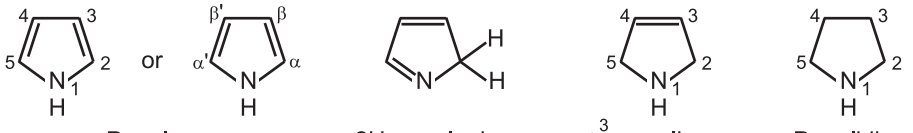


When the lone pair of electrons on N-atom does not involved in ring aromaticity, it can not be donated internally to other atoms of the ring through resonance. Due to its electronegative nature, the nitrogen atom pulls the electrons from other ring atoms through inductive effect to make the ring π - deficient. The N-atom retains electron density, δ -ve spreading a positive charge on the aromatic ring. Pyridine and pyrimidine are example of π - deficient rings.



3.2 PYRROLE

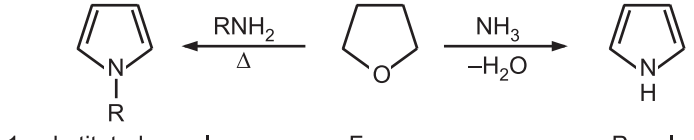
Pyrrole was fist isolated from coal tar in 1834. It is an aromatic heterocycle having weak aniline like odour. It is a colourless volatile liquid which like aniline darken by autoxidation. It has boiling point of 129 to 131°C.



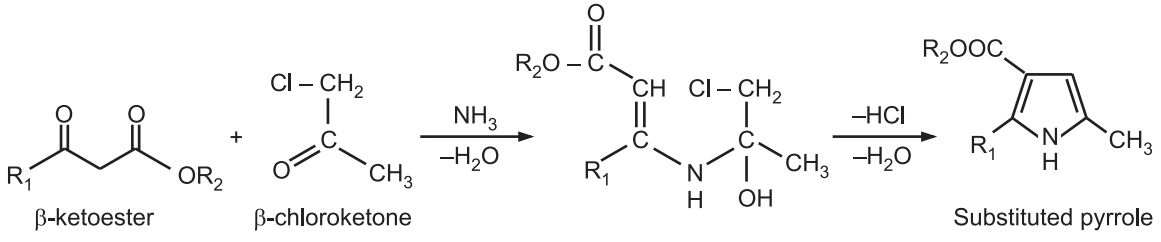
Pyrrole has three pairs of delocalized π electrons. Two of the pairs are shown as the bonds and the third pair is shown as a lone pair of nonbonding electrons on the nitrogen atom.

3.2.1 Chemical Synthesis

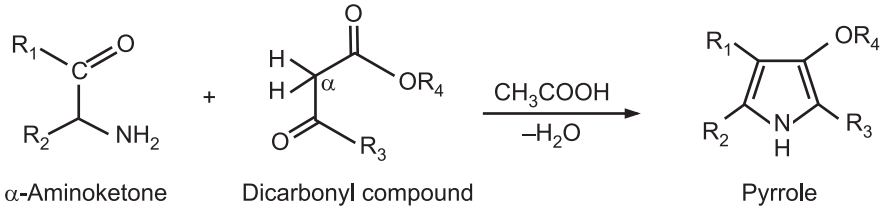
(1) Pyrrole is prepared industrially from furan by passing it over ammonia and steam and heated at 400°C in the presence of solid acid catalysts like SiO_2 and Al_2O_3.



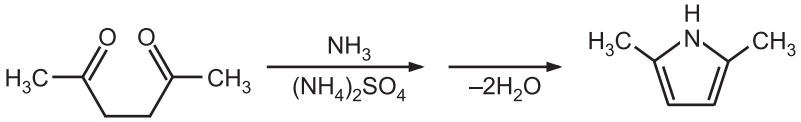
(2) Hantzsch Pyrrole synthesis: When α-haloketone or aldehyde is reacted with a β-ketoester or β-chloroketone and a base like ammonia/primary amine, it gives pyrrole. The base functions both as a reactant and as a catalyst.



(3) Knorr Pyrrole Synthesis: In this widely used method, α - amino ketone is condensed with another dicarbonyl compound containing an electron withdrawing group α to a carbonyl group (i.e., activated methylene group) in the presence of acetic acid.

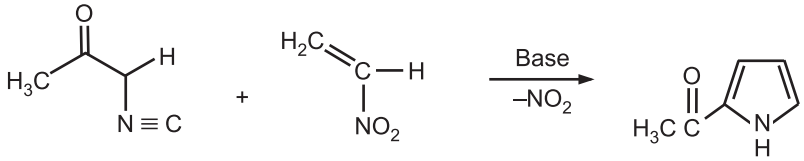


(4) Paal-Knorr Pyrrole Synthesis: It is a condensation reaction between 1,4-dicarbonyl compound with ammonia or a primary amine to form a substituted pyrrole. Pyrrole itself is formed from succinaldehyde and ammonia.



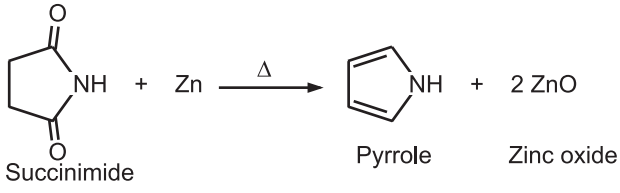
Acetylacetone 2,5-Dimethyl pyrrole

(5) Barton-Zard Synthesis: Pyrrole is obtained when an isocyanoacetate reacts with a nitroalkene in a 1, 4 – addition, followed by cyclization and elimination of nitro group.



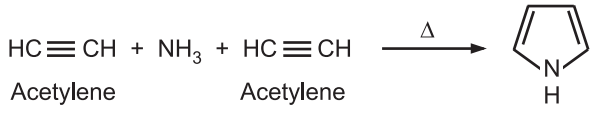
Isocyanoacetate Nitroethene Pyrrole

(6) From distillation of succinimide: Pyrrole is obtained by the distillation of succinimide with zinc dust.



Succinimide Pyrrole Zinc oxide

(7) From acetylene and ammonia: Pyrrole is obtained by passing acetylene and ammonia through a red hot tube.

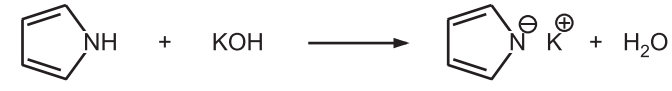


Acetylene Acetylene

3.2.2 Chemical Reactions

Pyrrole, furan and thiophene, all are π - excessive rings. Hence, all these rings are prone to electrophilic substitution reactions on the ring carbons. The order of reactivity for electrophile attack is pyrrole > furan > thiophene > benzene. The greater reactivity of pyrrole towards electrophiles is due to the greater electron releasing ability of N – atom than oxygen and sulfur atom. Thiophene is least reactive.

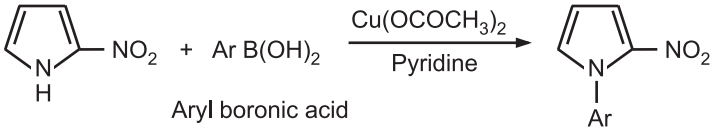
These heterocycles are π - excessive rings. Hence, these heterocycles are less reactive towards nucleophilic substitution reactions except deprotonation at the N-atom or C-atom. Pyrrole behaves both as a weak base and a weak acid. e.g.,



Pyrrole (weak acid) (Strong base) Potassium pyrrole

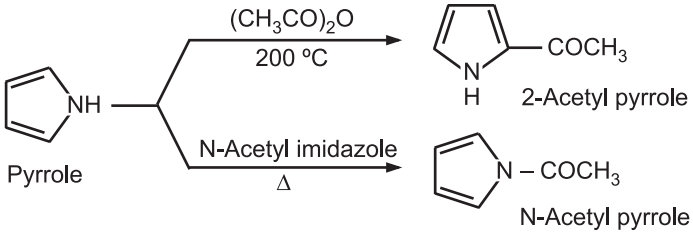
Hence, the proton attached to the nitrogen atom undergoes easy deprotonation in both acid and in alkali. Similar deprotonation of carbon atoms in the ring occurs only in more acidic conditions. The α - protons (C_2 & C_5) exchange occurs at twice the rate of the β-protons (C_3 & C_4).

(1) Alkylation and arylation: The sodium/potassium salt of pyrrole reacts with alkyl halide to give corresponding N – alkyl pyrrole. Presence of electron withdrawing substituent on pyrrole ring favours rapid N-alkylation or N-arylation.

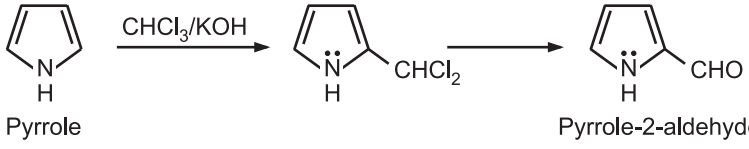


However mono C – alkylation of pyrrole can not be achieved by direct reaction with alkyl halides.

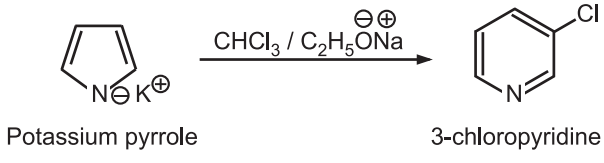
(2) Acylation: Pyrrole treated with acetic anhydride at 200°C gives 2 – acetyl pyrrole while N – acetyl pyrrole can be obtained by heating pyrrole with N – acetylimidazole.



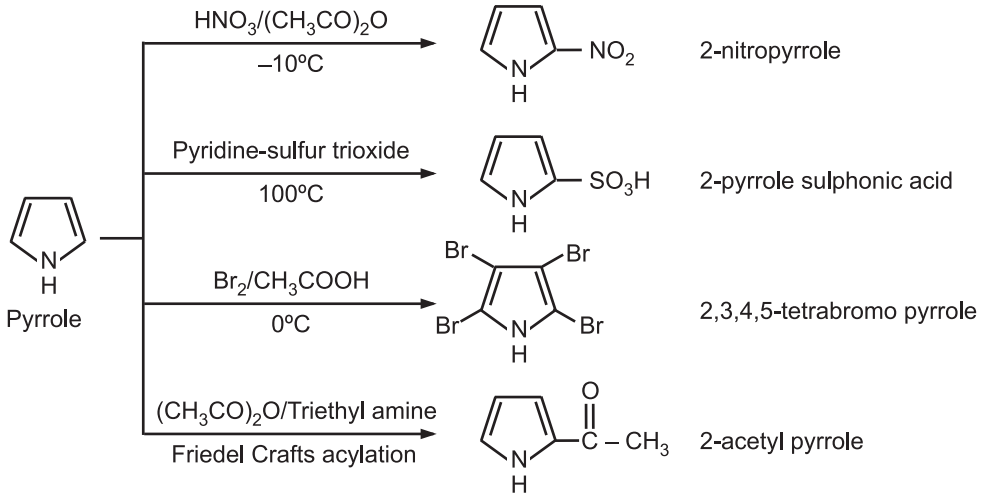
(3) Reimer – Tiemann reaction: In the presence of a strong base and chloroform, pyrrole undergoes Reimer – Tiemann reaction to form pyrrole – 2 – aldehyde.



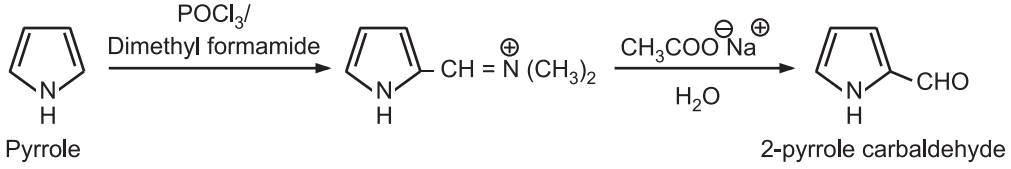
(4) Ring expansion: When potassium pyrrole is heated with chloroform and sodium ethoxide, the pyrrole (five – membered ring) expands to pyridine (six-membered ring).



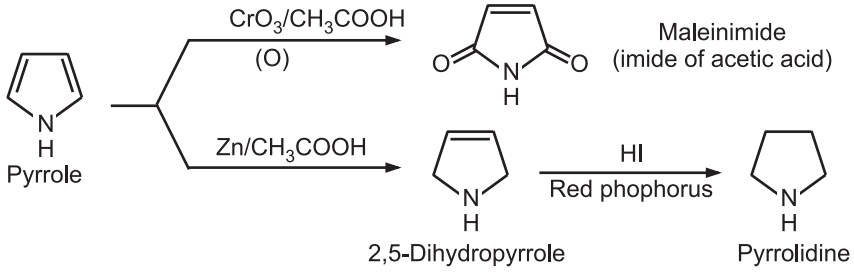
(5) Electrophilic substitution: The electrophilic substitution takes place preferably at C_2 or C_5 – positions. If these positions are already occupied then substitution takes place at C_3 or C_4 positions.



(6) Vilsmeier-Haack reaction: Pyrrole may be formylated by heating it with phosphorus oxychloride and dimethyl formamide. The intermediate is hydrolyzed in the presence of a mild base to 2 – pyrrole carbaldehyde.



(7) Oxidation and reduction: Pyrrole is oxidized to maleinimide and on reduction it gives pyrrolidine.

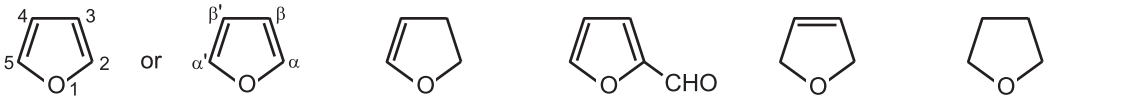


3.2.3 Applications in Drug Synthesis

Pyrrole is a structural constituent of haem, chlorophyll, Vitamin B_{12} and bile pigments. Pyrrole ring is also present in the drug tolmetin (NSAID), ketorolac (NSAID), sunitinib (anti-cancer), ageliferin (anti-bacterial), elopiprazole (antipsychotic), procyclidine (anti-muscarinic drug to treat parkinsonism) and atorvastatin (lipid lowering agent). Pyrrole is widely known as a biologically active scaffold having diversified therapeutic activities such as antipsychotic, β-adrenergic anatagonist, anxiolytic, antibacterial, antifungal, antimalarial and anticancer.

3.3 FURAN

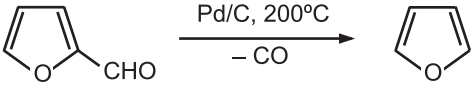
Furan was first reported by Heinrich Limpricht in 1870. It is a colourless, inflammable, volatile, liquid with boiling point of 31-32°C. The numbering and structures of furans are as follows:



Furan | 2,3-Dihydrofuran | Furfural | 2,5-Dihydro furan | 2,3,4,5-Tetrahydro furan

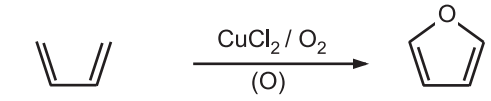
3.3.1 Chemical Synthesis

(1) The vapour phase decarboxylation of furfural in the presence of palladium and charcoal gives furan.



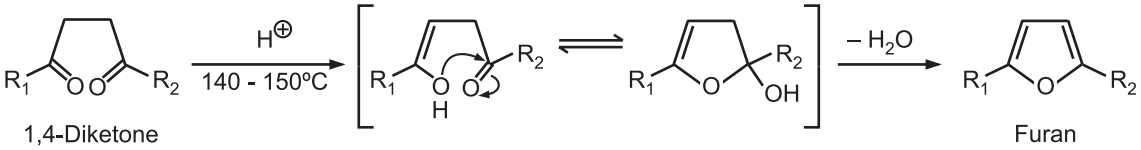
Furfural Furan

(2) 1,3-Butadiene can be converted to furan by the copper-catalyzed oxidation.



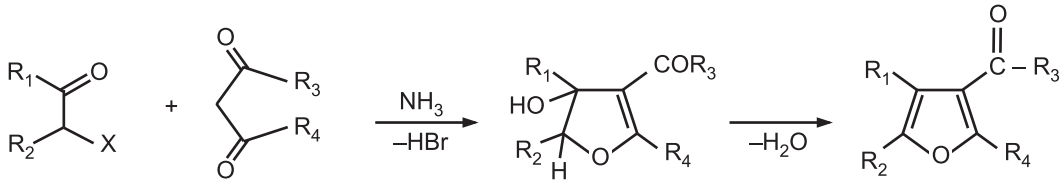
1,3-Butadiene Furan

(3) Paal-Knorr Synthesis: Under non-aqueous acidic conditions, 1, 4 – diketones undergo cyclization followed by dehydration to give furans.

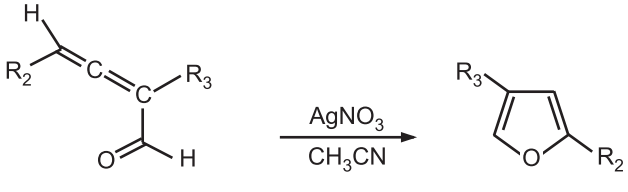


1,4-Diketone Furan

(4) Fiest-Benary Synthesis: It is a condensation reaction between an α - haloketone with a β - keto ester (or a β - diketone) in the presence of a base like ammonia or pyridine.

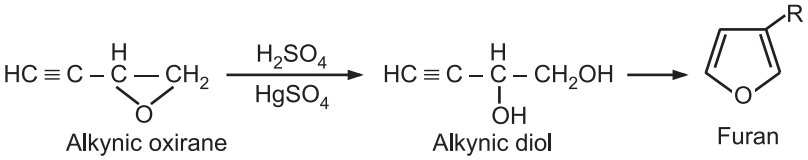


(5) Allenyl ketones undergoes cyclization in the presence of silver nitrate or silver borontetrafluoride in CH_3CN to give furans.

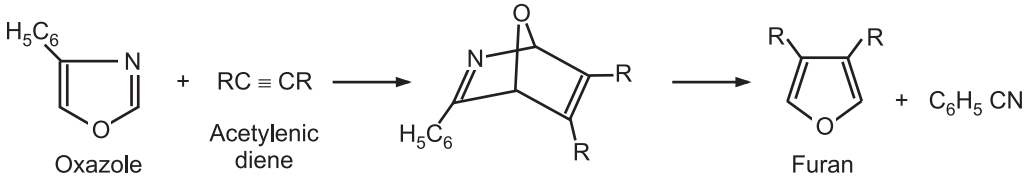


Allenyl ketone Furan

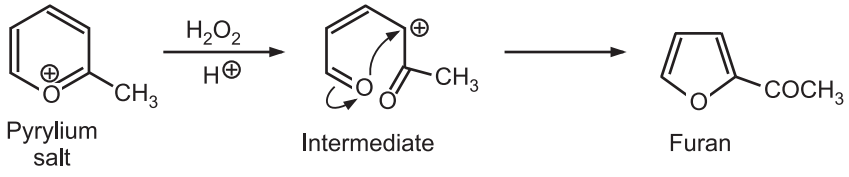
(6) Ring expansion: Alkynic oxirans when treated with sulfuric acid and mercury sulfate, undergo ring expansion to produce furans.



(7) From other heterocycles: Oxazoles undergo Diels-Alder cycloaddition reaction with acetylenic dienophiles. The resulting product provides furan upon loss of nitrile.



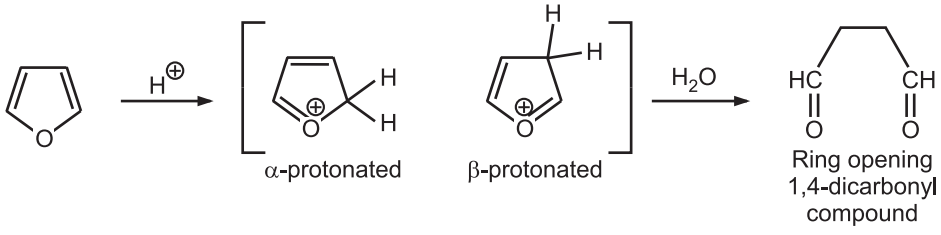
(8) From Ring contraction: Oxidative ring contraction of pyrylium salts with aqueous hydrogen peroxide and perchloric acid leads to formation of 2-acylfurans.



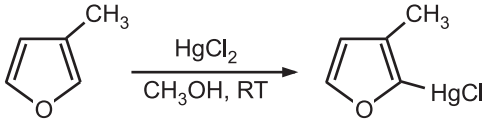
3.3.2 Chemical Reactions

Furan is a π-excessive heterocycle and hence prefers electrophilic substitution reactions. At the same time, it behaves chemically as a typical diene and exhibits greater reactivity towards addition reactions.

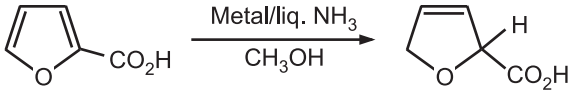
(1) Protonation: Furans substituted with electron - withdrawing substituents are stable towards acid. However the presence of electron-releasing substituents on furan leads to generation of reactive electrophiles during protonation which activate polymerization and the ring opening reactions.



(2) Mercuration: Furan readily undergoes mercuration.



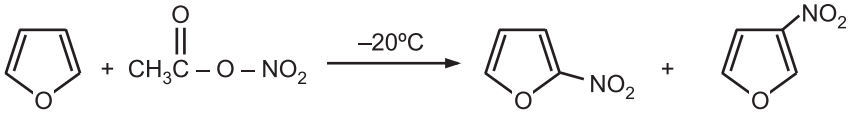
(3) Reduction: Simple furan is difficult to reduce to a tetra hydrofuran, without ring opening. Furoic acid can be reduced to dihydro derivative.



Furoic acid — 3,4-Dihydrofuroic acid

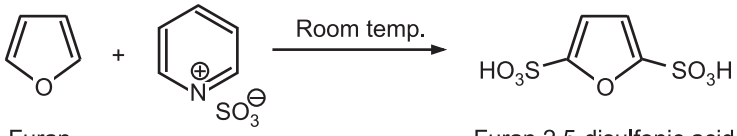
(4) Electrophilic Substitution:

(i) Nitration: Furan is nitrated with mild nitrating agent, acetyl nitrate, at low temperature.



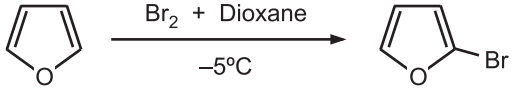
Furan — 2-Nitro furan (major) — 3-Nitro furan (minor)

(ii) Sulfonation: Furan is sulfonated with the complex of sulfur trioxide and pyridine or dioxane to give 2, 5 – disubstituted furan even at room temperature.



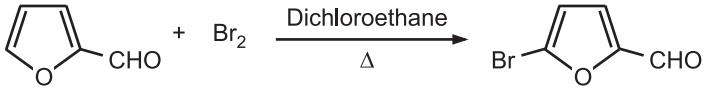
Furan — Pyridine-sulfur trioxide complex — Furan 2,5-disulfonic acid

(iii) Halogenation: The high reactivity of furan with chlorine and bromine at room temperature results in polyhalogenated products even at room temperature. Hence, milder conditions are required to yield mono-chloro or mono – bromo furans. Bromination of furan in DMF or dioxane at –5°C provides 2-bromofuran.



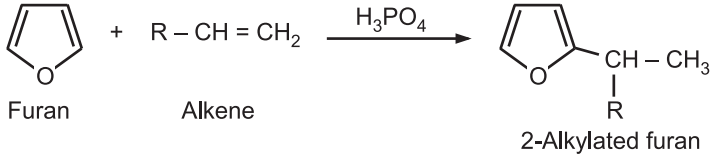
Furan — 2-Bromofuran

Furan substituted with an electron withdrawing substituent at position-2 generally provides 5-bromo derivative.



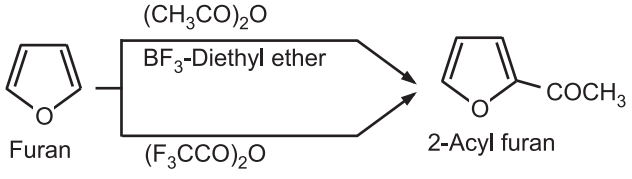
Furan-2-aldehyde — 5-bromo-furan-2- aldehyde

(iv) Alkylation: Furan does not undergo Friedel-Crafts alkylation due to its acid sensitivity. Furan can be alkylated at position-2 using alkene in the presence of mild catalysts like phosphoric or boron trifluoride.

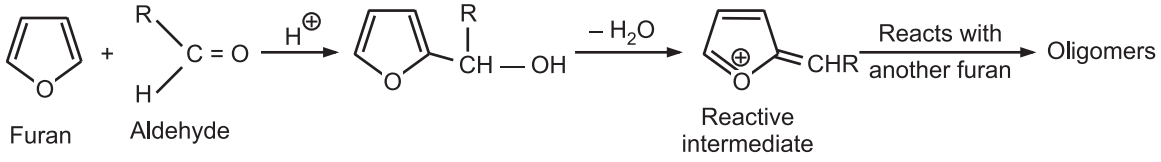


Furan — Alkene — 2-Alkylated furan

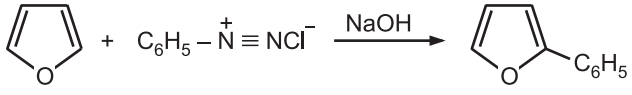
(v) Acylation: The acylation of furan with acid anhydride or acid halides normally requires mild catalysts like phosphoric acid or boron trifluoride. No catalyst is required if trifluoroacetic anhydride is used as acylating agent.

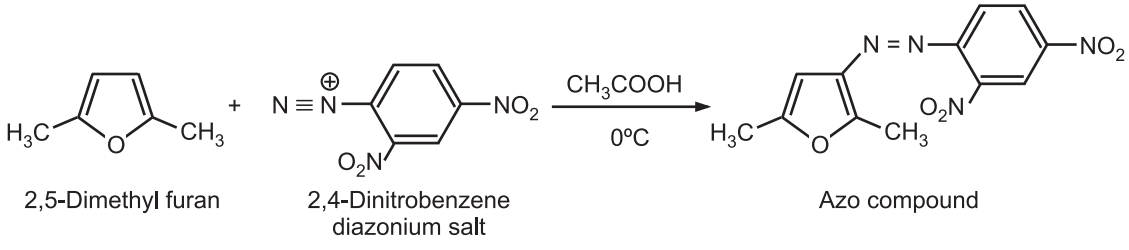


(5) Condensation with aldehydes and ketones: In this acid catalysed reaction, furan condenses with aldehydes to produce a mixture of oligomers. A macrocycle is obtained by condensation of furan with acetone.

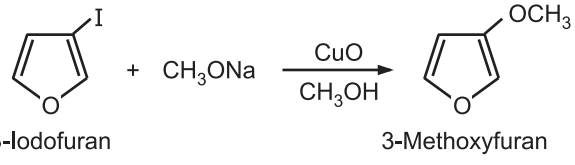


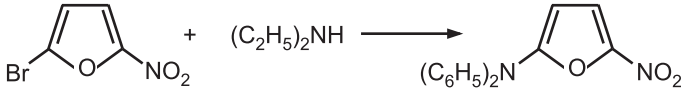
(6) Reaction with diazonium salts: Furan reacts with benzene diazonium salt to give 2-phenyl furan rather than formation of an azo compound.



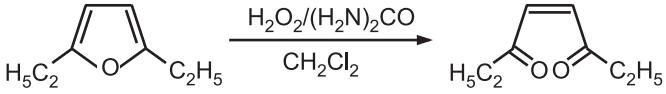


(7) Reactions with nucleophilic reagents: Halofurans show more reactivity towards nucleophile than simple furan. The presence of electron withdrawing substituents (nitro, carboxy or carboalkoxy) in halofurans further increases their reactivity.





(8) Oxidation: Ring opening occurs when furan is treated with sodium hypochlorite, hydrogen peroxide or meta chloroperbenzoic acid.

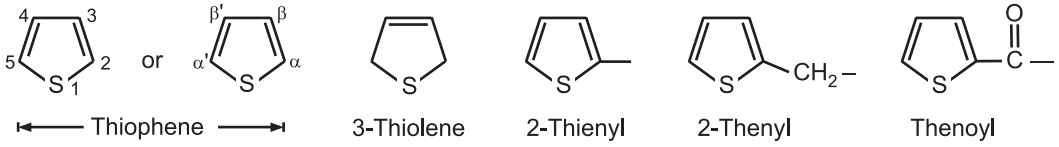


3.3.3 Applications in Drug Synthesis

Furan is an important scaffold present in drugs like, ranitidine (anit-ulcer), nitrofurazone (anti-bacterial), ascorbic acid (vitamin C) and many natural terpenoids.

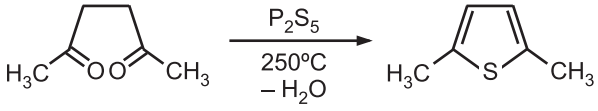
3.4 THIOPHENE

Thiophene belongs to a class of heterocyclic compounds containing a five membered ring made up of one sulfur as a heteroatom. Thiophene is a colourless liquid having the boiling point of 84°C. It was isolated as an impurity in commercial benzene in 1882 by Victor Meyer. It is a π - excessive aromatic heterocycle.



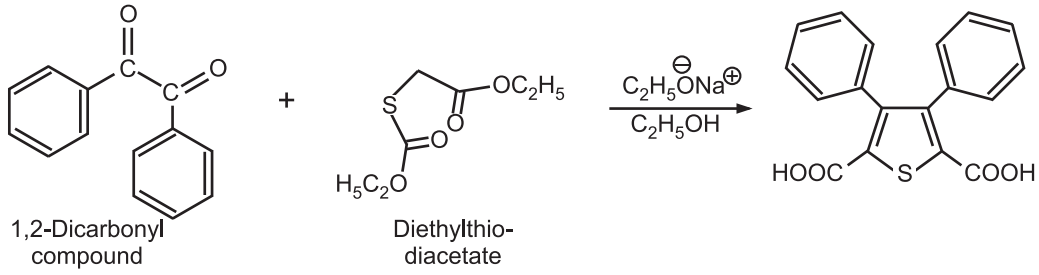
3.4.1 Chemical Synthesis

(1) Paal-Knorr Synthesis: In this method, 1, 4 – dicarbonyl compounds can be heated with phosphorus pentasulfide (a source of sulfur) to give thiophene.

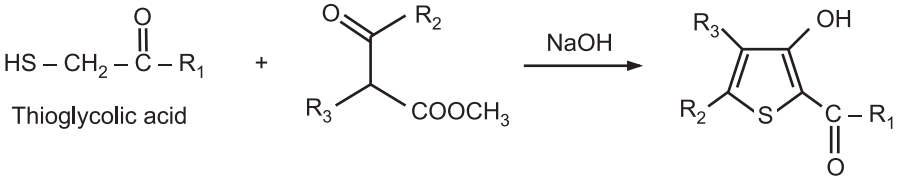


The basic mechanism of this synthetic procedure involves cyclic condensation of 1, 4-diketones (a) with primary amine (pyrrole synthesis), (b) with a sulfur source (thiophene synthesis) or (c) dehydration of diketone (furan synthesis). Phosphorus pentasulfide or bis (trimethylsilyl) sulfide acts as sulfurizing agent as well as dehydrating agent. Hydrogen sulphide in the presence of an acid catalyst is also effective.

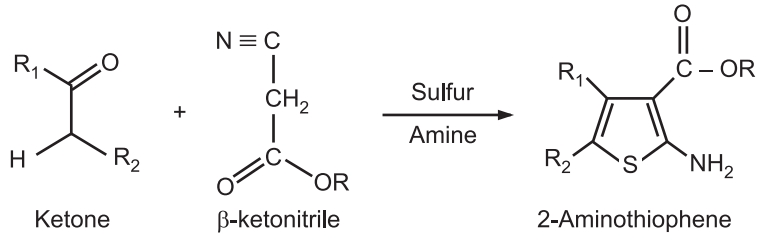
(2) Hinsberg Synthesis: Two consecutive aldol condensations between 1, 2-dicarbonyl compound and diethylthiodiacetate in the presence of a strong base gives thiophene.



(3) Fiesselmann Thiophene Synthesis: It is a base catalyzed condensation reaction of thioglycolic acid with α, β-acetylenic esters to give 3-hydroxy-2-thiophene carboxylic acid.

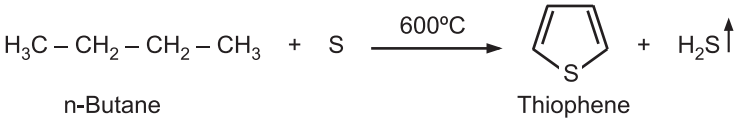


(4) Gewald Aminothiophene Synthesis: It is a base catalysed condensation of a ketone with a β–ketonitrile to form an olefin, followed by cyclization with elemental sulfur to give 2-aminothiophenes.

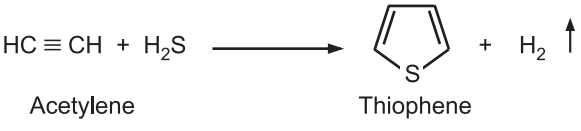


(5) Industrial Methods:

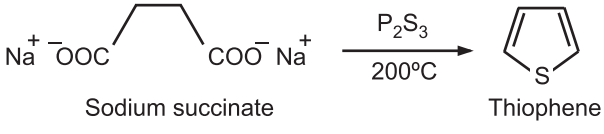
(i) Thiophene can be synthesized on industrial scale heating n-butane and sulfur at high temperature.



(ii) Using n-butane the sulfur first causes dehydrogenation and then interacts with the alkene by addition. Further dehydrogenation leads to aromatization of ring. A mixture of acetylene and hydrogen sulfide is passed through a tube containing alumina at 400°C.



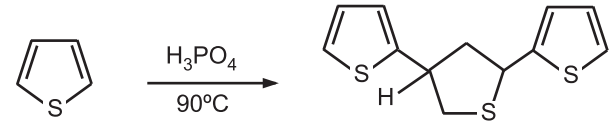
(iii) A mixture of sodium succinate and phosphorus trisulfide is heated at 200°C to give thiophene.



3.4.2 Chemical Reactions

Thiophene is slightly more nucleophilic than benzene. Negative charge is more accumulated on C_2 – and C_5 – atoms. While sulfur bears a positive charge. Hence, it easily undergoes electrophilic substitution preferably at C_2 – and C_5 – positions.

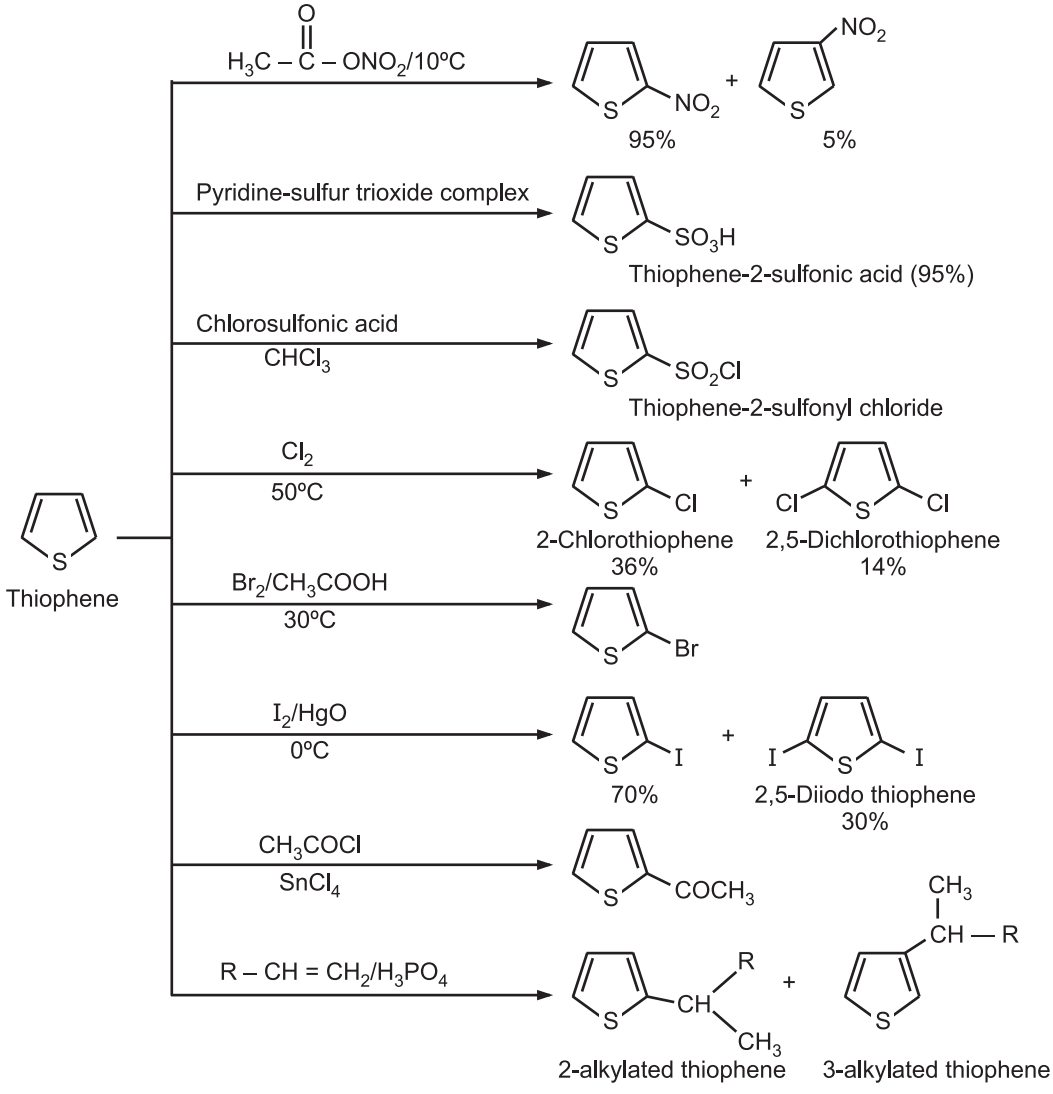
(1) Protonation: Thiophene is very stable to the action of acids. Very strong acids like the action of hot phosphoric acid gives thiophene trimer.



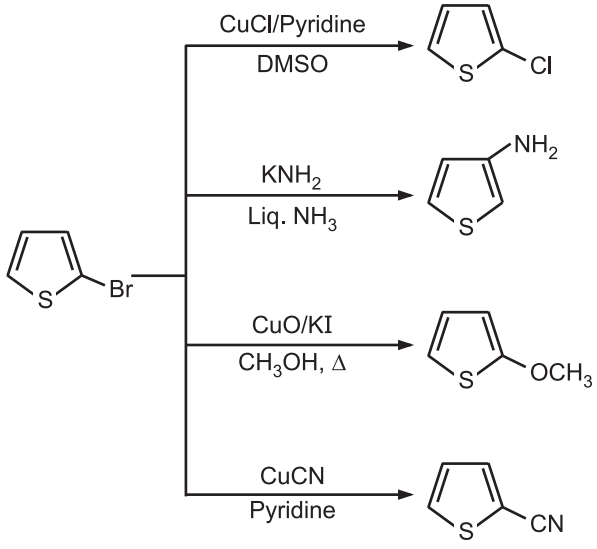
Thiophene Thiophene trimer

(2) Oxidation: Thiophene ring is stable to the action of various oxidizing agents. However the side chains can be oxidized to carboxylic acid groups. When heated with nitric acid, the ring breaks down to maleic acid and oxalic acid.

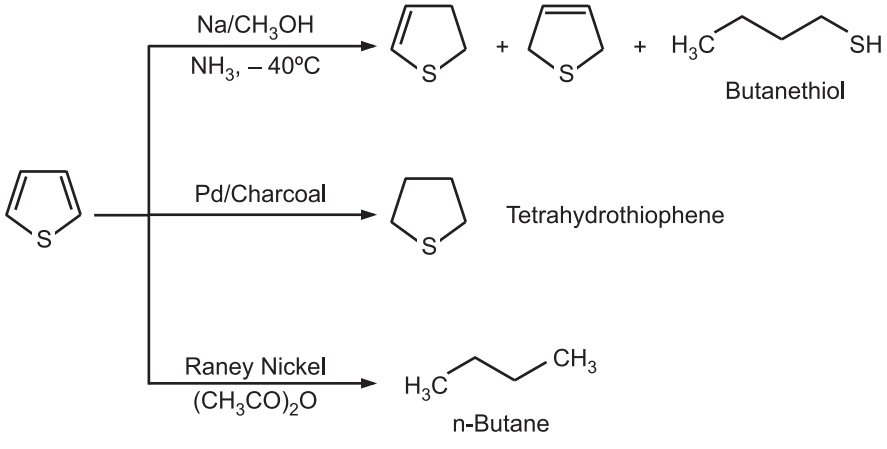
(3) Electrophilic Substitution: The reactivity order for electrophilic substitution reaction is: pyrrole > furan > thiophene >benzene. The preferred site of attack in thiophene is C_2-position.



(4) Nucleophilic Substitution: Thiophene substituted with electron withdrawing substituents are much more reactive to the nucleophilic substitution.



(5) Reduction:

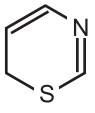


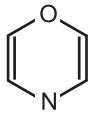
3.4.3 Applications in Drug Synthesis

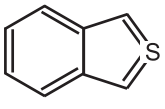
Thiophene derivatives possess remarkable activites like antibacterial, anti-inflammatory, anti-anxiety, anti-psychotic, anti-arrhythmic and anticancer. Examples include lomoxicam (thiophene analog of piroxicam), pyrantel (anti-parasitic), raltitrexed (anticancer), cephalothin (antimicrobial), suproprofen (anti-inflammatory), ticrynafen (anti-hypertensive), clotiazepam (anti-anxiety), ticlopidine (platelet aggregation inhibitor), etc.

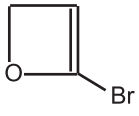
QUESTIONS

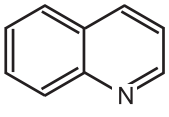
1. Discuss knorr-pyrrole synthesis with reaction mechanism.
2. Write two corresponding drugs of furan.
3. Write method of preparation and reaction of furan.
4. Write methods of preparation of reactions of pyrrole.
5. Give resonance structure of furan and one reaction of it.
6. Write any three reactions of pyrrole.
7. Write short note on pyrrole.
8. Write note on Furan.
9. Write note on nitrogen containing heterocycles.
10. Discuss why imidazole is more acidic than pyrrole.
11. Give difference between reactivity of pyrrole and pyridine for electrophilic and nucleophilic reagents.
12. Give comparison of furan, pyrrol and thiophene in term of differences in reaction.
13. Write note on synthesis of furan.
14. Give numbering and IUPAC nomenclature of following.

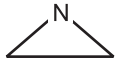
(i) 

(ii) 

(iii) 

(iv) 

(v) 

(vi) 

(vii) 

15. Explain electrophilic substitution of pyrrole.
16. Give reason - Electrophilic substitution occurs in pyrrole ring while nucleophilic substitution in neutral benzene ring structure of indole. Explain with example.
17. Write any two reactions of thiophene.
18. Write note on: Fiest Benary Synthesis of Furan.
19. Why furan undergoes electrophilic substitution reactions preferentially at C_2 and C_5 position?

20. Give detailed account of methods of synthesis and reaction of thiophene.
21. Give structure, numbering of following heterocycles with one example of drug belonging to each.
    (i) Cinnoline
    (ii) Benzoxazole
    (iii) Benzimidazole
    (iv) Xanthine
    (v) Pyrrole
22. Write note on Dies-Alder reaction and Gomberg reaction.
23. Give reason: Pyridine is much stronger base than pyrrole and draw its resonating structure.

❖❖❖

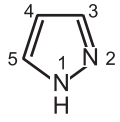
Unit...IV

SYNTHESIS, REACTIONS AND MEDICINAL USES OF HETEROCYCLES

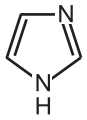
♦ **SYNOPSIS** ♦

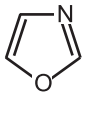
4.1 PYRAZOLE

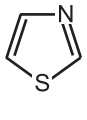
Five membered heterocyclics containing two nitrogen atoms in the adjacent 1,2-position are designated as pyrazoles. When two heteroatoms are present in a 1, 3-position, they are named as



Pyrazole
(1,2-diazole)


Imidazole

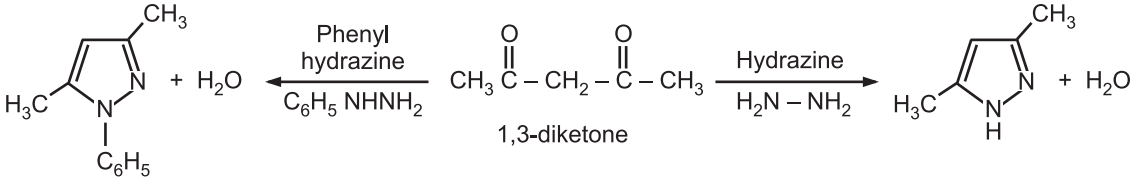

Oxazole


Thiazole

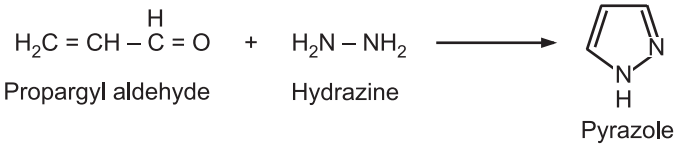
Pyrazole was discovered by Buchner in 1889. It is a colourless soild having m.p. of 70°C. Pyrazoles have been used as antioxidants in fuels and is a basic skeleton in food colourant, tartrazine and drugs like phenylbutazone, celecoxib, stanozolol etc. It is a weak base.

4.1.1 Chemical Synthesis

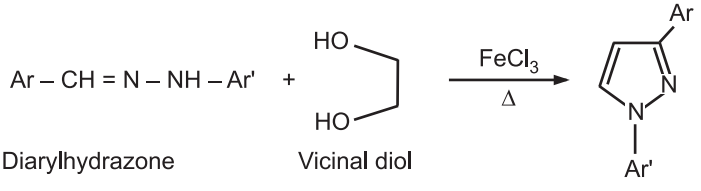
(i) Pyrazole may be synthesized by reacting acetylacetone with either hydrazine or phenyl hydrazine.



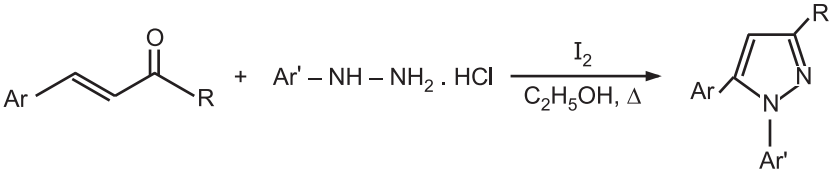
(ii) Pyrazole itself can be formed by the reaction of hydrazine with propargyl aldehyde.



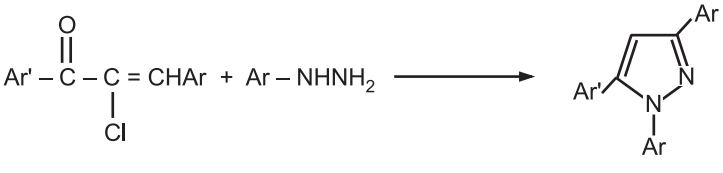
(iii) An iron catalyzed reaction of diarylhydrazones and vicinal diols give, 1, 3-substituted pyrazoles.



(iv) An α, β-unsaturated aldehydes/ketones readily react with hydrazine salts in an I_2 – mediated reaction to give substituted pyrazole.

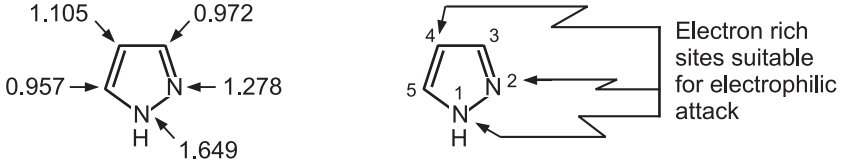


(v) An α, β-ethylene carbonyl derivative reacts easily with hydrazine to give substituted pyrazole.



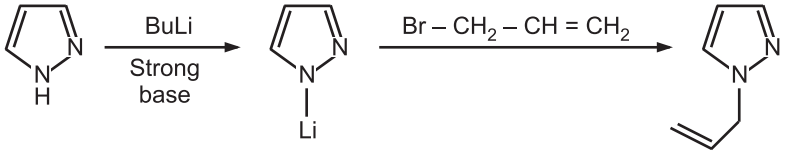
4.1.2 Chemical Reactions

The N-atom at position-1 is unreactive. It can lose its proton (H atom) easily in the presence of the base and offers the site of substitution reaction. The N-atom at position-2 with two electrons is basic and therefore reacts easily with electrophiles. The combined electron richness of both N-atoms reduce the charge density at C_3 and C_5, making C_4 available for electrophilic attack. Deprotonation at C_3 can occur in the presence of strong base, leading to ring opening.

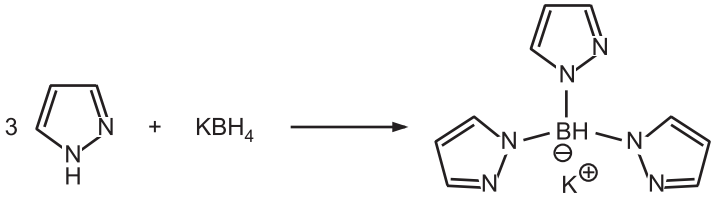


Electron density on Pyrazole

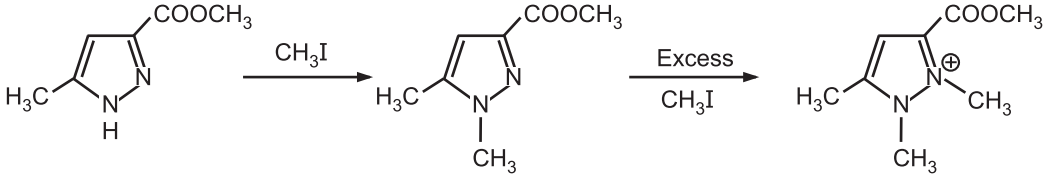
(i) The N_1 atom easily loses its proton with a strong base. The resulting nucleophile on nitrogen can afterwards react with an electrophile.



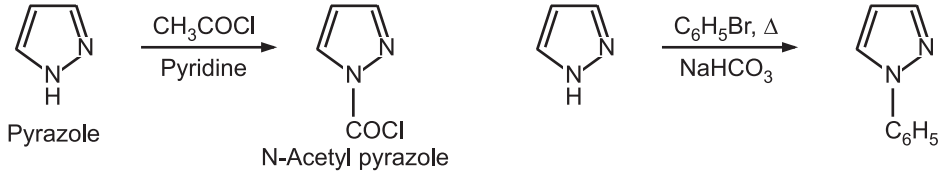
(ii) Scorpionate (tridentate ligand) formation: Pyrazole reacts with potassium borohydride to form a tridentate ligand known as scorpionate.



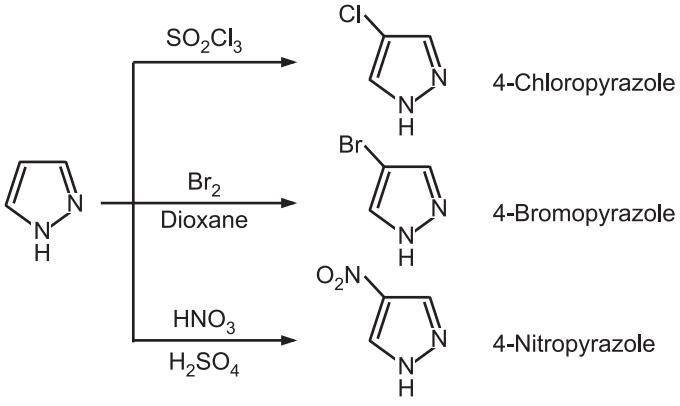
(iii) The free –NH group of pyrazole can be easily alkylated using alkyl halides, diazomethane or dimethylsulfate.



Excess of alkylating agent causes quaternization. Acylation on the free –NH group can be readily done using acetyl chloride in the presence of a weak base such as pyridine.



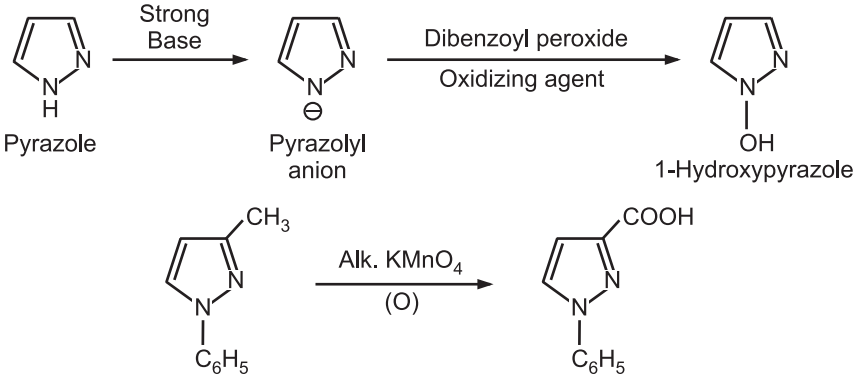
(iv) The electrophilic substitution in pyrazole occurs readily at position-4.



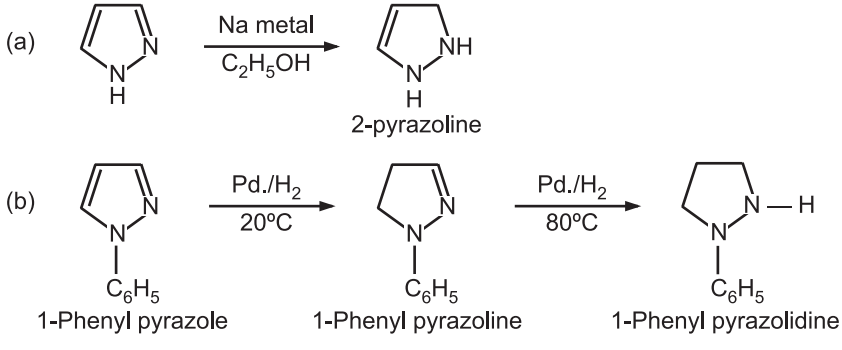
(v) As all the 3 carbons and 2 nitrogen atoms in pyrazole are having good electron density (electron rich), pyrazole does not undergo nucleophilic substitution reactions under the usual reaction conditions.

(vi) Oxidation reaction: The pyrazole ring is remarkably stable to the action of oxidizing agent but the side chain may be oxidized.

For example,



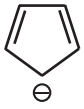
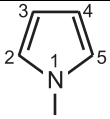
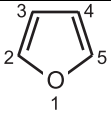
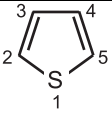
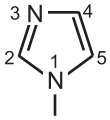
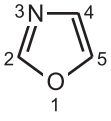
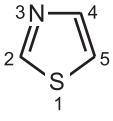
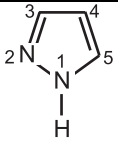
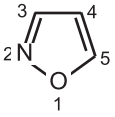
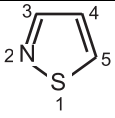
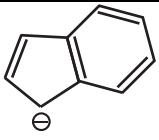
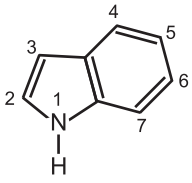
(vii) Reduction reaction: Unsubstituted pyrazole is relatively stable to catalytic and chemical reductive conditions. Pyrazole derivatives may undergo reduction under variety of conditions. e.g.,



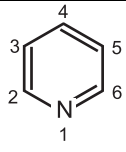
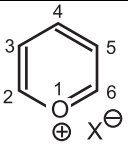
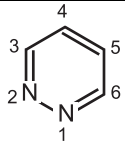
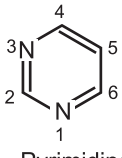
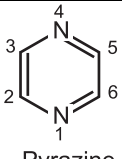
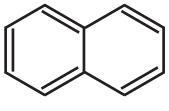
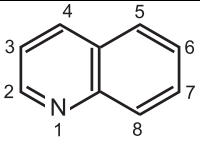
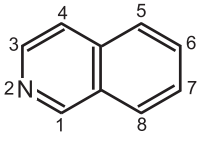
4.1.3 Applications in Drug Synthesis

Pyrazole derivatives are used for their analgesic, antipyretic, anti-inflammatory (e.g., antipyrine, phenylbutazone, celecoxib), antibacterial, tranquilizing, anticancer and antidiabetic activities.

Classification – Aromatic Five Membered

Carbocycle		Heterocycles	
	 Pyrrole	 Furan	 Thiophene
1,3-Azoles	 Imidazole	 Oxazole	 Thiazole
1,2-Azoles	 Pyrazole	 Isoxazole	 Isothiazole
	 Indole		

Classification – Aromatic Six Membered

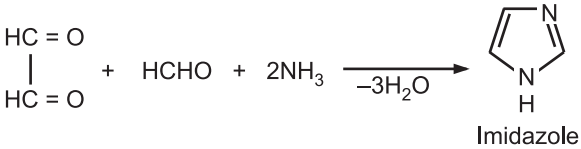
	 Pyridine	 Pyrylium	 Pyridazine
	 Pyrimidine	 Pyrazine	
 **Naphthalene**	 Quinoline	 Isoquinoline	

4.2 IMIDAZOLE

It is a heterocyclic aromatic organic compound. It is an example of 1, 3-diazole i.e., it is a pentacyclic structure with 03 carbons and 02 nitrogens located at 1, 3-position. It was earlier called glyoxaline as it was first prepared in 1858 from glyoxal and ammonia. It is a colourless liquid having boiling point of 256°C. Imidazole is more basic than pyridine and pyrazole. Introduction of alkyl groups into the ring increases the basicity further. The name "Imidazole" was given by German chemist, Arthur Rudolf Hantzsch in 1887. It is an aromatic and highly polar compound.

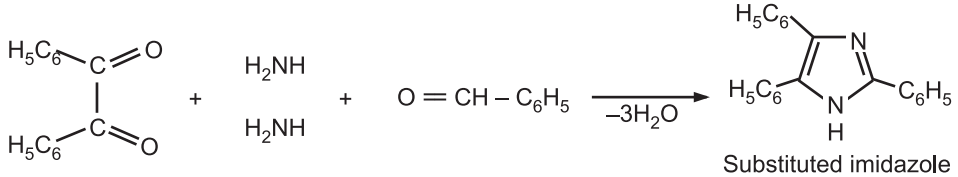
4.2.1 Chemical Synthesis

(i) Debus Method: Glyoxal, formaldehyde and ammonia condensed to form imidazole (glyoxaline) in Debus Method reported in 1858. It provides 2-monosubstituted and 2, (3, 4 homo) trisubstituted imidazoles.



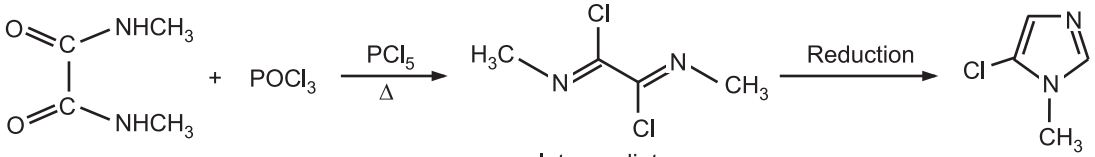
Imidazole

(ii) Radiszewski synthesis: It consists of condensing a glyoxal (e.g., benzil), an aldehyde (e.g., benzaldehyde) in the presence of ammonia. Formamide may be used in place of ammonia.



α-diketone (Benzil) Ammonia Substituted imidazole

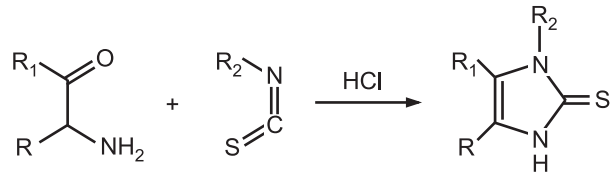
(iii) Wallach Synthesis: The reaction of N, N′-disubstituted oxamide with phosphorus oxychloride gives chlorine containing intermediate which upon reduction with hydriodic acids, gets converted to 1-substituted imidazole. It provides 1, 2-disubstituted chloroimidazoles.



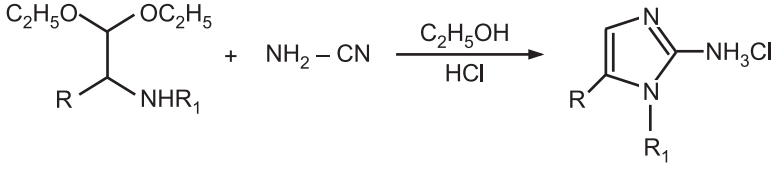
Intermediate

(iv) Marckwald synthesis: It is the reaction between α-aminoketones with cyanates, thiocyanates or isothiocyanates producing 3 H-imidazoline-2-thiones (2-mercaptoimidazoles). The latter can be readily converted to imidazole by dehydrogenation.

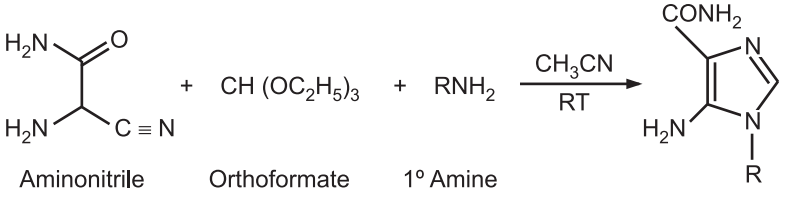
(a)



(b)

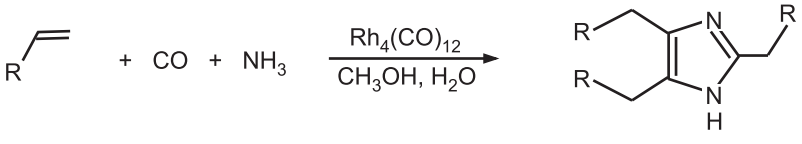


(v) From aminonitrile and aldehyde:

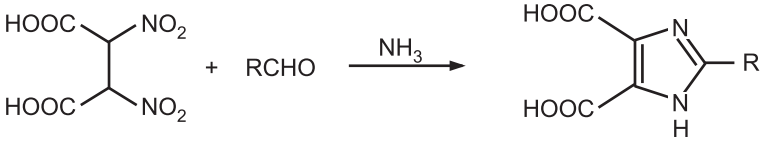


Aminonitrile Orthoformate 1° Amine

(vi) A reaction between an alkene, carbon monoxide and ammonia leads to formation of imidazole derivative.

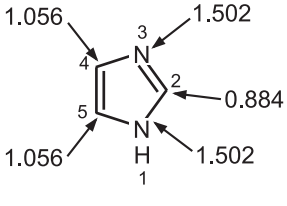


(vii) Maquenne Synthesis:



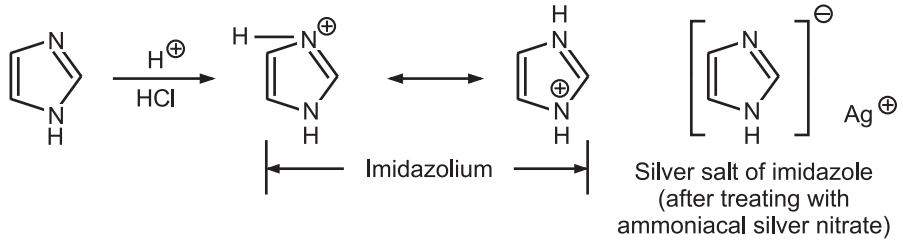
4.2.2 Chemical Reactions

Imidazole is a base and an excellent nucleophile. It easily undergo electrophilic (alkylating, acylating) substitution reactions at the –NH nitrogen. However, the C_4 and C_5 atoms of imidazole are also susceptible for electrophilic attacks. Due to the resonance structures, the position most prone to nucleophilic attack is C-2.



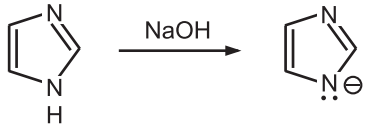
Imidazole ring contains N_1 atom (pyrrole like nitrogen) and N_3 atom (pyridine like nitrogen). The pyrrole like nitrogen is acidic while the pyridine like nitrogen is basic and nucleophile. From the structure, it appears that both N-atoms have highest electron density followed by C_4 and C_5 atoms. The C_2-atom is sandwitched between more electronegative N-atoms and hence most electron deficient. Hence the C_2 atom is most prone to the nucleophilic attack. While rest of the atoms (C_4, C_5, N_1 and N_3) are susceptible for electrophilic attack.

(i) Reaction with Acids: Imidazole forms stable crystalline salts with strong acids by protonation of N_3-atom.



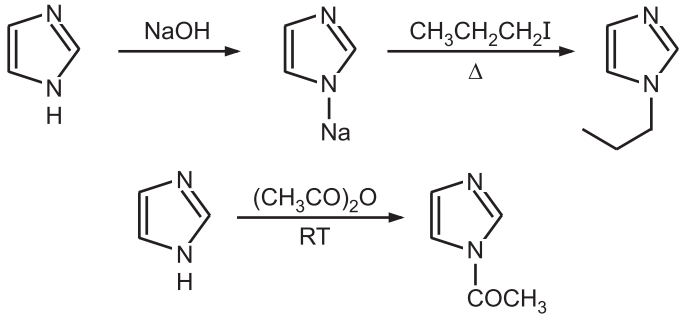
Silver salt of imidazole (after treating with ammoniacal silver nitrate)

On the other side, imidozle can act as an acid and the proton on N_1 atom can be removed by a strong base. Thus imidazole can act as acid and base. It is more acidic than pyrrole and more basic than pyridine.

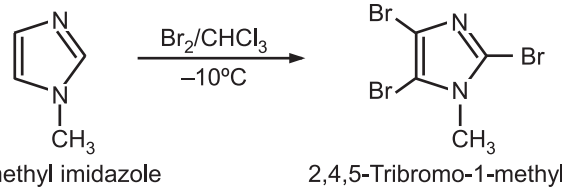


(ii) Electrophilic Substitution reaction:

(a) N-alkylation and N-acylation:



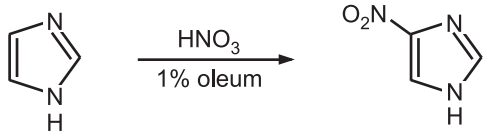
(b) Halogention:



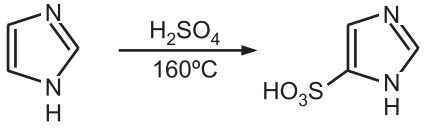
1-methyl imidazole

2,4,5-Tribromo-1-methylimidazole

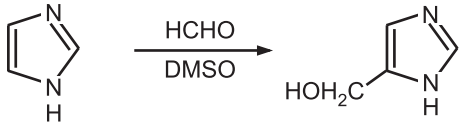
(c) Nitration:



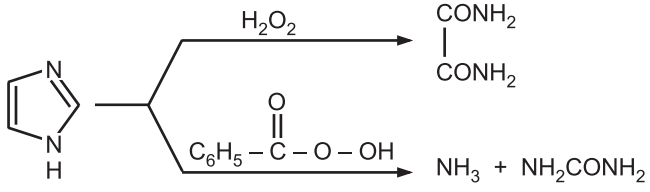
(d) Sulfonation:



(e) Reaction with aldehydes and ketones: N-unsubstituted imidazole undergoes hydroxymethylation at C_4-position when treated with HCHO (formaldehyde) in the presence of DMSO.

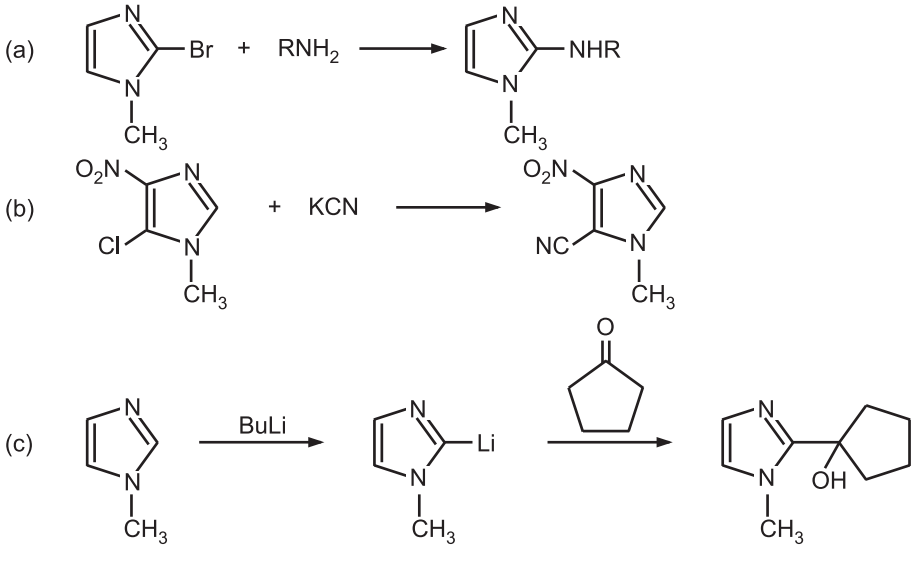


(iii) Action of oxidizing agents: Imidazole is stable to auto oxidation and to the action of chromic acid but is attacked by hydrogen peroxide or perbenzoic acid.



(iv) Reaction with nucleophilic reagents: Imidazoles do not undergo nucleophilic substitution. If electron withdrawing groups are present, nucleophilic substitution readily attack at C_2-position.

For example, 2-haloimidazoles undergo uncleophilic substitution reactions with the replacement of halogen by nucleophile.

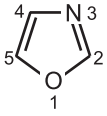


4.2.3 Applications in Drug Synthesis

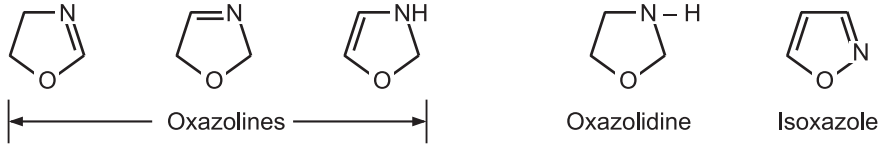
Imidazole is a parent skeleton in amino acid, histidine and an autacoid, histamine. Important drugs containing imidazole ring include ketoconazole (antifungal), midazolam (sedative) and metronidazole (antibiotics). It is a main skeleton present in biotin (vitamin), nucleic acid and various alkaloids. Losartan (angiotensin receptor blocker), Eprosartan (angiotensin receptor blocker), azomycin (antibioitic) and clotrimazole (anticancer) also contain imidazole nucleus.

4.3 OXAZOLE

Oxazole is a 1, 3-azole having an oxygen atom and a pyridine type nitrogen atom at the 3-position in a five membered ring. The scientist Hantzsch was first to introduce it in 1887. Oxazole is a liquid with a boiling point of 69°C. Unlike imidazole and thiazole, the oxazole is not naturally occurring. Oxazoles are weakly basic in nature. The lone pair of electrons on the pyridine type nitrogen is not involved in maintaining aromaticity but it is available for protonation. Thus, the lone pair of electrons imparts basicity to the molecule.

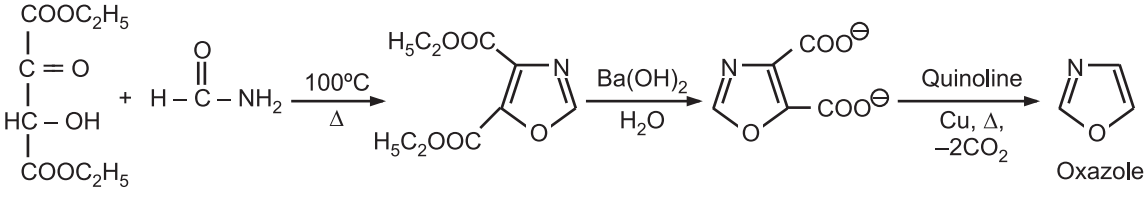


The partially reduced oxazoles are called **oxazolines** while fully saturated oxazole is called **oxazolidine**.

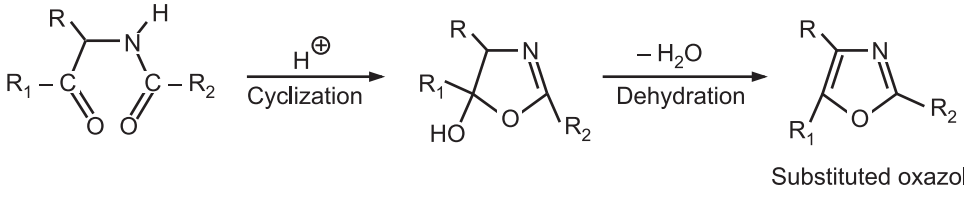


4.3.1 Chemical Synthesis

(i) Ethyl α-hydroxy keto succinate reacts with formamide to give diethyl-oxazole-4, 5-dicarboxylate. In next step it is subjected to hydrolysis and subsequent decarboxylation to oxazole.

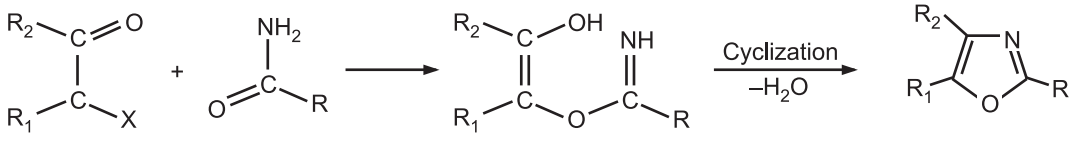


(ii) Robinson-Gabriel Synthesis: In this method, an α-acylamino ketone undergoes cyclization and dehydration to give 2, 5 –diaryloxazoles.

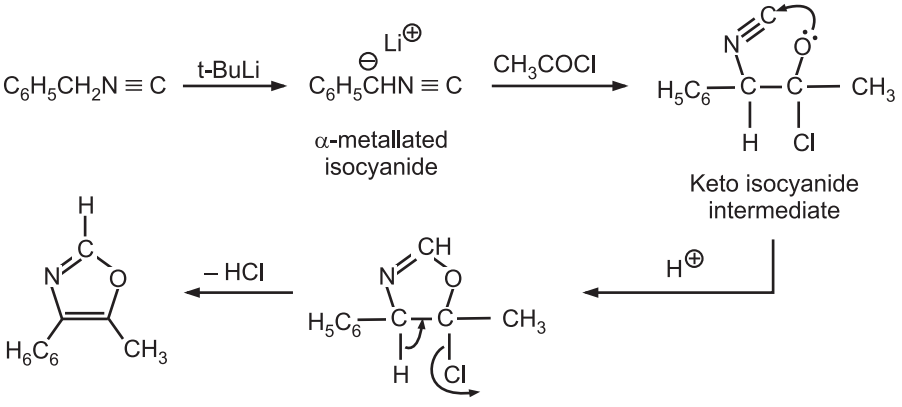


Polyphosphoric acid, phosgene or anhydrous hydrogen fluoride are used to induce cyclization while H_2SO_4, PCl_3, $POCl_3$ or $SOCl_2$ may be used as dehydrating agent in this reaction.

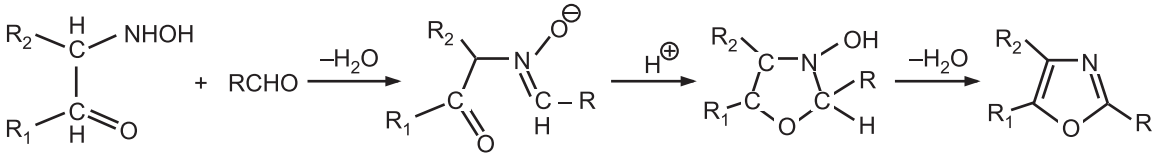
(iii) Reaction of α-haloketones with primary amides:



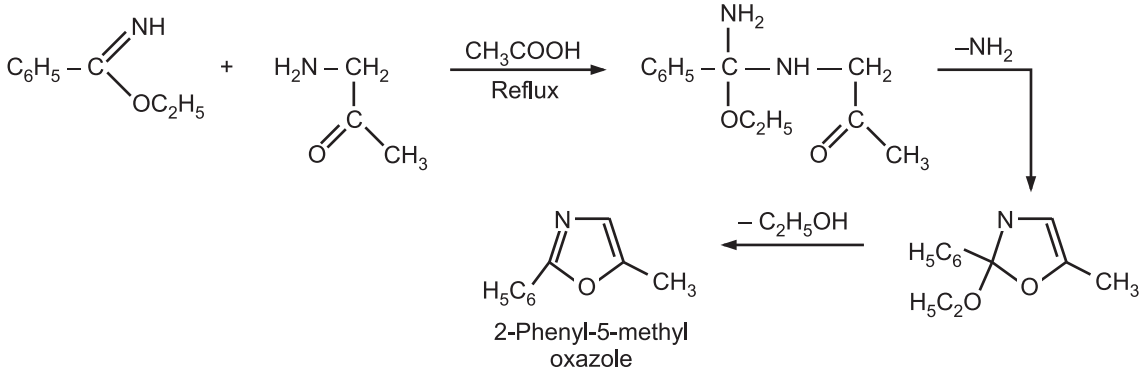
(iv) From isocyanides with acid chlorides: Isocyanides when treated with t-butyllithium gives α - metallated isocyanide. The latter when reacted with carboxylic acid derivatives (e.g., acid chloride, ester or amide) gives oxazole.



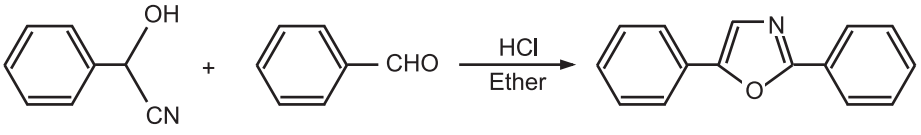
(v) Reaction of α-Hydroxyamino ketones with aldehyde: The α-hydroxyamino ketone reacts with aldehyde in the presence of sulfuric acid and acetic anhydride to give oxazole. The C_2 – atom in oxazole comes from the aldehyde.



(vi) From α - Aminocarbonyl compounds:



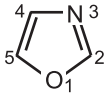
(vii) Fischer Oxazole synthesis: This synthesis was discovered by Emil Fischer in 1896. In this method, a cyanohydrin reacts with an aldehyde in the presence of anhydrous HCl to give substituted oxazole.



Mandelic acid nitrile | Benzaldehyde | 2,5-Diphenyl oxazole

4.3.2 Chemical Reactions

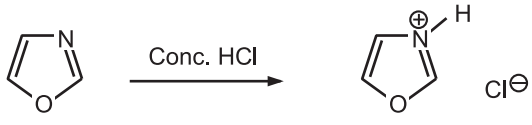
The oxazole ring contains:



(a) Pyridine-type nitrogen at 3-position: It explains protonation (basicity), N-alkylation and nucleophilic attack at C_2-atom.

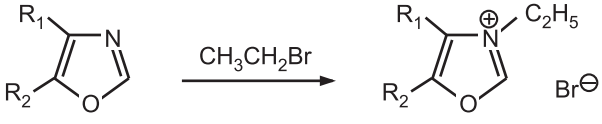
(b) Furan type oxygen at 1-position: It explains diene-type behavior of oxazole to undergo Diels-Alder reactions with alkenic and alkynic dienophiles (cycloaddition reactions). The presence of electron releasing substitutions on the oxazole ring-facilitates the reactions with dienophiles.

(i) Protonation (Basicity): Oxazole is a weak base. It reacts with acids to form unstable salts (hydrochloride/picrate salts).



Oxazole | Oxazole hydrochloride

(ii) N-alkylation: Oxazoles form quaternary salts, N-alkyloxazolium salts with alkylating agents.

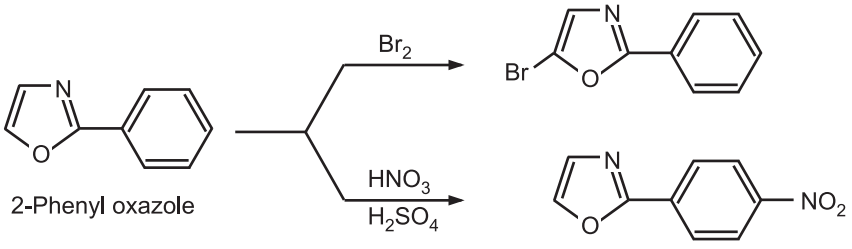


Oxazole | Oxazole quaternary salt

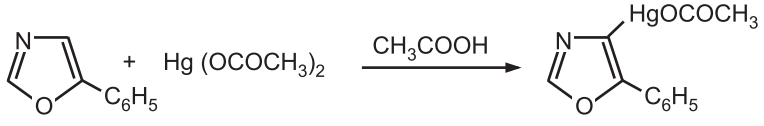
(iii) Electrophilic substitution reactions: The oxazole ring does not undergo electrophilic substitutions easily unless the ring is substituted with electron releasing substituent. The order of reactivity of positions in oxazole ring is $C_4 > C_5 > C_2$.

Nitration, sulfonation and chlorosulfonation do not occur in unsubstituted oxazole ring due to highly electron deficient oxazolium cation. When the electron releasing substituents are present in the ring, electrophile easily attacks.

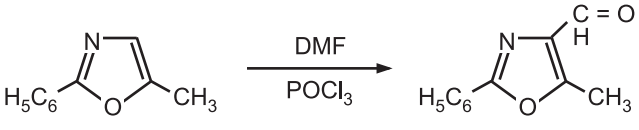
E.g.,



Another example of electrophilic substitution is Mercuration of oxazole with mercuric acetate in acetic acid.

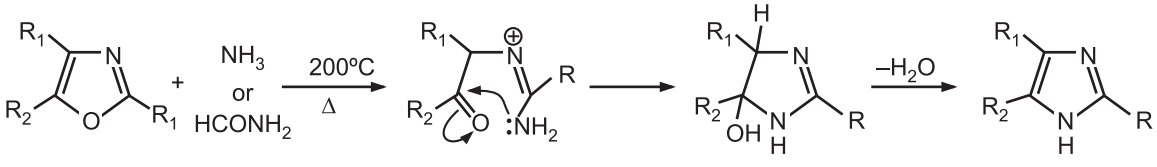


Vilsmeier – Haack formylation is yet another example

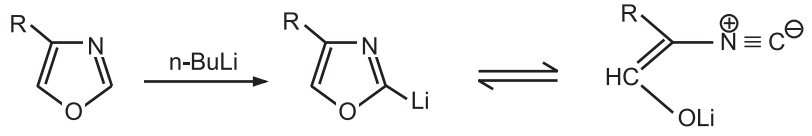


(iv) Nucleophilic substitution reactions: Oxazole with unsubstituted 2-position get easily deprotonated at C_2-position by a strong base. Otherwise oxazole rarely undergo nucelophilic substitution reactions. Electron withdrawing substituent at C_4 facilitates nucleophilic attack at most electron deficient C_2-position. For example, halogen atom at C_2 of oxazole ring is easily replaced by nucleophile.

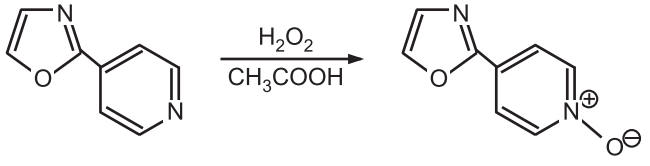
In most of the cases, nucleophile attack on oxazole ring rather result in the cleavage of oxazole ring than actual nucleophilic substitution reactions. For example, oxazoles get transformed into imidazoles via ring cleavage when treated with ammonia /formamide (nucleophile).



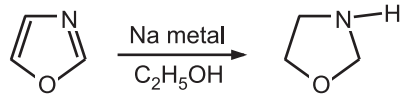
(v) Metallation: Lithium preferentially attack the most electron deficient C_2-atom. The resulting 2-lithio-oxazoles are unstable and get cleaved to the open chain isocyanides.



(vi) Oxidation: The oxazole ring is opened by the action of oxidizing agents such as cold potassium permagnate, chromic acid and ozone. Oxazole is normally stable to the action of hydrogen peroxide. 2 – substituted oxazoles can be converted to N-oxides.



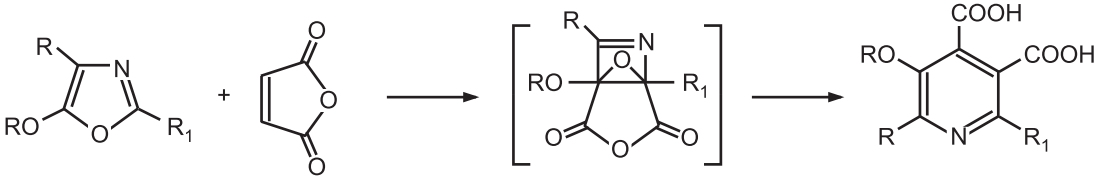
(vii) Reduction: Oxazoles are relatively easily reduced. Reduction of the oxazole ring to oxazolidines can be effectively done with sodium in ethanol. Other reducing agents cause reduction and cleavage of the ring to give open chain products.



Oxazole Oxazolidine

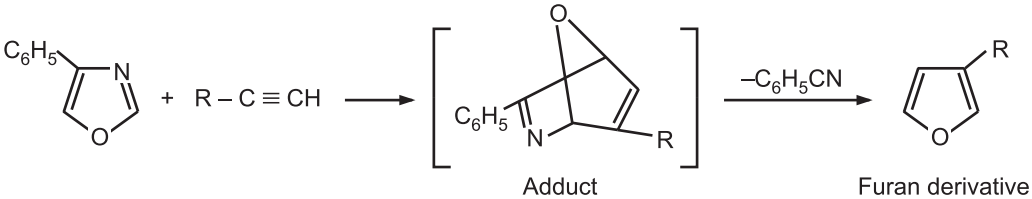
(viii) Cycloaddition reactions: Oxazoles easily undergo cycloaddition across 2, 5-positions. The presence of electron donating substituents on the oxazole ring facilitates the reactions with dienophiles. The adducts so obtained serve as important precursors for substituted pyridine or furan derivatives. Cycloadditions have been reported with alkene, alkyne and benzyne dienophiles.

(i) Alkene dienophile:



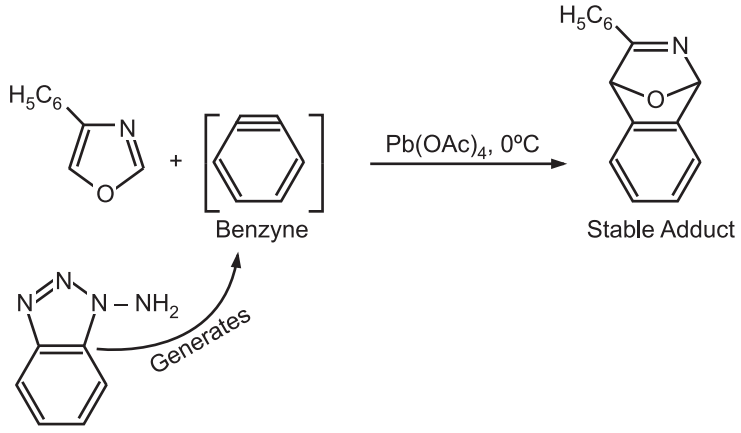
Adduct Pyridine derivative

(ii) Alkyne dienophile:



Adduct Furan derivative

(iii) Benzyne dienophile:

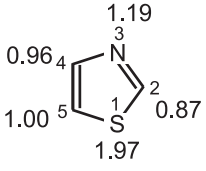


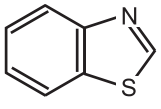
4.3.3 Applications in Drug Synthesis

Oxazole is one of the important components in penicillin (antibiotic) structure. Oxazole family includes oxazoles, isoxazoles, oxazolines, oxadiazoles, oxazolidones, benzoxazoles, etc. Oxazoles display versatile biological activities including antibacterial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory, analgesic, antidiabetic, etc.

4.4 THIAZOLE

It is a pale yellow liquid having a boiling point of 116-118°C. It is an aromatic compound having odor similar to pyridine. It is a weaker base than pyridine. Thiazole was first described by Hantzsch and Weber in 1887. The partially reduced thiazoles are called thiazolines and completely reduced thiazole is called thiazolidine.





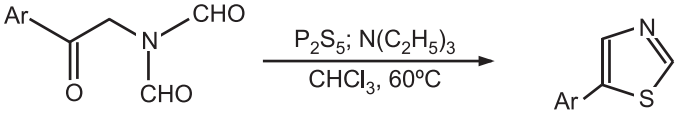
Benzothiazole

2-Thiazoline

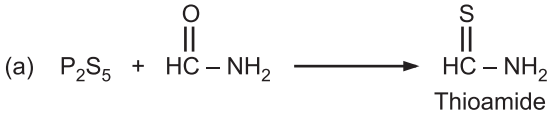
Thiazolidine

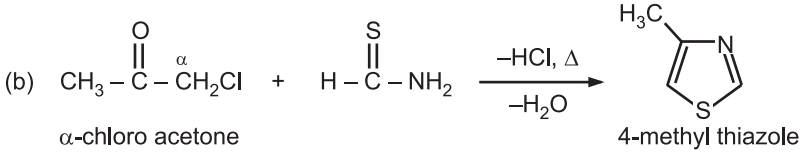
4.4.1 Chemical Synthesis

(i) Treatment of N, N-diformylaminomethyl aryl ketones with phosphorus pentasulfide and triethylamine in chloroform gives 5-arylthiazoles.

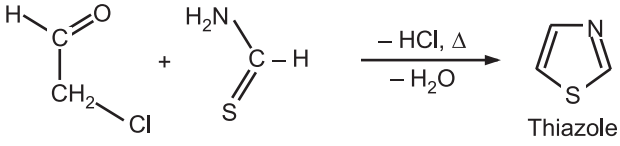


(ii) Hantzsch's Synthesis: It is a condensation reaction between α - halo carbonyl compound with an appropriate thiomide or thiourea. The thioamide can be obtained by reacting phosphorus pentasulfide and formamide at room temperature.

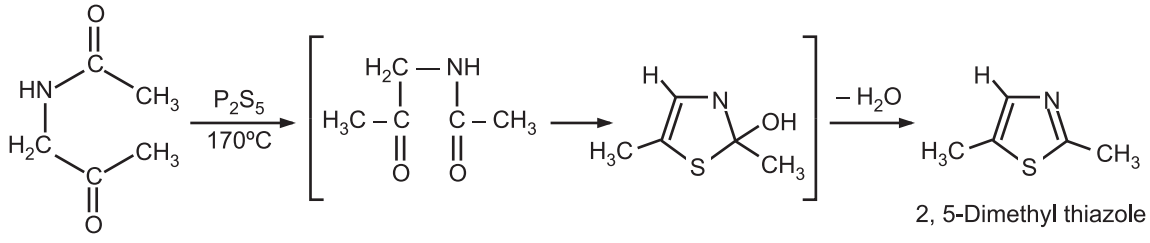




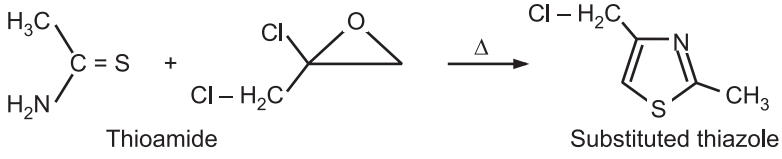
Chloroacetaldehyde on condensation with thioformamide yields unsubstituted thiazole.



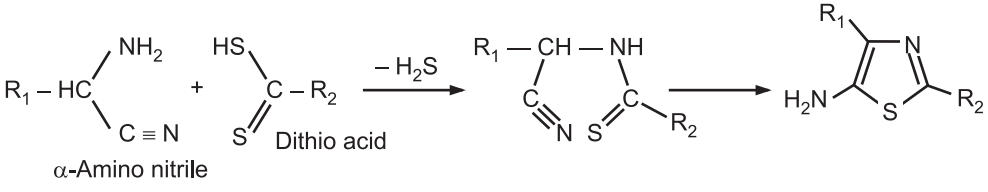
(iii) Gabriel synthesis: The α-acylamino ketones react with phosphorus pentasulfide to give 2- or 5- or 2, 5-disubstituted thiazoles.



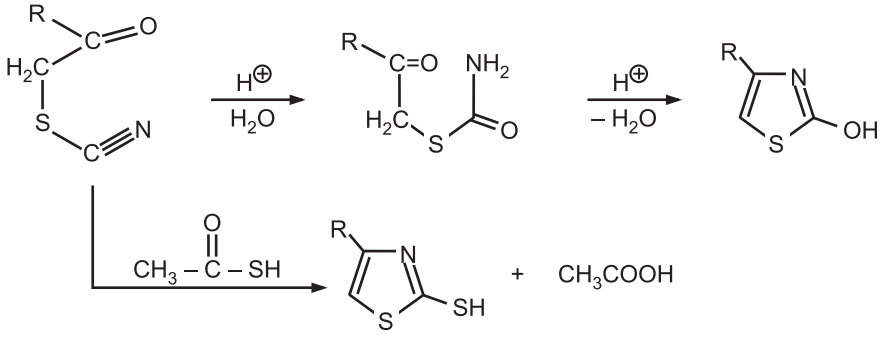
(iv) From thioamides: Thioamide is reacted with substituted 2-chloroxiranes to give thiazole derivatives.



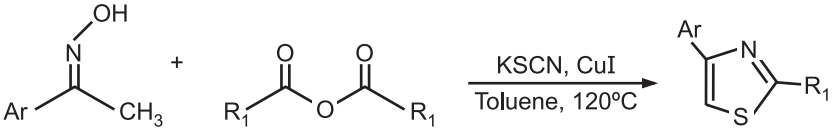
(v) Cook-Heilborn's synthesis: Under mild conditions, α-aminonitriles are treated with dithioacids or esters, carbon disulfide, carbon oxysulfide or isothiocyanates to yield 5-aminothiazoles.



(vi) Tcherniac's Synthesis: The 2-substituted thiazoles are obtained either from acidic hydrolysis of α-thiocyano ketones or its treatment with sulfur compounds.



(vii) A copper catalyzed condensation of oximes, anhydrides in the presence of potassium thiocyanate (KSCN) under mild reaction conditions, produces thiazoles in very good yields.

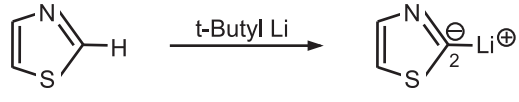


4.4.2 Chemical Reactions

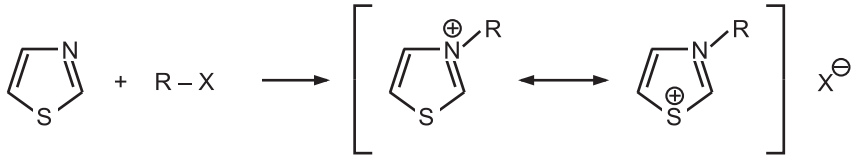
Thiazole contains thiophene type sulfer atom at the position-1 and pyridine type nitrogen at the position-3. It's chemical reactivity is similar to other 1, 3-azoels (i.e., imidazole and oxazole).

(i) Protonation: Thiazoles get easily protonated at N_3 position due to lone pair of electrons available with nitrogen. In thiazole ring, the position-2 is most electron deficient, position-4 almost neutral and position-5 is slightly electron rich.

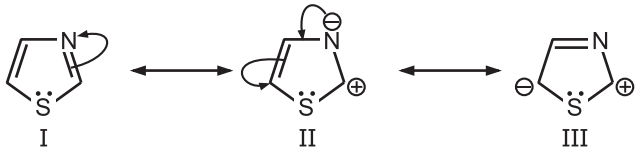
(ii) Deprotonation at C_2: The organolithium compounds cause removal of proton at C_2. The resulting nucteophilic site at C_2 then reacts with a range of electrophiles such as aldehydes, akylhalides and ketones.



(iii) N – Alkylation: Thiazoles react with alkyl halides to form thiazolium cations. This cation is resonance stabilized with the positive charge residing mostly on the sulfur atom.



(iv) Electrophilic substitution reactions: Thiazole has following resonating structures. All electrophilic and nucleophilic reactions of thiazole can be explained on the basis of these resonance structures.

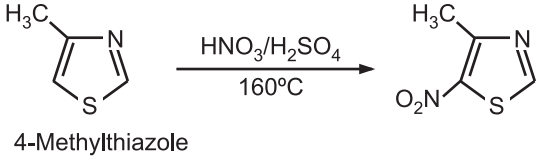


The 4, 5-double bond is aromatic and undergoes electrophilic substitution at 4- or 5-position depending on nature of a substituent occupied by 2-position. The sulfur atom always behaves as an electron donor to its adjacent carbons.

(a) At N_3-atom: The loan pair of electrons on N_3-atom is less reactive. Hence, N-alkylation occurs at slower rate in thiazole.

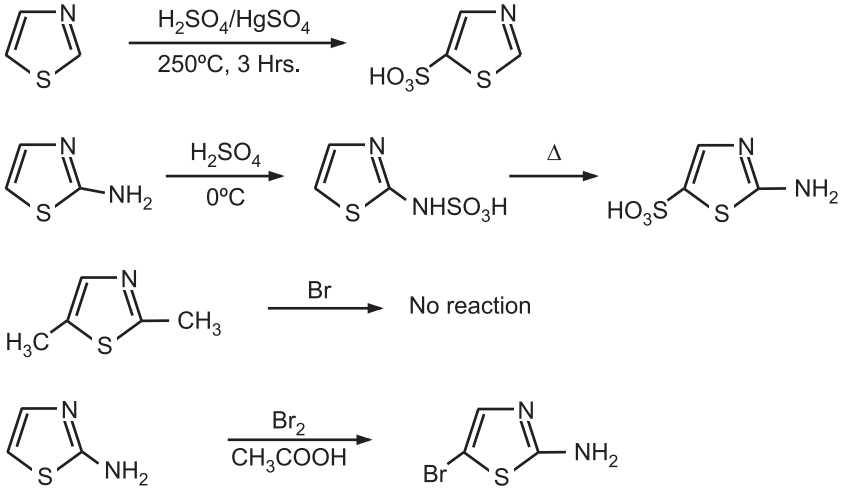
(b) Nitration: In acidic media, the attack usually takes place through the formation of thiazolium (N – protonated) cation. The positive charge on the protonated nitrogen of the thiazolium ion deactivates the ring considerably towards electrophilic attack. Nitration of thiazole is rather difficult and is not nitrated even in oleum at 160°C.

However, 4-methylthiazole is nitrated at position – 5 under relatively mild conditions.

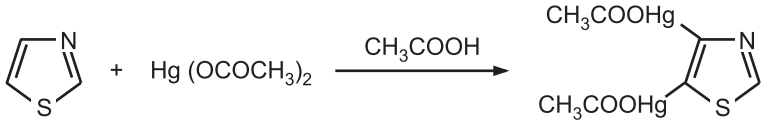


4-Methylthiazole

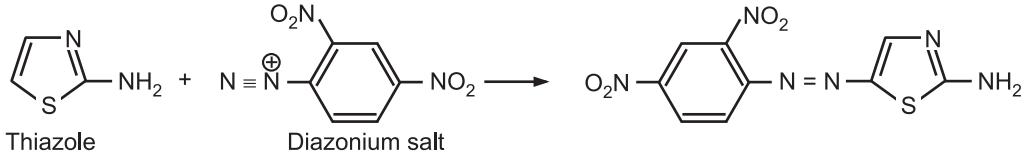
(c) Sulphonation and halogenation: In thiazole ring, C_5 is the preferred position of attack for all electrophiles. It the C_5 position is already substituted, electrophile does not attack on other positions. The presence of electron-donating substituent at C_2-position makes easy the attack of electrophile at C_5-position even under mild conditions. e.g.,



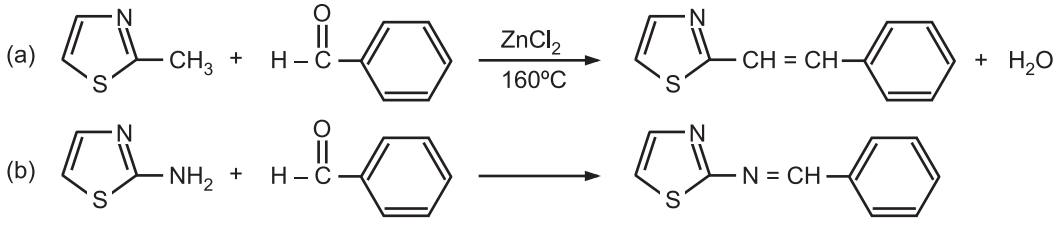
(v) Mercuration: On treatment with mercury acetate, thiazole is mercurated at preference order of $C_5 > C_4 > C_2$.



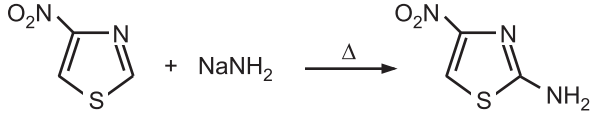
(vi) Diazo Coupling: Thiazoles easily react with diazonium salts to give coloured dyes.



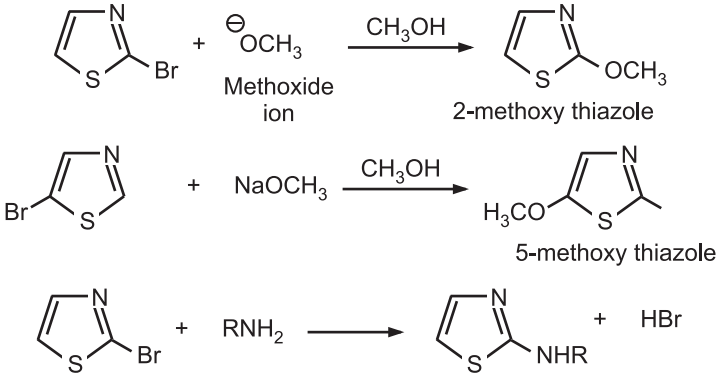
(vii) Condensation reactions: The 2-methyl thiazole and 2-amino thiazole undergo condensation reaction with aromatic aldehydes to give biheterocycles.



(viii) Nucleophilic Substitution reaction: In thiazole, the C_2 – position is prone to nucleophilic attack due to its electron deficient nature and hence most suitable for the nucleophilic attack. For nucleophilic reactions to occur, either we need a strong nucleophile or activation of the ring. e.g., quaternization of the ring nitrogen significantly enhance the rate of nucleophlic attack at C_2 making C_2-hydrogens more acidic.



Similarly nucleophile attack thiazole ring by displacing the halogen atom attached to any of C_2–, C_4– or C_5– position.



(ix) Oxidation: Thiazole ring is generally stable to oxidation by permagnate, chromic acid, selenium dioxide and concentrated nitric acid.

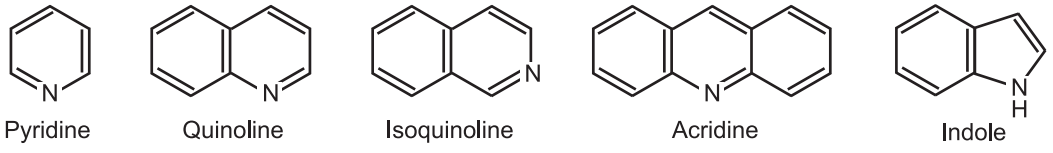
(x) Reduction: It is also stable towards catalytic hydrogenation platinum and to the reduction by metal in hydrochloric acid. Reduction using activated Raney nickel leads to desulfuration of thiazole ring followed by decomposition of resulting intermediate.

4.4.3 Applications in Drug Synthesis

Vitamin thiamine (B_1) contains both pyrimidine and thiazole ring systems. The ring is also present in meloxicam (non-steroidal anit-inflammatory). It is also an important scaffold in antibacterial, antifungal, antidiabetic, anticancer and anticonvulsant drug design. These include nitazoxanide (anti-viral), thiabendazole, (anthelmintic), fanetizole (immuno-modulator), fentiazac (NSAID), sulfathiazole (antibacterial), nizatidine (H_2 – receptor blocker), thiamethoxam (systemic insecticide), etc Penicillins contain reduced thiazole ring (thiaozolidine).

4.5 AROMATICITY IN HETEROCYCLES

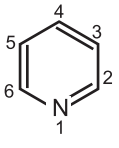
Any cyclic planar system associated with (4n + 2) π-electrons is said to be an aromatic. The lone pair of electrons on the heteroatom governs the degree of aromaticity by its extent of participation in cyclic delocalization of π-electrons.



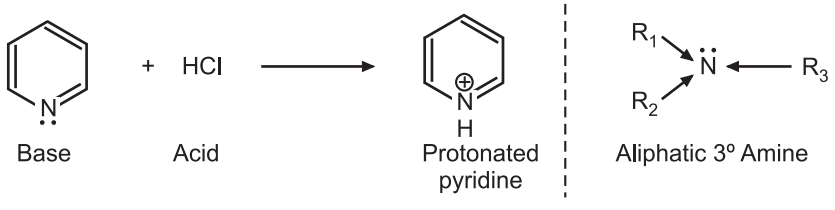
Pyridine Quinoline Isoquinoline Acridine Indole

4.6 PYRIDINE

It is a colourless liquid with a boiling point of 115°C. It has a fishy odour. It was first obtained from bone oil in 1849 and coal tar. Pyridine is mainly used as a solvent and as a base. The lone pair on N-atom is located in an sp^2 hybridized orbital and is not involved to maintain aromaticity. The lone pair of electrons is available for protonation and explains the basicity of pyridine. Electron donating substituent at 2 – and 6 – positions enhances the basicity.



Pyridine is considerably more basic than pyrrole and less basic than aliphatic 3° amine.

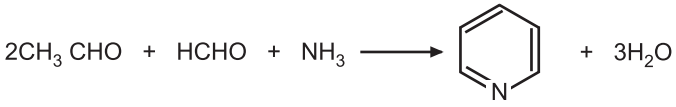


Base Acid Protonated pyridine Aliphatic 3° Amine

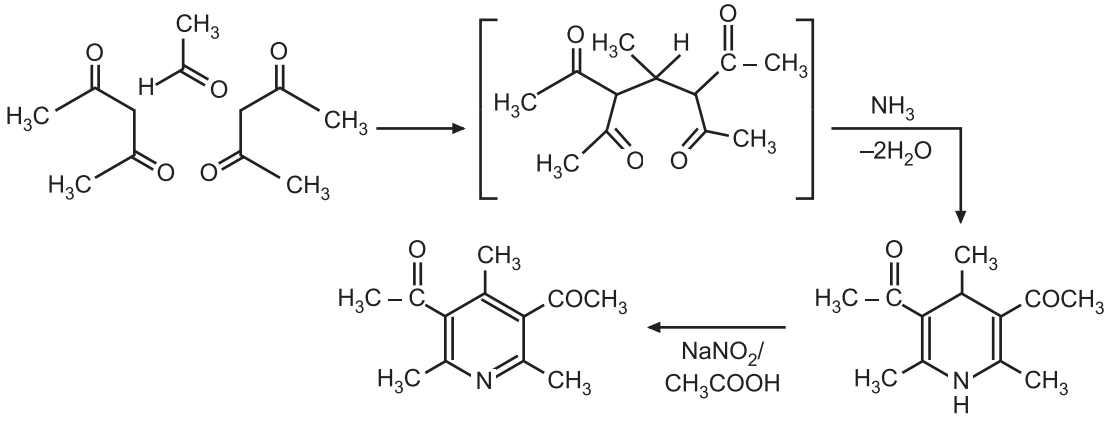
The alkyl group is an electron donating group. In aliphatic 3° amine, all the three alkyl groups donate electrons to the N-atom, thereby making lone pair of electrons on N-atom even more easily available for protonation. Hence, pyridine is less basic than aliphatic 3° amine.

4.6.1 Chemical Synthesis

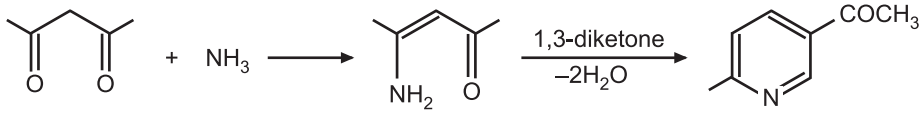
(1) Pyridine is synthesized by reacting acetaldehyde with formaldehyde and ammonia.



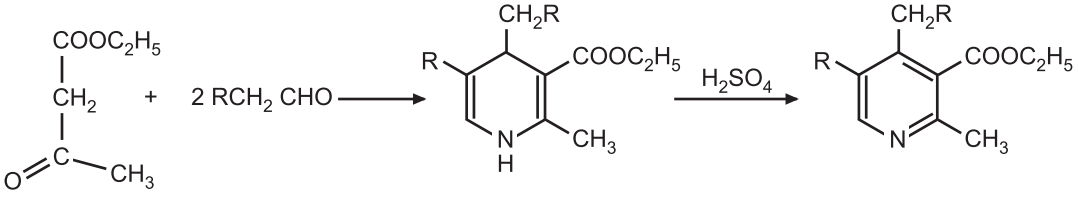
(2) Hantzsch synthesis: It is a condensation reaction between an aldehyde, two equivalents of 1, 3-dicarbonyl compound and ammonia.



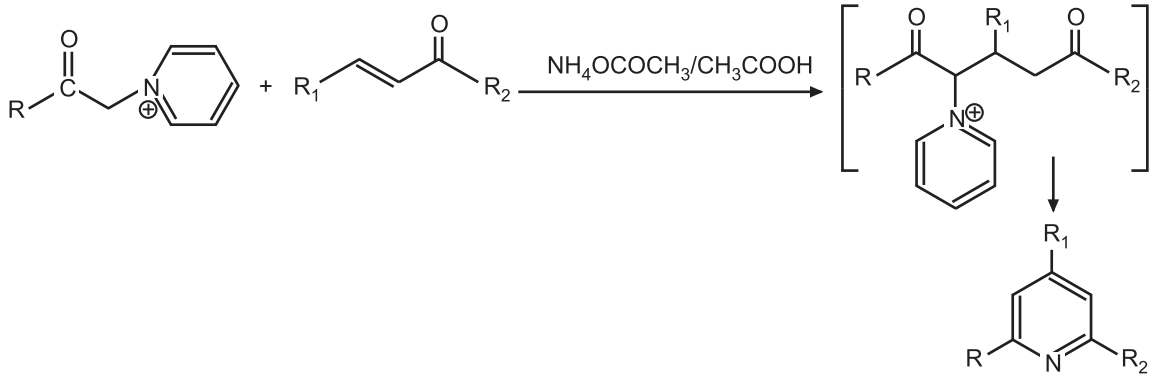
(3) From 1,3-dicarbonyl compound and 3-aminoacrylate: Unsymmetrically substituted pyridine can be synthesized by reaction between a 1,3-dicarbonyl compound with 3-aminoacrylate.



(4) Guareschi Thorpe Synthesis: Two molecules of aldehydes condense with the keto ester to give substituted pyridine.

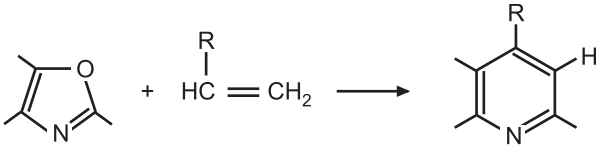


(5) Krohnke pyridine synthesis: The α-pyridinium methyl ketone salts react with α, β-unsaturated carbonyl compounds to give 2, 4, 6-trisubstituted pyridines.



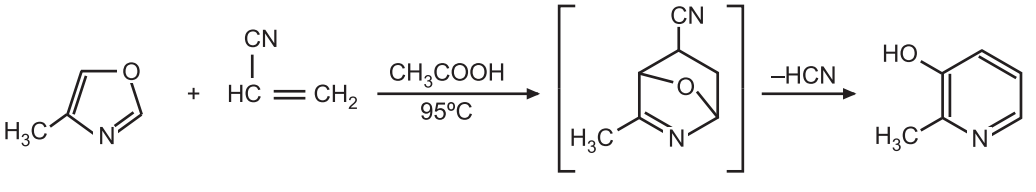
(6) Cycloaddition reaction: Various electrocyclic additions have been used to give pyridines as the final products.

(i)

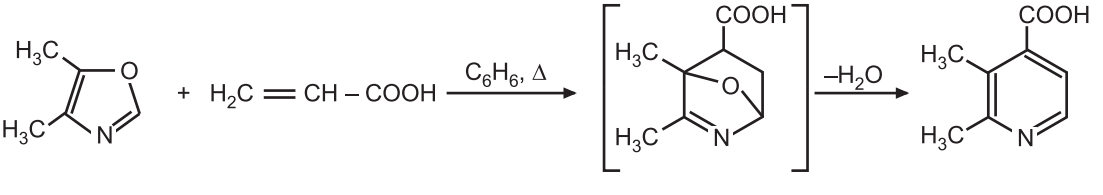


Oxazole Alkene

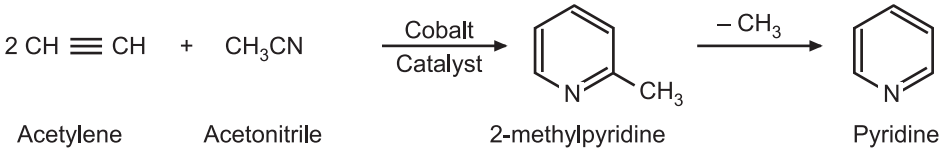
(ii)



(iii)

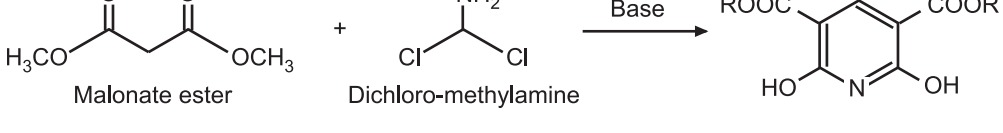


(7) Bonnemann Cyclization: It involves trimerization of one part of a nitrile molecule and two parts of acetylene either by heat or by light.



Acetylene Acetonitrile 2-methylpyridine Pyridine

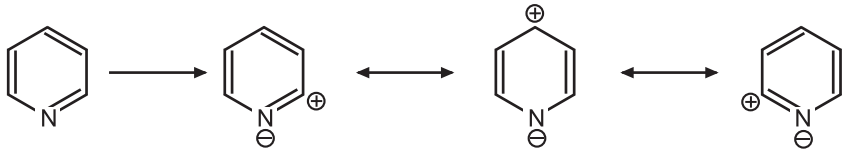
(8) Gattermann – Skita synthesis:



Malonate ester Dichloro-methylamine

4.6.2 Chemical Reactions

The electronegative nitrogen in the pyridine ring makes the pyridine molecule relatively electron deficient. Hence unlike benzene.



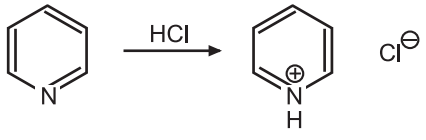
(i) Pyridine does not undergo electrophilic aromatic substitution readily.

(ii) Pyridine is more prone to nucleophilic substitution at positions 2 and 4 and metalation of the ring by strong organometallic bases, and

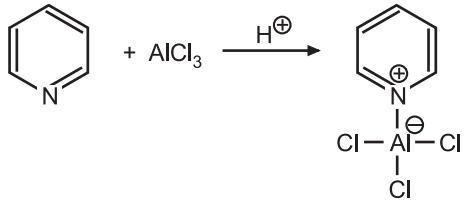
(iii) Like tertiary amine, pyridine undergoes N – protonation and undergoes oxidation to form N-oxide.

(a) N-Protonation: The lone pair of electrons on the nitrogen atom in pyridine is available for extra bonding. When a pyridine reacts with acids, metallic ions or acyl, sulfonyl, anhydrides, it forms quaternary salts.

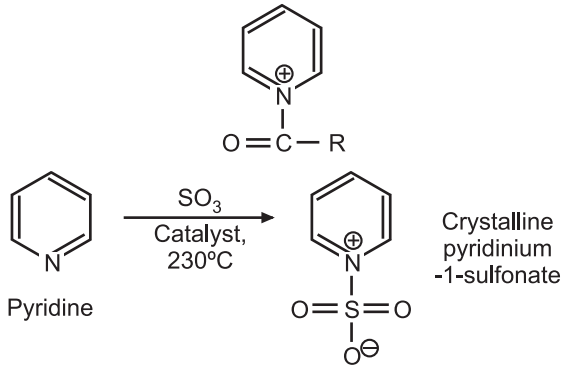
(i) Pyridines form crystalline, hygroscopic salts with most protic acids.



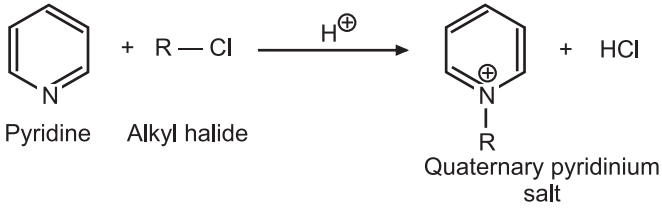
(ii) Metallic ions such as aluminium, boron, berrylium, etc. form complex with basic pyridine.



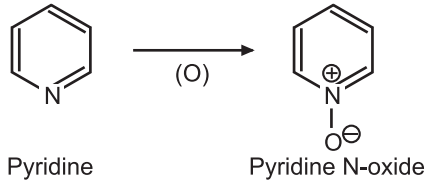
(iii) Acyl, sulfonyl or anhydrides readily react with pyridine to form quaternary salts which function as acylating and sulfonating agents.



(iv) Alkyl halides and sulfates readily react with pyridines giving quaternary pyridinium salts.

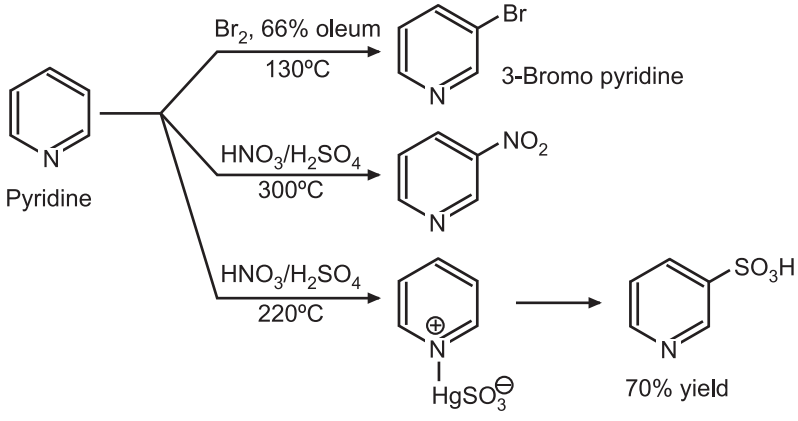


(v) Pyridine easily reacts with percarboxylic acids to give N-oxides.



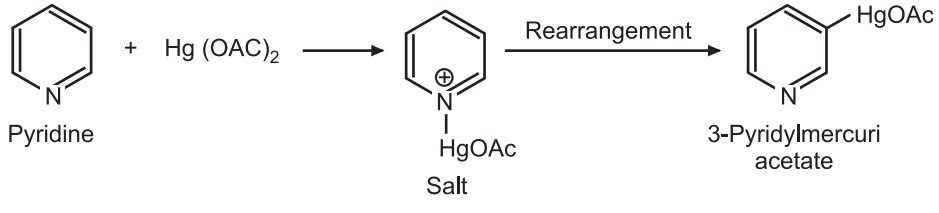
(b) Electrophilic Substitution: Benzene readily undergoes electrophilic substitution reactions. In pyridine, an electronegative N-atom creates π-electron deficiency at each C-atom and deactivates the ring towards electrophiles. The protonation of N-atom (acidic reaction condition) further deactivates the ring. Hence, pyridine undergo electrophilic substitution with extreme difficulty and only under extreme reaction conditions.

(i) Halogenation and nitration:

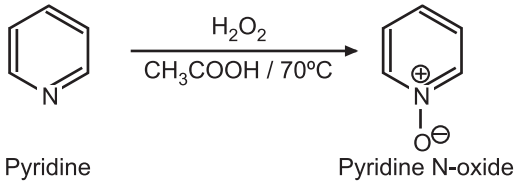


(ii) Friedel-Crafts Reaction: Pyridine forms a complex with $AlCl_3$ which is highly unreactive. Hence, pyridine does not undergo Friedel-Crafts reactions.

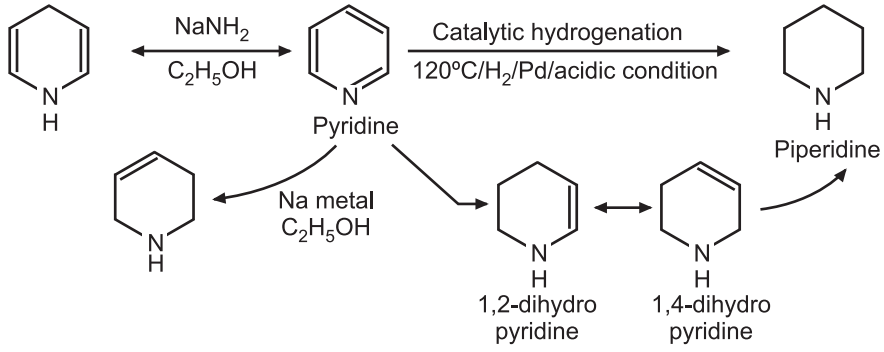
(iii) Mercuration: When pyridine is heated with mercuric acetate at 170-180°C, the salt initially formed undergoes rearrangement to give 3-pyridylmercuriacetate.



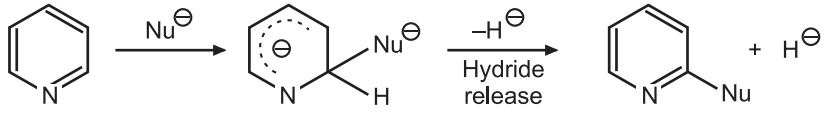
(c) Oxidation: Pyridine ring is resistant to oxidation, but the N-atom being highly electron rich, can easily be oxidized by hydrogen peroxide or various peracids to pyridine-N-oxide.



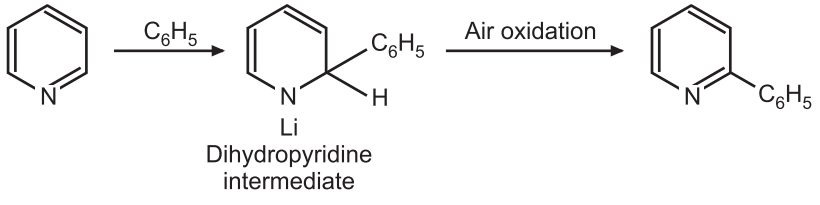
(d) Reduction: Since pyridine easily reacts with nucleophiles, it may be reduced by nucleophilic reducing agents.



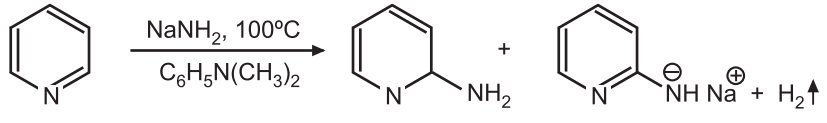
(e) Nucleophilic substitution: Electrophilic substitution is the characteristic reaction of benzene while nucleophilic substitution is the characteristic of pyridine. Nucleophilic substitution takes place at C_2 and C_4 positions.



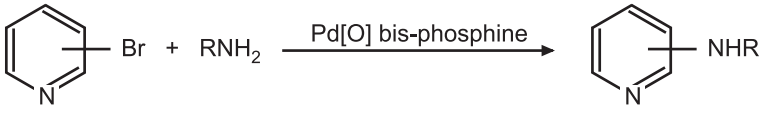
(i) Alkylation and arylation: Pyridine reacts with alkyl or aryl lithiums to give a dihydropyridie intermediate which then gets converted into substituted peridine.



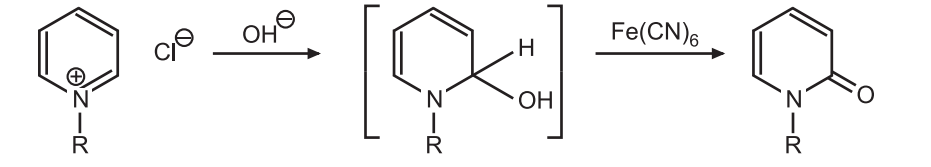
(ii) Amination: Pyridine reacts with sodamide to give 2-aminopyridine. It is called chichibabin reaction.



Bromopyridines undergo nucleophilic substitution in a palladium phosphine catalysed reaction.



(iii) Hydroxylation: Pyridinium salts are more reactive than pyridine towards nucleophilic substitution. For example, pyridinium salt reacts with alkaline potassium ferricyanide to give N-substituted 2-pyridones.



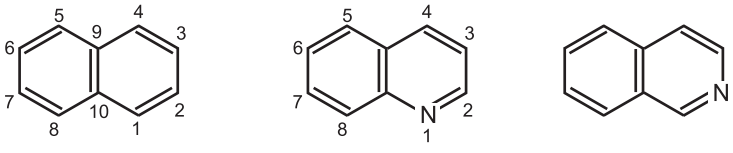
Pyridinium salt N-substituted-2-pyridone

4.6.3 Applications in Drug Synthesis

It is present as a core skeleton in sulfapyridine (antibacterial), tripelenamine, mepyramine (antihistaminic), nicacin, pyridoxine (vitamin), isoniazid (anti – T. B.), etc.

4.7 QUINOLINE

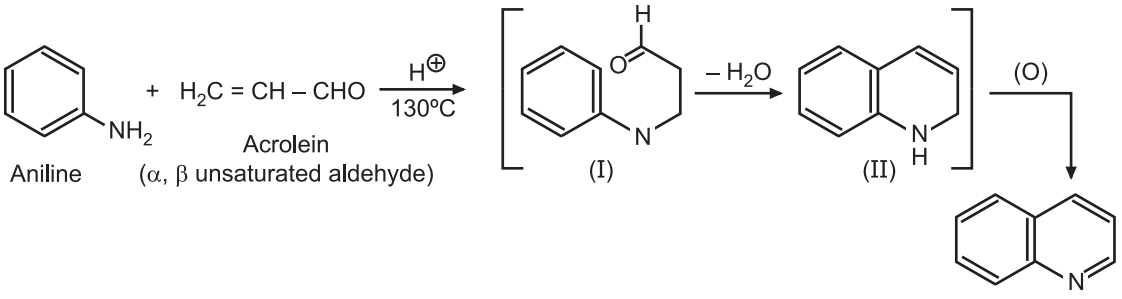
Quinoline or 1-azanaphthalene is a colourless liquid with sweetish odour and has a high boiling point of 237°C. It was first isolated in 1834 from coal tar. Quinoline and isoquinoline are benzopyridines, which are composed of a benzene ring fused to a pyridine ring. Quinoline is a weakly basic compound. Electron releasing substituents at the 2 and 4 positions of quinoline increase the basicity. The electrophilic attack will take place at electron rich C_5 and C_8 positions. Due to presence of electronegative N-atom close to C_2, the C_2 and C_4-positions are electron deficient. Hence, nucleophilic attack takes place preferentially at the C_2 and C_4 positions.



Naphthalene Quinoline (1-azanaphthalene) Isoquinoline

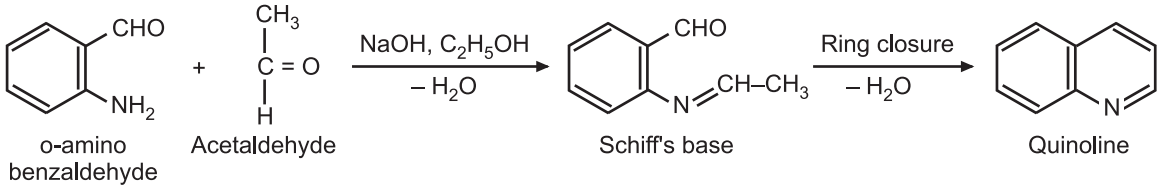
4.7.1 Chemical Synthesis

(1) Skraup synthesis: When aniline, concentrated sulfuric acid, glycerol and a mild oxidizing agent are heated together, quinoline is formed. The reaction begins when glycerol is first dehydrated by concentrated sulfuric acid to acrolein. Aniline is then added begins to it to produce 1, 2-dihydroquinoline.



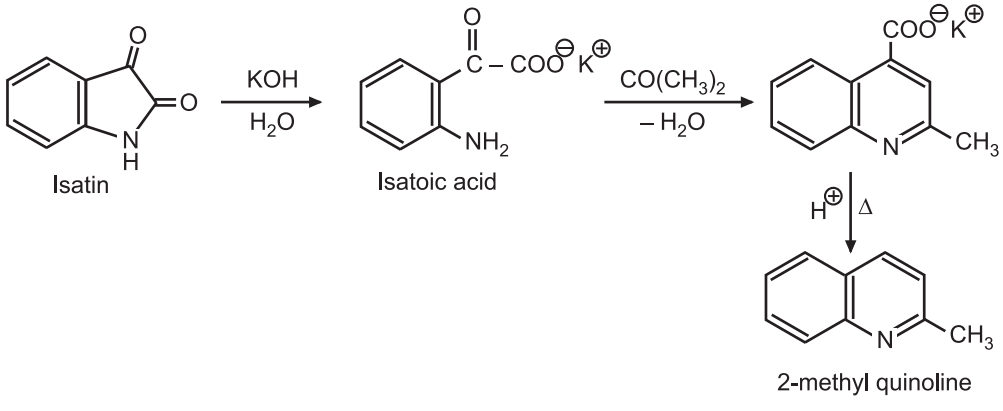
The 1, 2-dihydroquinoline is further oxidized to give quinoline. Aniline adds to acrolein through Michael addition to give aniline propanal (I). Substituted anilines give quinoline derivatives in which substituents appear in benzene ring portion.

(2) Friedlander synthesis: When o-aminobenzaldehyde or o-aminoacetophenone condenses with an aldehyde or ketone (which must contain an active α-methylene group) in alcoholic sodium hydroxide solution, it yields quinoline.

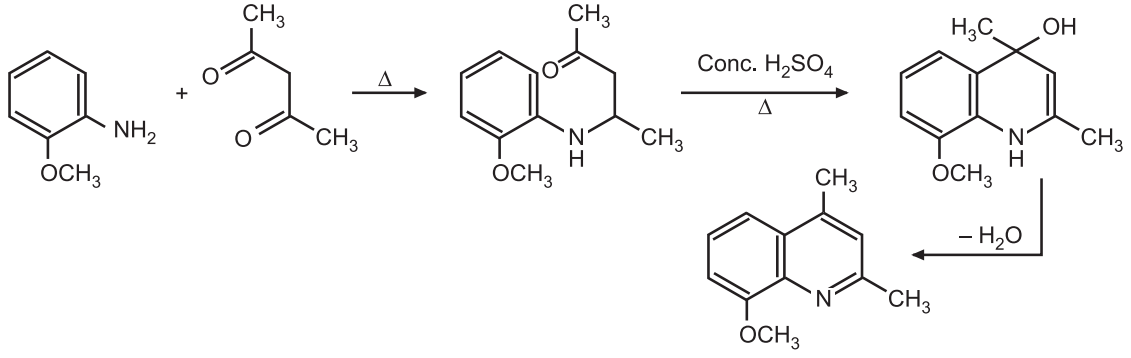


2-substituted quinoline derivatives are usually prepared by this method.

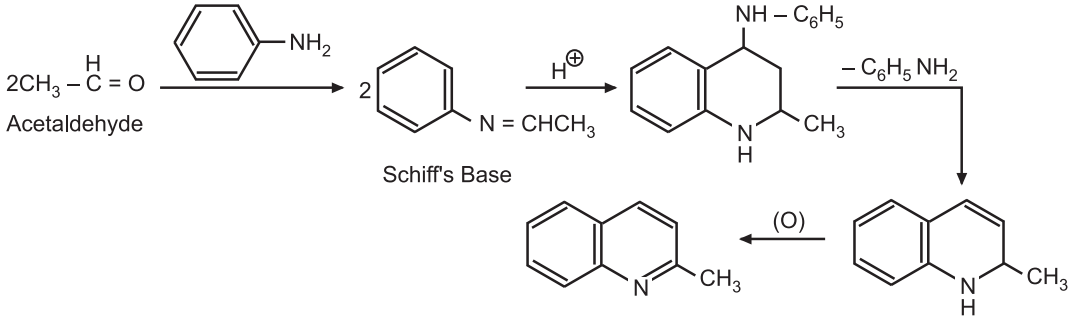
(3) Pfitzinger synthesis: In this method, isatin in the presence of a base, is converted to isatoic acid which is condensed with a ketone to give quinoline-4-carboxylic acid. The carboxylic acid group can be removed by pyrolysis with calcium oxide to give substituted quinolines.



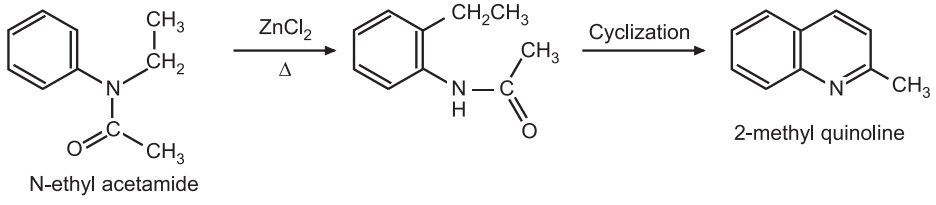
(4) Combes synthesis: Condensation of 1, 3-dicarbonyl compound with an arylamine gives a β-amino enone which undergoes cyclization with a loss of water to give quinoline.



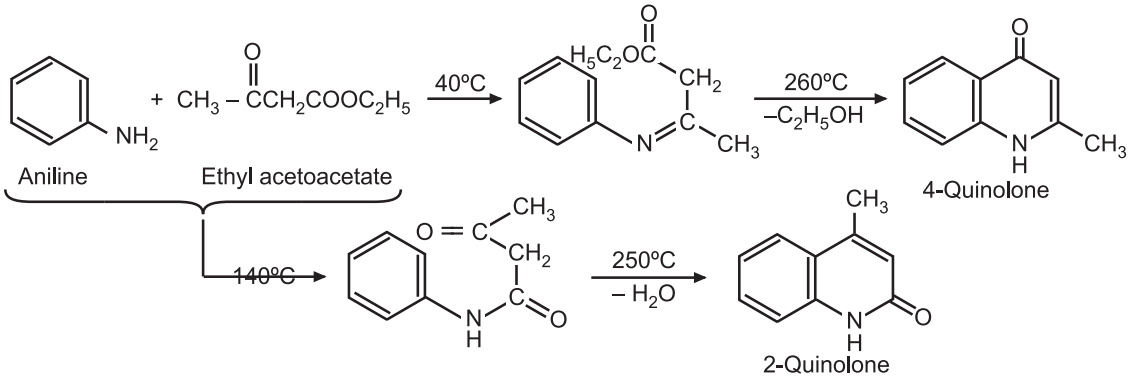
(5) Doebner Miller Synthesis: An aniline and two moles of acetaldehyde are heated in the presence of HCl to form Schiff's base. Two molecules of this Schiff's base condense to form quinoline derivative.



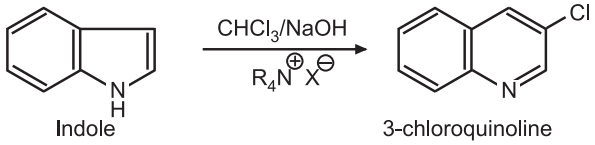
(6) Pictet Method:



(7) Conrad – Limpach – Knorr synthesis: Anilines react with β-keto esters (e.g., ethyl acetoacetate) at lower temperature to give a β-aminoacrylate which upon cyclization gives a 4-quinolone. At high temperature, β-ketoester anilides are formed which upon cyclization gives 2-quinolones.



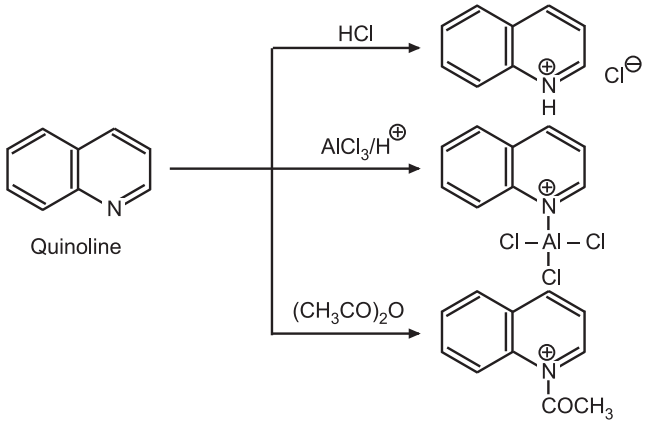
(8) Indole reacts with chloroform and sodium hydroxide in the presence of tetra-alkyl ammonium salt to give chloroquinoline.



4.7.2 Chemical Reactions

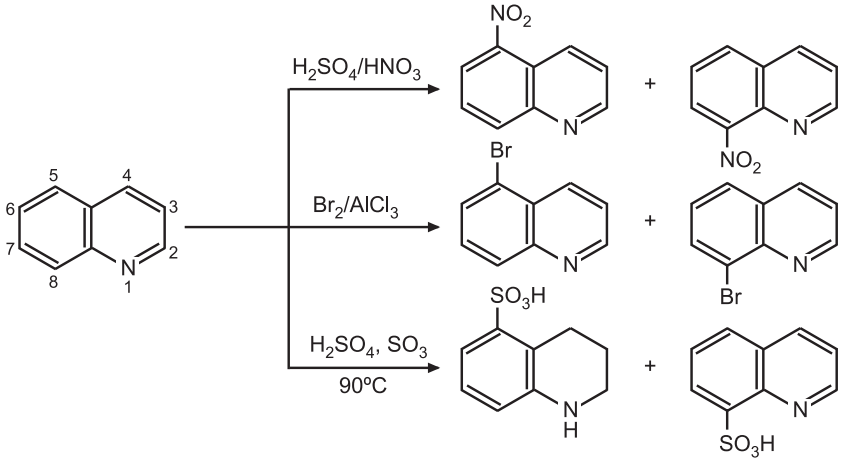
Quinoline is a weak base. The electron rich N-atom of quinoline is the main site for attack by electrophile. This N-atom deactivates the ring towards electrophilic attack. Hence, electrophilic substitution on quinoline ring requires vigorous reaction condition. The electron rich N-atom makes the pyridine ring (hetero ring) more π-electron deficient. Hence, electrophilic attack occurs at the benzo rather than more resistant hetero ring. While nucleophilic attack occurs at hetero ring rather than benzo-ring.

(1) Addition to nitrogen: The lone pair of electrons on the N-atom is available for extra bonding. When quinoline reacts with acids, metallic ions or acyl, sulfonyl, anhydrides, it forms quaternary salts.

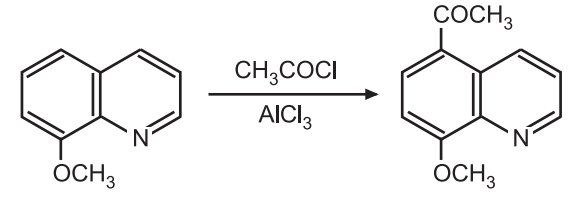


(2) Electrophilic substitution: Electrophilic substitution preferably occurs at positions 5 and 8.

(a)



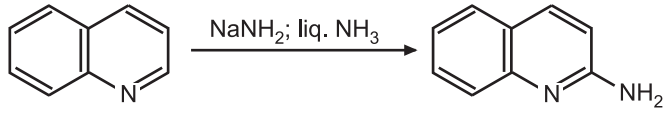
(b) Acylation and alkylation: The quinoline ring is already deactivated by the N-atom. Hence, alkylation and acylation occurs only in those rings which have a strong electron donating substituents.



8-Methoxyquinoline 5-Acetoxy-8-methoxy quinoline

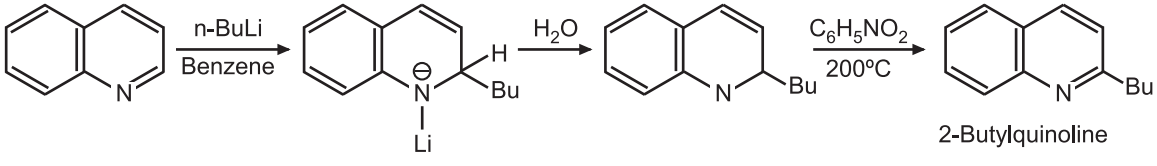
(3) Nucleophilic substitution: Quinoline readily gives nucleophilic reaction. This reaction preferably occurs at position 2. If position 2 is already occupied then attack may occur at position 4. For example,

(a)



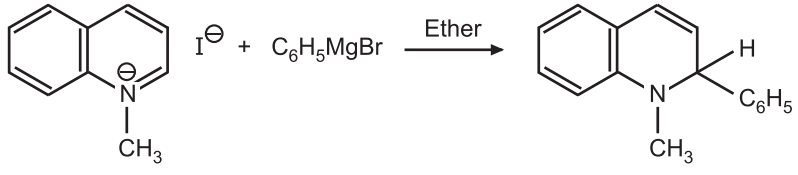
2-Aminoquinoline

(b) Quinoline can be alkylated using organolithium reagents.



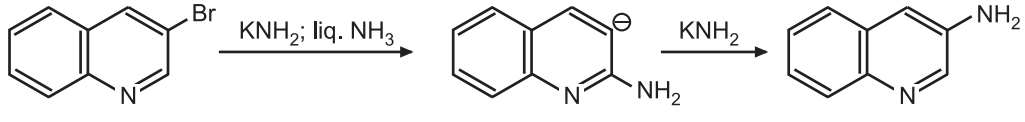
2-Butylquinoline

(c) Treatment with Grignard reagent results into formation of substituted 1, 2-dihydroquinoline.



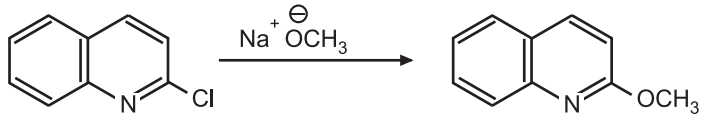
(d) Nucleophiles such as $-NH_2$ or $-OCH_3$ may attack the quinoline ring by displacing halogen atom. Examples:

(i)

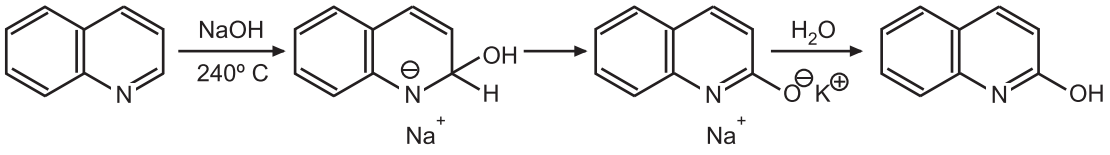


3-bromo quinoline 3-amino quinoline

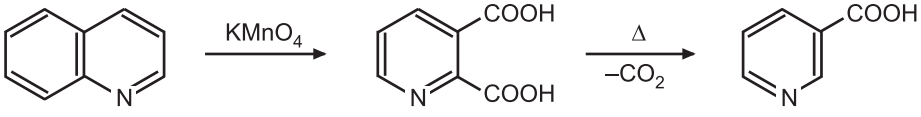
(ii)



2-chloro quinoline 2-methoxy quinoline

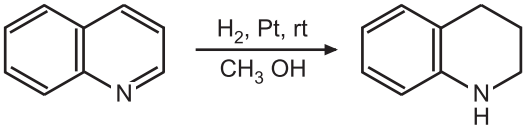
(iii) 

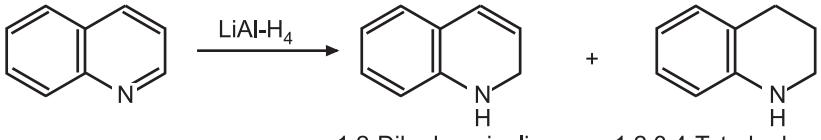
(4) Oxidation: Quinoline is resistant to oxidation. Under vigorous condition, pyridine ring remains intact while the benzene ring is opened up on treatment with alkaline $KMnO_4$.



Quinolinic acid Nicotinic acid (Niacin)

(5) Reduction: Quinoline is reduced to 1, 2, 3, 4 – tetrahydroquinoline using catalytic hydrogenation in methanol.





1,2-Dihydroquinoline 1,2,3,4-Tetrahydroquinoline

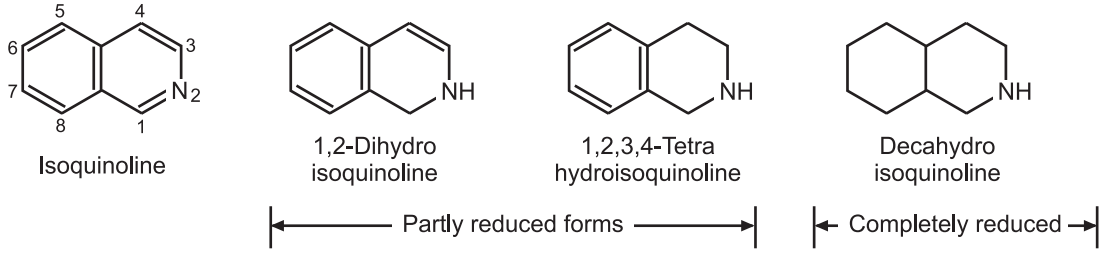
Lithium in liquid ammonia can produce, 1, 4 – dihydroquinoline under certain conditions. In acid medium, the benzene ring can be selectively reduced.

4.7.3 Applications in Drug Synthesis

Quinoline is a core component in the structure of chloroquine (antimalarial), papaverine (smooth muscle relaxant), quinapril (antihypertensive), singulair (anti-asthma), hydroxychloroquine (antimalarial), narcotine (depressant), emetine (emetic: vomiting inducer), dimethisoquin (anaesthetic), etc.

4.8 ISOQUINOLINE

Isoquinoline is a colourless hygroscopic liquid having an unpleasant odour. Like quinoline, it is also a weak base. It was first isolated from coal tar by Hoogewerff and Dorp in 1885.

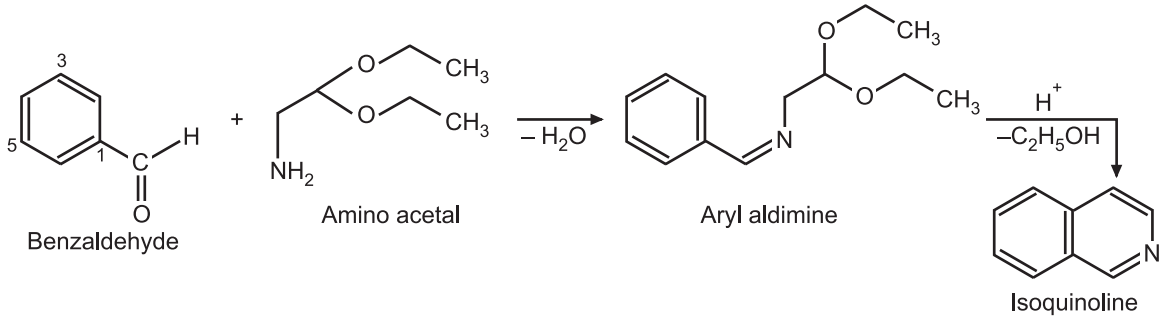


Isoquinoline 1,2-Dihydro isoquinoline 1,2,3,4-Tetra hydroisoquinoline Decahydro isoquinoline

Partly reduced forms Completely reduced

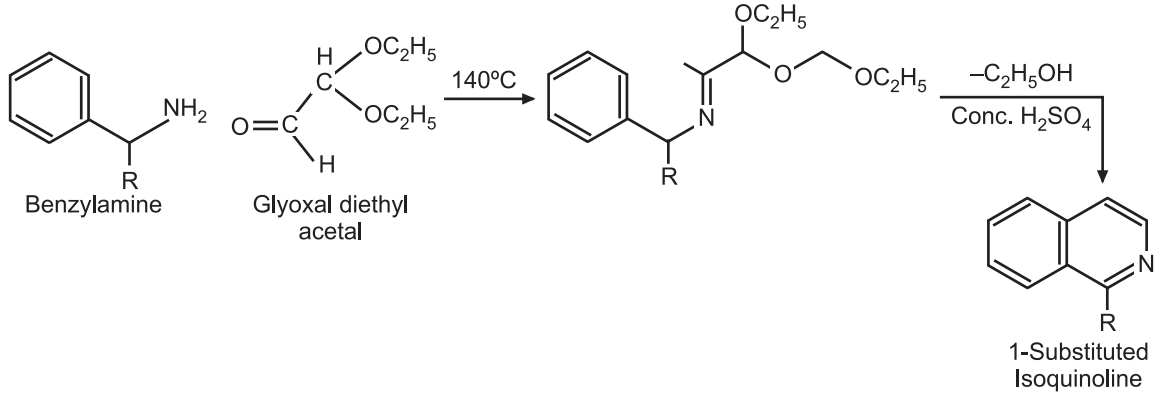
4.8.1 Chemical Synthesis

(1) Pomeranz-Fritsch reaction: In this reaction, benzaldehyde is condensed with aminoacetal to form an aryl aldimine. The aldimine is cyclized using strong acid such as concentrated Sulfuric acid or phosphorous pentoxide.

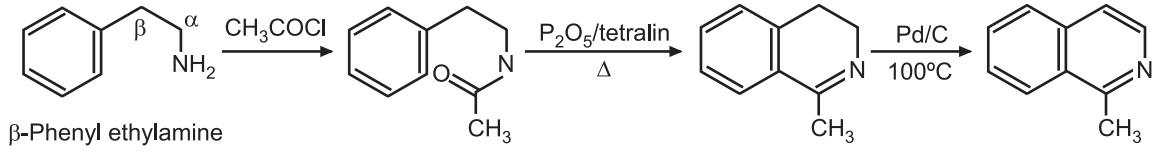


The electron donating groups (if present at 3 and/ or 5 position in benzaldhyde) increase the rate of reaction while electron withdrawing groups decrease the rate.

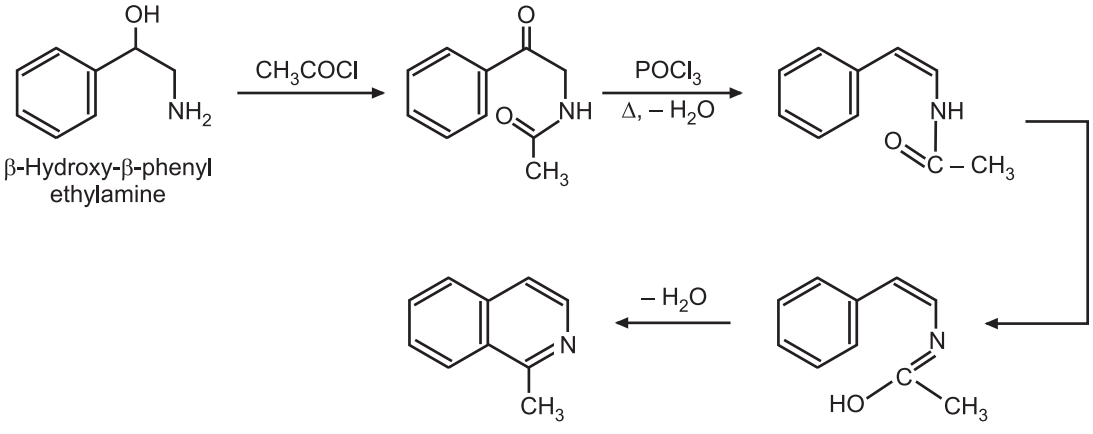
(2) Schlitttler – Muller Modification: When benzylamine condenses with glyoxal diethyl acetal, the resulting imine can be cyclized with acid to give 1-substituted isoquinoline. It is a modification of Pomeranz-Fritsch reaction.



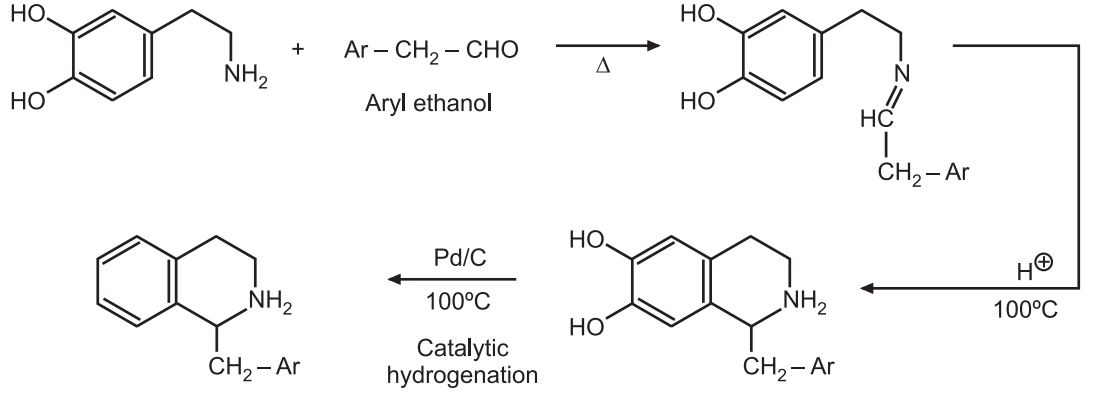
(3) Bischler-Napieralski synthesis: In this reaction, a β-phenyl ethylamine is acylated using acid-chloride/anhydride to form an amide. This amide can be cyclised with a loss of water using a Lewis acid (phosphoryl chloride or phosphorous pentoxide) to give 1-substituted-3, 4-dihydro isoquinoline. This intermediate can be readily dehydrogenated to isoquinoline using palladium, sulfur or diphenyl disulfide.



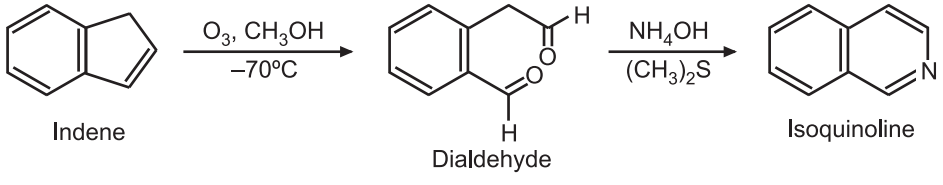
(4) Pictet-Gams modification: In this method, β-phenylethylamine is replaced by β-hydroxy-β-phenylethylamine which is heated with cyclization catalyst, $POCl_3$.



(5) Pictet-Spengler synthesis: When arylethanamines react with aldehyde, it gives imines. Under acid catalysed cyclization, the imine gets converted to 1, 2, 3, 4 – tetrahydro-isoquinoline. If electron donating substituents are present on phenyl ring, ring closure (i.e., cyclization) occurs under very mild conditions. e.g.,



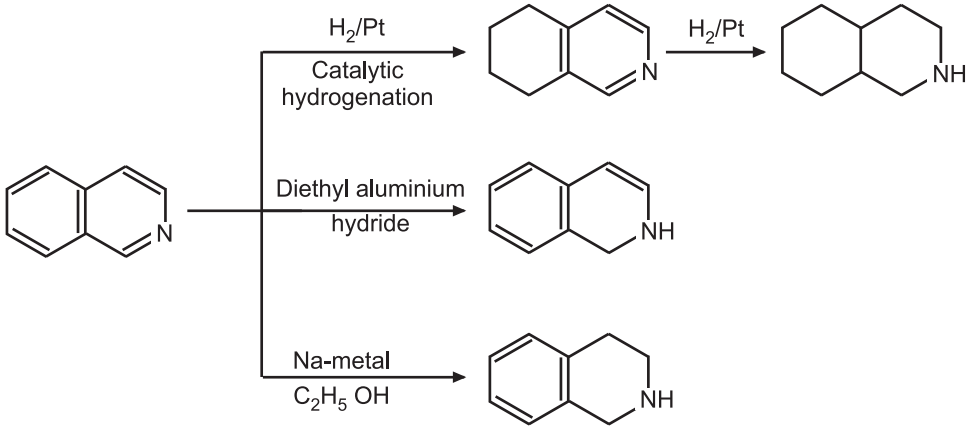
(6) Ozonolysis of indene: Indene when treated with ozone at –70°C, it provides homophthal-aldehyde. This dialdehyde is reduced followed by cyclization with dimethylsulfide in the presence of NH_4OH.



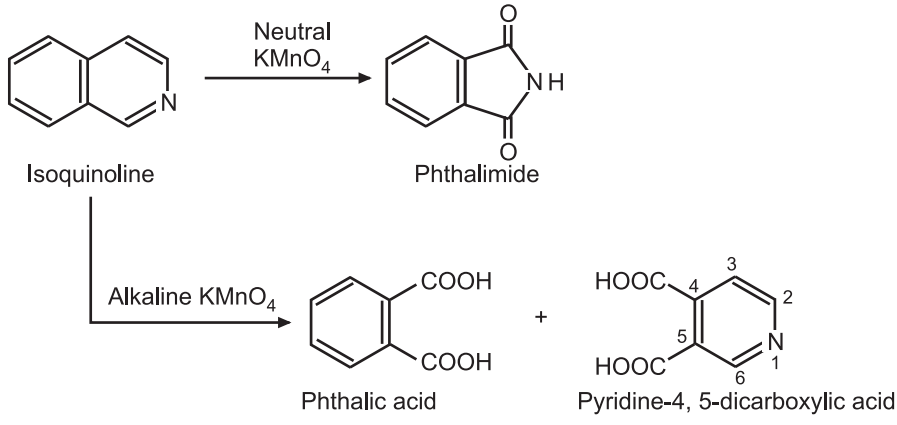
4.8.2 Chemical Reaction

As like pyridine, isoquinoline is a weak base. It protonates to form salts upon treatment with strong acids. The lone pair of electrons available on N-atom and aromatic nature of isoquinoline compel it to behave similar to quinoline in its chemical reactions. For example, like quinoline, 5- and 8-positions of isoquinoline are most susceptible to electrophile attack while the nucleophile attacks preferably at 1-position or at 3-position if position-1 is already occupied.

(a) Reduction: Isoquinoline gives rise to different reduced products under the attack of different reducing agents.



(b) Oxidation: Isoquinoline is resistant to oxidation. If vigorous conditions employed, isoquinoline undergoes ring cleavage to give degradation products.

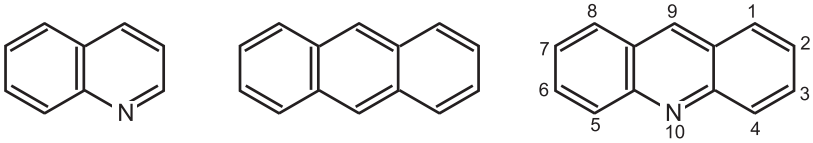


4.8.3 Applications in Drug Synthesis

Isoquinoline is a core part of structure of many drugs. These drugs include dimethisoquin (anesthetic), debrisoquine, quinapril (antihypertensive), papaverine (vasodilator) and many therapeutically active alkaloids like berberine, emetine, etc.

4.9 ACRIDINE

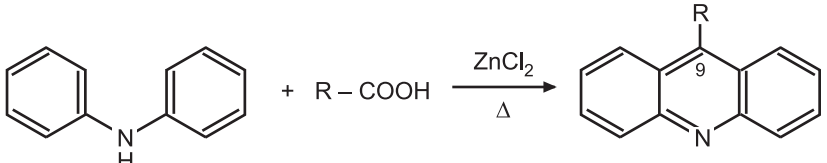
It is a colourless aromatic compound having a melting point of 106-110°C. It is structurally related to anthracene with one of the central atom replaced by nitrogen. It was first isolated from coal tar in 1870 by Carl Grabe and Heinrich Caro. Like pyridine, it is mildly basic.



Quinoline Anthracene Acridine

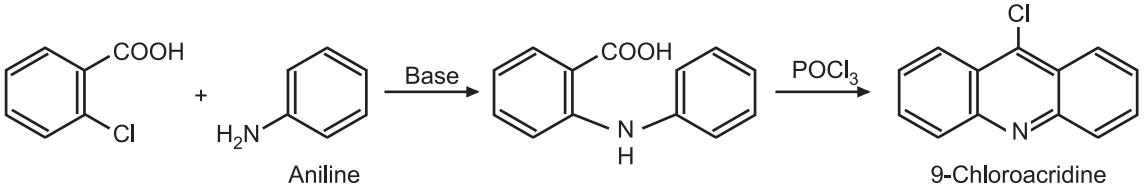
4.9.1 Chemical Synthesis

(1) Bernthsen acridine synthesis: When diphenyl amine is condensed with carboxylic acids in presence of zinc chloride, it provides acridines.



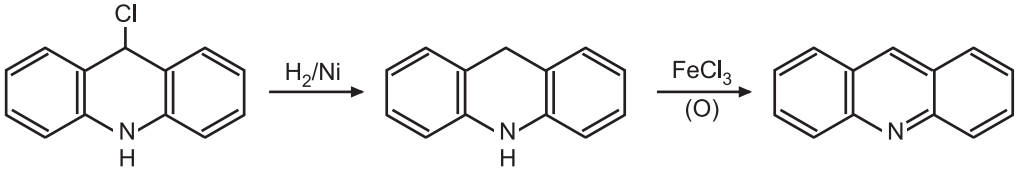
Diphenyl amine 9-substituted acridines

(2) From o-chlorobenzoic acid (Ullmann synthesis): Aniline and o-chlorobenzoic acid are condensed to form diphenylamino-2-carboxylic acid. This acid is cyclized with $POCl_3$ to give 9-chloroacridine.



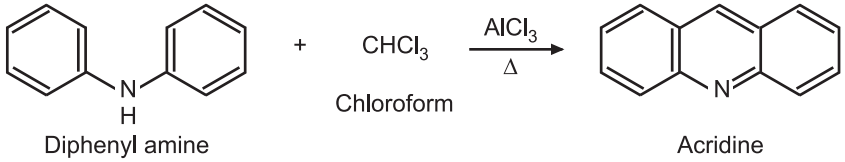
Aniline 9-Chloroacridine

The 9-chloroacridine is first reduced by catalytic hydrogenation followed by oxidation using ferric chloride to give acridine.



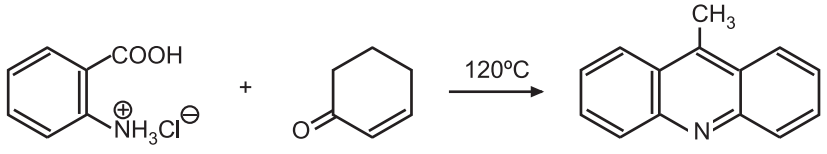
9-Chloroacridine 9,10-Dihydro acridine Acridine

(3) Diphenylamine is condensed with chloroform in presence of $AlCl_3$ to give acridine.



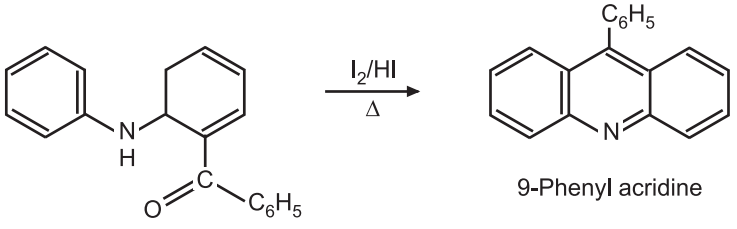
Diphenyl amine Chloroform Acridine

(4) Friedlander synthesis: The salt of anthranilic acid is treated with cyclohex-2-enone at 120°C to give 9-methyl acridine.



Anthranilic acid salt | Cyclohex-2-enone | 9-Methyl acridine

(5) From C-acylated diphenylamines: The diphenylamine is first acylated. The acylated diphenylamine is heated in the presence of I_2/HI to give 9-phenylacridine.

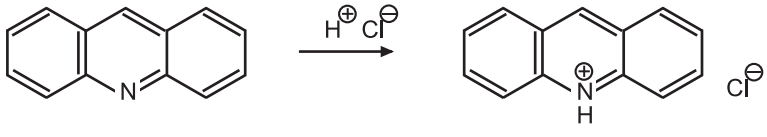


Phenyl-(6-phenylaminocyclohexa-1,3-dienyl) methanone | 9-Phenyl acridine

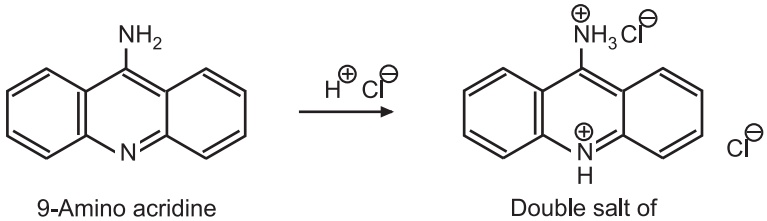
4.9.2 Chemical Reactions

Acridine is the aza derivative of anthracene. It is a weak base. The lone pair of electrons available on N-atom and aromatic nature of acridine compel it to behave chemically, similar to pyridine and quinoline.

(a) N-protonation: Acridine being a weak base, forms soluble salt by protonation at N-atom using its lone pair of electrons. Amino-acridine forms a double salt where the ring N-atom is first to get protonated.

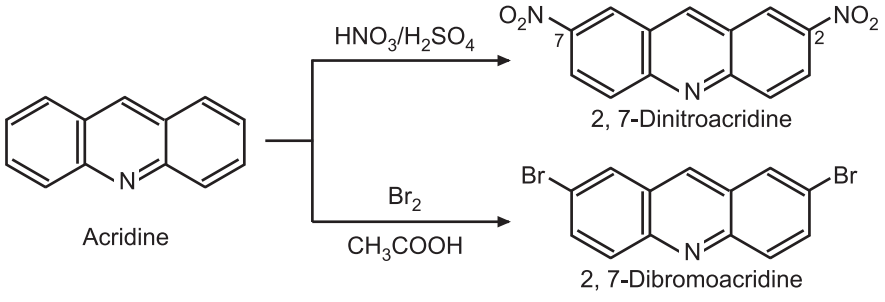


Acridine | Acridine salt

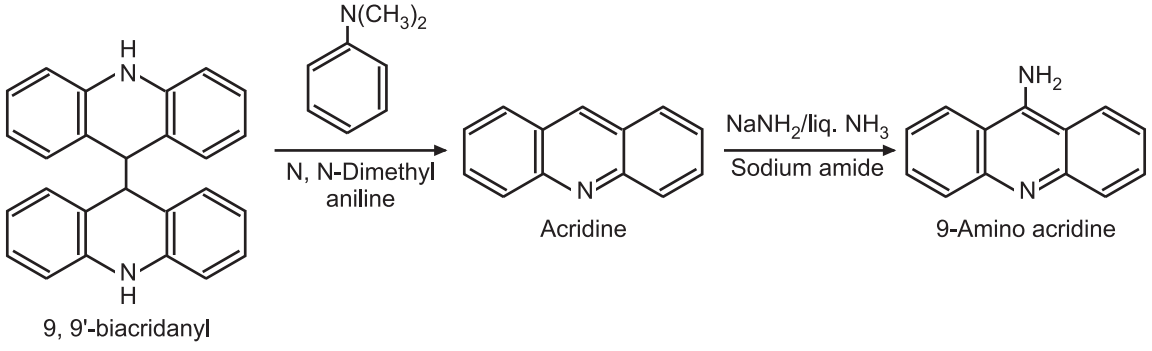


9-Amino acridine | Double salt of 9-aminoacridine

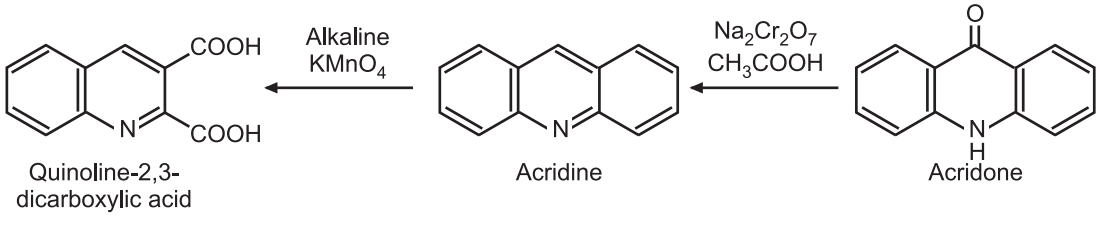
(b) Electrophilic substitution: The electrophile attacks the benzenoid ring preferably at 2- and 7-positions resulting in di-substitution. e.g.,



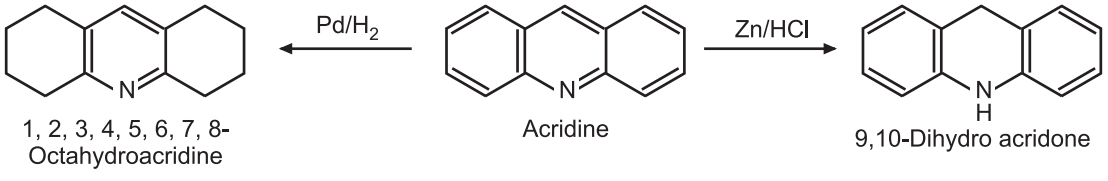
(c) Nucleophilic substitution: The quaternary salts of acridine are more reactive towards nucleophilic reagents. In acridine, the electron density at position-9 is low in comparison to 1-, 2-, 3- and 4- positions. Hence, nucleophile preferably attacks at 9-position.



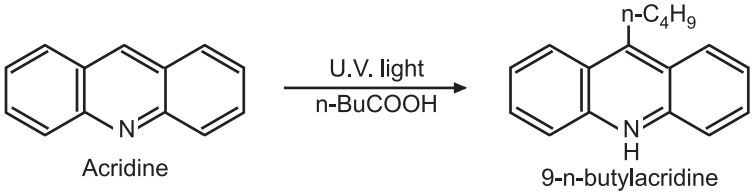
(d) Oxidation: Acridine is oxidized by dichromate in acetic acid to give acridone. The oxidative ring cleavage occurs by $KMnO_4$ in alkaline medium forming quinoline -2, 3-dicarboxylic acid.



(e) Reduction: The benzene rings of acridine can be selectively reduced by catalytic hydrogenation while the pyridine ring can be selectively reduced by Zn/HCl to give 9, 10-dihydroacridine.



(f) Reductive alkylation: Acridine reacts with n-pentanoic acid in the presence of U. V. light to give 9-n-butylacridine.

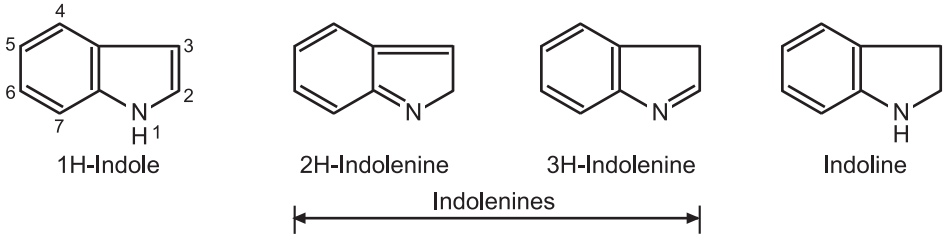


4.9.3 Applications in Drug Synthesis

Many drugs in the market have acridine as a core skeleton. These drugs include bucricaine (anaesthetic), quinacrine (or mepacrine: antimalarial), 9-ammoacridine (disinfectant), proflavin (antibacterial), nitracrine (anticancer), acriflavin (antiseptic), etc.

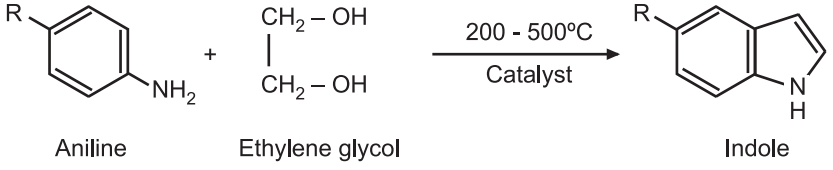
4.10 INDOLE

It is an aromatic heterocyclic compound consisting of a benzene ring fused to a pyrrole ring. it is a white solid having the melting point 52-54°C. Indole was first obtained in 1866 by zinc dust distillation of oxindole. The tautomeric forms of indole are known as indolenines.

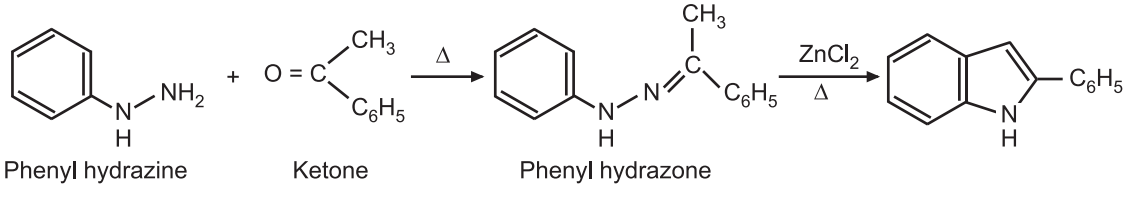


4.10.1 Chemical Synthesis

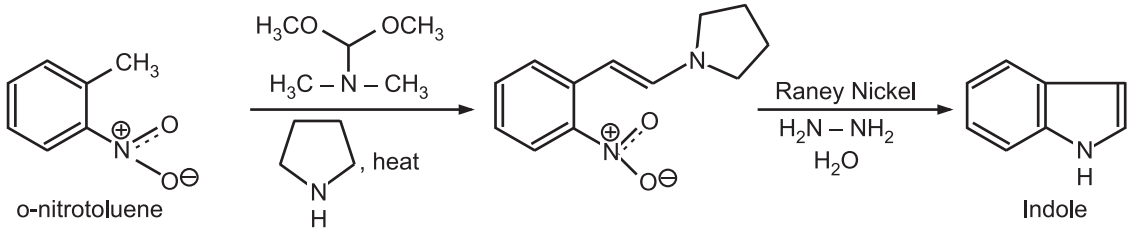
(1) Aniline via vapour-phase reaction with ethylene glycol in the presence of catalyst gives indoles.



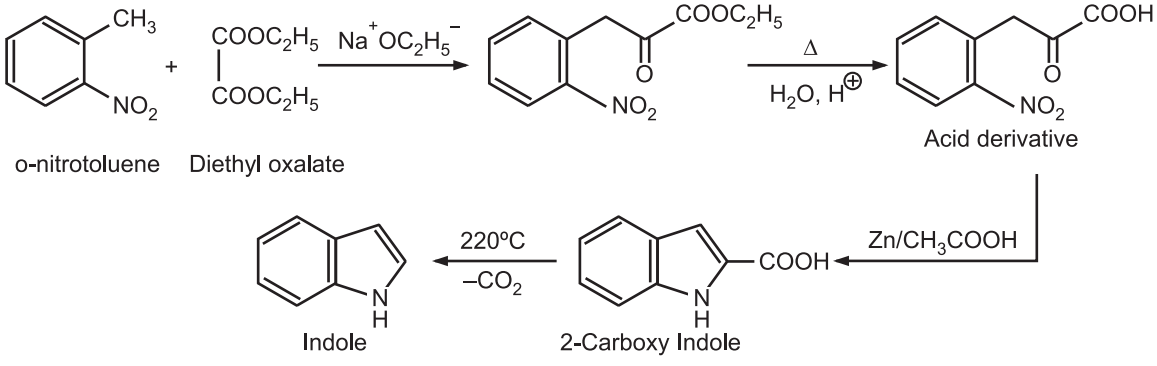
(2) Fischer-Indole synthesis: This method was developed in 1883 by Emil Fischer. It is used to synthesize 2- and/or 3-substituted indoles. It consists of heating an arylhydrazine with an aldehyde or ketone, followed by acid catalyzed rearrangement of resulting arylhydrazone with a loss of ammonia give an indole.



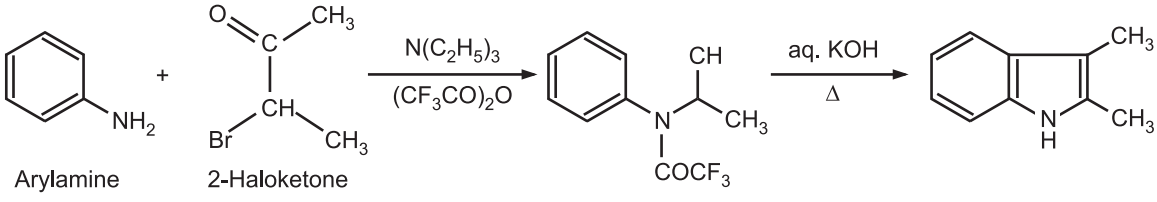
(3) Leimgruber-Batcho indole synthesis: In this reaction, o-nitrotoluence reacts with pyrrolidine in the presence of N, N-dimethyl formamide dimethyl acetal (DMFDMA) to give an enamine. This enamine undergoes reductive cyclization to give an indole.



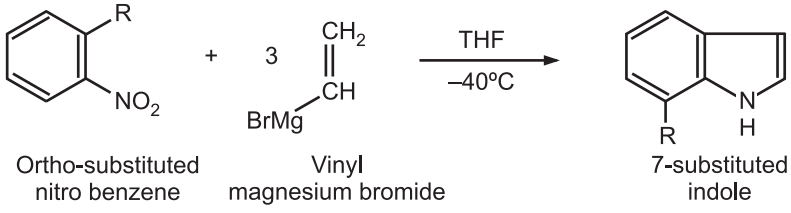
(4) Reissert synthesis: The methyl group ortho to nitro on a benzene ring is acidic enough to get condensed with diethyl oxalate in the presence of sodium ethoxide. After hydrolysis the resulting acid undergoes reductive cyclization to give an indole.



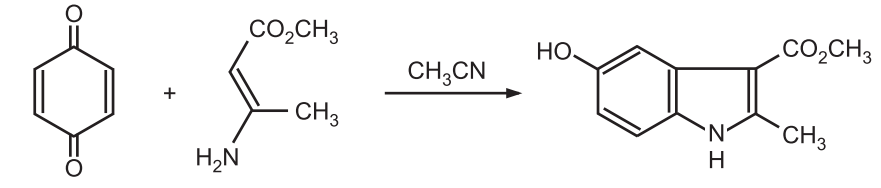
(5) Bischler synthesis: An arylamine is treated with 2-haloketone to give α-arylaminoketone which on heating with a strong acid or zinc chloride undergoes cyclization to give an indole.



(6) Bartoli synthesis: In this method, o-substituted nitrobenzene is treated with three moles equivalents of vinyl magnesium bromide to give 7-substituted indoles.

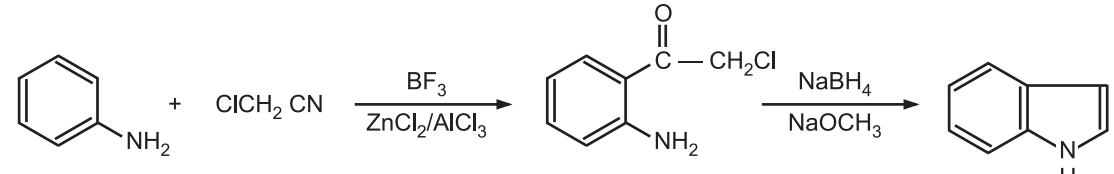


(7) Nenitzescu synthesis: Costin Nenitzescu reported this method in 1929. In this method, benzoquinone reacts with β-aminocrotonic ester to give 5-hydroxy indole derivatives.



Benzoquinone β-amino crotonic ester 5-hydroxy indole derivative

(8) Sugasawa synthesis: Arylamine undergoes Friedel-Crafts acylation using nitrile and boron trifluoride to give 2-amino chloroacetophenone.



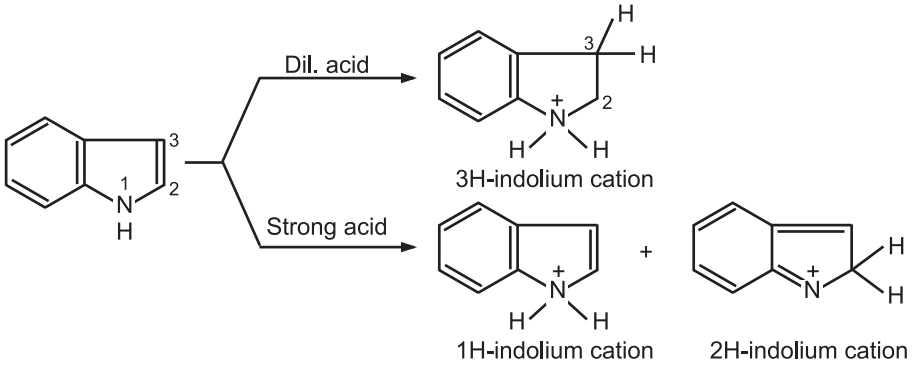
Arylamine Chloro acetonitrile 2-Amino chloroacetophenone

It is followed by reductive cyclization of the intermediate using $NaBH_4$ to give 2, 3-unsubstituted indole derivatives. This reaction is not suitable for anilines with a strong electron-withdrawing substituents.

4.10.2 Chemical Reactions

Indoles are aromatic heterocyclic compounds where the ring nitrogen atom is not basic. Indoles are very weak bases.

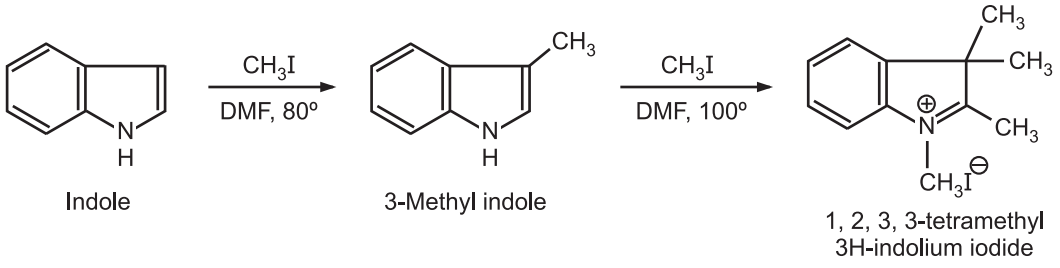
(1) Protonation:



3H-indolium cation 1H-indolium cation 2H-indolium cation

(2) Alkylation: The lone pair of electrons on ring N-atom is a part of aromatic sextet and not available free and exclusively at nitrogen atom. Hence, indoles do not react with alkyl halides at room temperature. However indole reacts with methyliodide in DMF

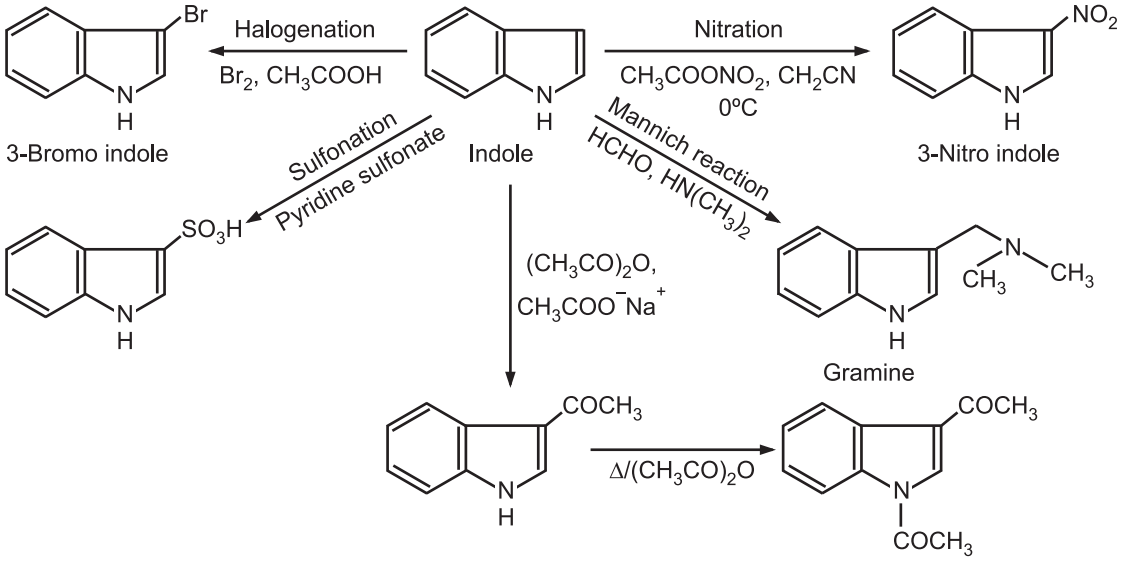
at about 80°C to give 3-methyl indole. As temperature is gradually raised above 100°C, 1, 2, 3, 3-tetramethyl-3H-indolium iodide is formed.



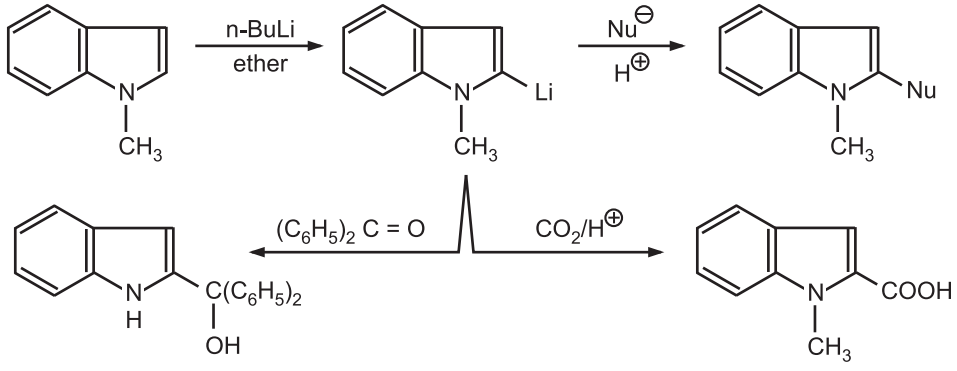
(3) Electrophilic substitution: Indole itself is π-electron excessive system. Since, electron density is higher on carbon atoms in pyrrole part of indole, electrophilic substitution readily occurs in the heterocyclic ring in the following preference order.

C_3 – atom > N-atom > C_2 – atom

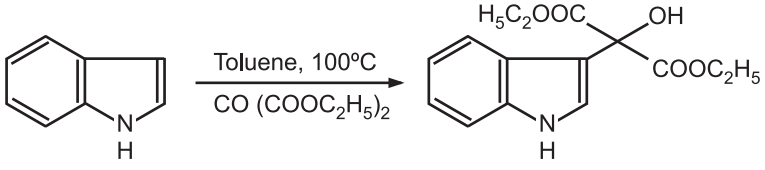
When the positions 3- and 2- are occupied, the electrophile attacks in the benzene ring. The attack of electrophile at position-3 generates carbocation which efficiently uses electron lone pair on N-atom and do not disturb the aromaticity of benzene ring. While electrophile attack of position-2 generates carbocation, which disrupt the aromatic character by delocalizing the positive charge over benzene ring.



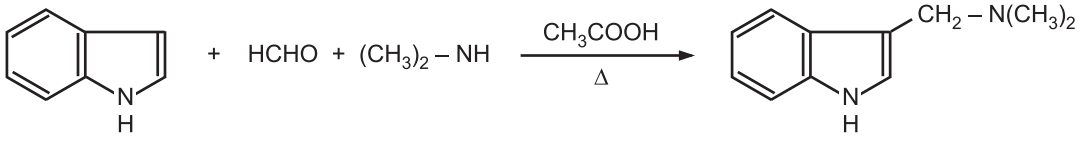
(4) Nucleophilic substitution: Indoles undergo very few nucleophilic substitution reactions. These reactions do not occur in indoles by direct displacement of ring bound substituent. Initially the indole is deprotonated by readily displacable nucleophilic reagent such as n-BuLi. The nucleophile then attacks at C-2 position by displacing the Li-atom.



(5) Reaction with aldehydes and ketones: Under acid catalysed conditions, indoles react with aldehydes and ketones to give indol-3-ylcarbinols.

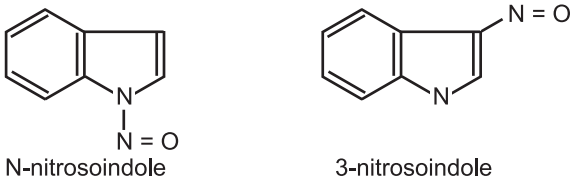


(6) Mannich reaction: Indole reacts with a mixture of formaldehyde and dimethylamine in acetic acid to give Mannich base at C_3-position.



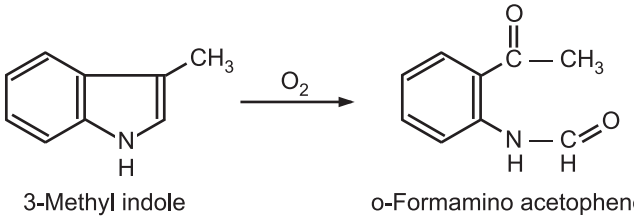
Indole Dimethyl amine Gramine (Mannich base)

(7) Diazo-coupling and nitrosation: In a base catalysed process, indoles react with nitrosating agents to give N-nitroso- and 3-nitroso indoles.



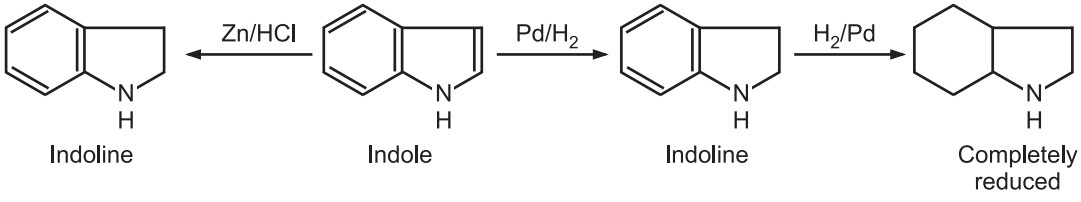
N-nitrosoindole 3-nitrosoindole

(8) Oxidation: In the presence of air and light, indole is auto-oxidised to a resinous material. A methyl substituent at C_3-position in indole stabilizes the ring and gives o-formamino acetophenone through cleavage of indole 2,3-double bond. When 3-methyl indole is oxidized using oxygen, ozone, sodium hypoiodate or perbenzoic acid.

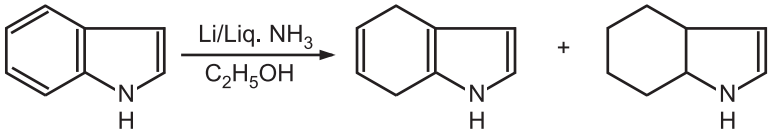


3-Methyl indole o-Formamino acetophenone

(9) Reduction: The indole ring can be reduced selectively in the benzenoid or heterocyclic ring. For example, zinc/HCl converts indole into indoline. Such conversion also occurs under catalytic reduction of indole in acidic medium.



While lithium/liquid ammonia reduces the benzene ring only.

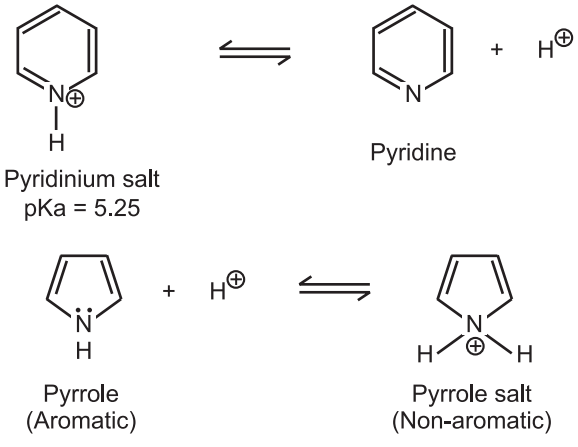


4.10.3 Application in Drug Synthesis

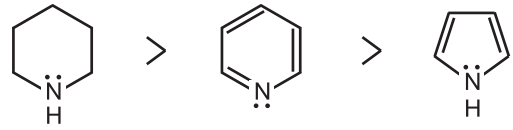
Indole is a core part of the structure of serotonin (neurotransmitter, autacoid), vinblastine (anti-cancer), indomethacin (NSAIDs), besipirdine (effective in treatment of Alzheimer's disease), fendosal (NSAIDs), Ondasetron (antiemetic in cancer chemotherapy) brassinin (anticancer), melatonin (hormone), etc.

4.11 BASICITY OF PYRIDINE

Pyridine is a weakly basic compound. The nitrogen bears a basic lone pair of electrons than lies outside the ring on an sp^2 hybrid orbital and is available for protonation. In pyrrole, the lone pair on the N-atom is already involved in the aromatic array of pi electrons. Protonation of pyrrole results in loss of aromaticity and is therefore unfavourable. Because the lone pair is not part of the aromatic ring, pyridine is a base. Pyridine can act as Lewis base by donating its lone pair of electrons to a Lewis acid, forming pyridinium salts.

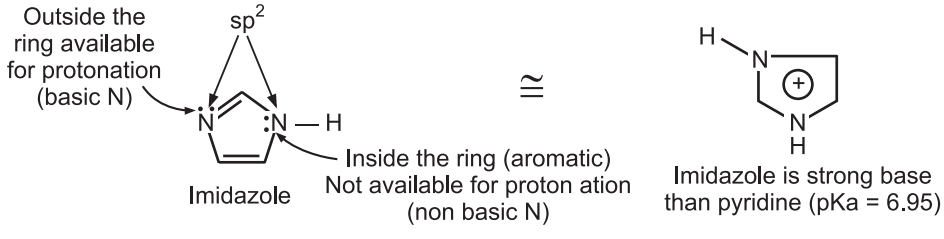


In pyridine, the lone pair is on sp^2 hybridized nitrogen atom (more electronegative). The sp^2 hybridized orbital contains (100/3) = 33.33% s-character while sp^3 hybrid orbital contains only (100/4) = 25% s-character. More the s-character, smaller the hybrid orbital. Hence, sp^2 is smaller in size than sp^3 hybrid orbital. The lone pair on nitrogen in sp^2 hybrid orbital (pyridine) is much closer to the nitrogen nucleus than that of sp^3 hybrid orbital (piperidine). The lone pair of electrons in sp^2 hybridized orbital is thus held more tightly by the nucleus than in sp^3 hybridized orbital and hence lone pair of electrons in pyridine is less readily available for protonation than aniline or other aliphatic amines.



In aniline, the lone pair is on sp^3 hybridized nitrogen (less electronegative). This makes pyridine less basic than aniline. Unlike pyridine, however in aniline the lone pair is in resonance with the pi electrons of the phenyl ring. This lowers the basicity of aniline and makes pyridine more basic than aniline.

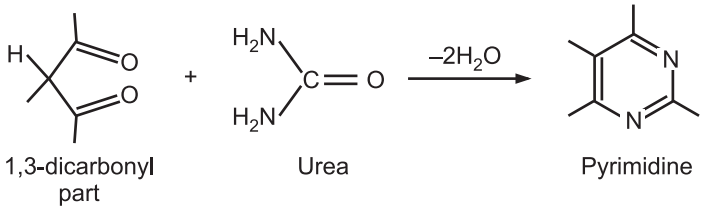
Imidazole is about 100 times more basic than pyridine. The increased basicity results from resonance stabilization of the positive charge to both nitrogen atoms present in imidazole.



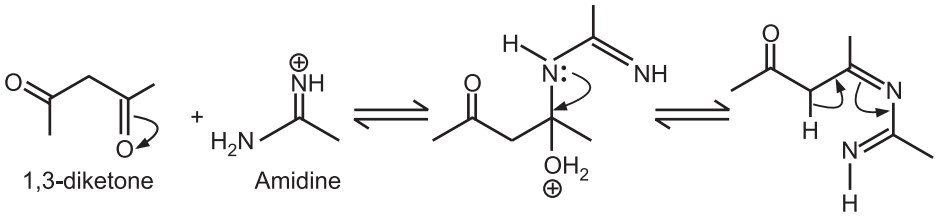
4.12 SYNTHESIS AND MEDICINAL USES

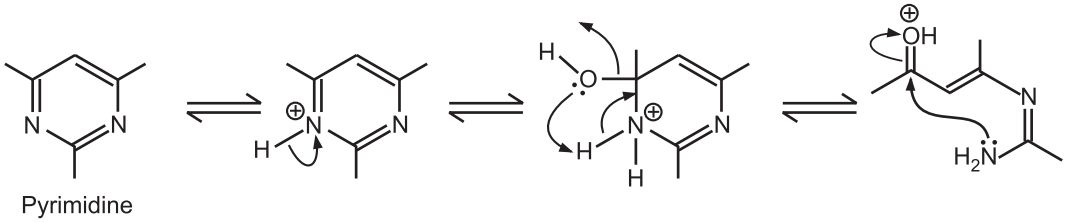
4.12.1 Pyrimidine

The synthesis of pyrimidine is based on the combination of a 1, 3-dicarbonyl component with an amidine (N-C-N fragment) present either as a urea, amide or guanidine.



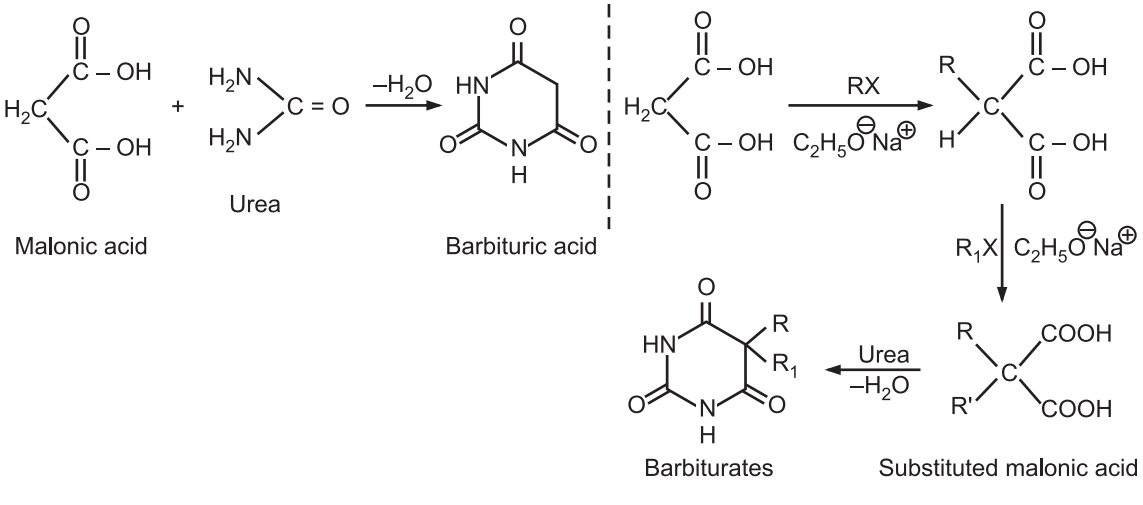
Synthesis:





Medicinal Uses: Thymine, cytosine and uracil are the essential building blocks of nucleic acids RNA and DNA. Pyrimidine is an important structural component of cytosine, uracil and thymine (RNA and DNA), vitamin B_1 (thiamine), barbiturates (sedative/hypnotics), veranal (hypnotics), sulfadiazine (antibacterial), amicetin (antibiotic), lamivudine (anti-AIDS), flucytosine (antifungal), etc.

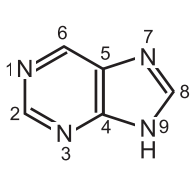
Barbiturates: Barbituric acid was first synthesized in 1864. Barbiturates are CNS-depressants.

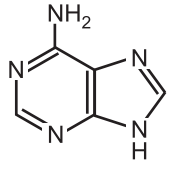


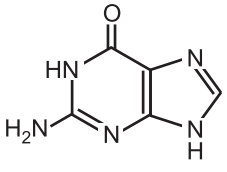
4.12.2 Purine

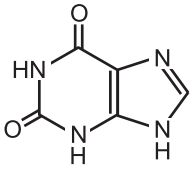
It is a heteocyclic aromatic compound that consists of a pyrimidine ring fused to an imidazole ring. Together with certain pyrimidine bases, purines are constituents of DNA and RNA. Purines also act as hormones and neurotransmitters and are present in some coenzymes.

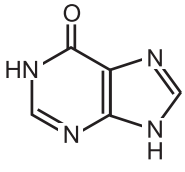
Biologically important purines include.

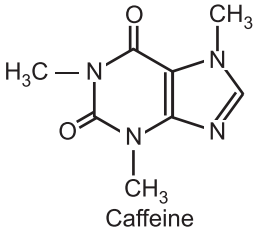

Purine

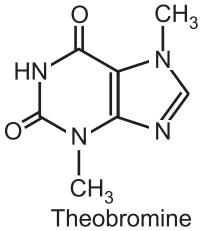

Adenine

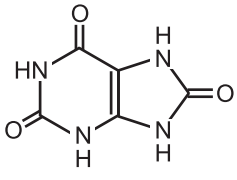

Guanine


Xanthine


Hypoxanthine


Caffeine

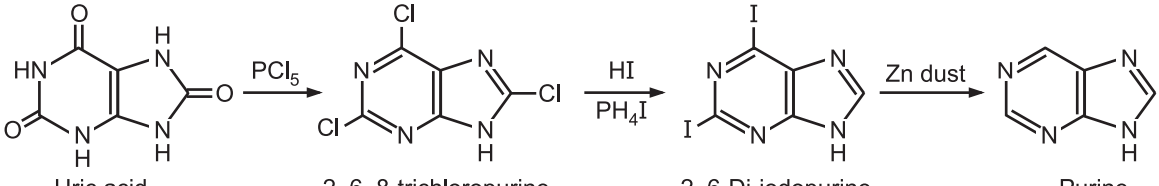

Theobromine


Uric acid

It was first synthesized by German chemist Emil Fischer in 1884.

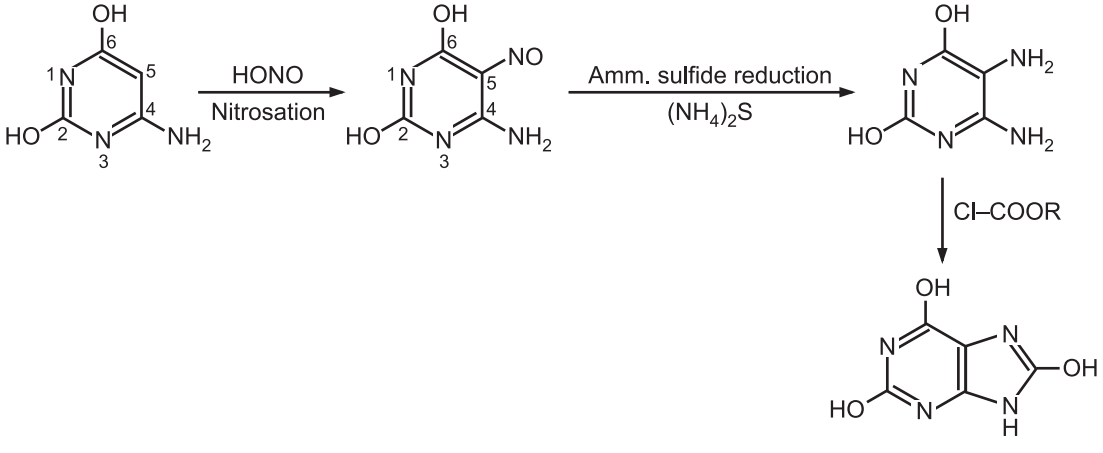
Synthesis:

(1)

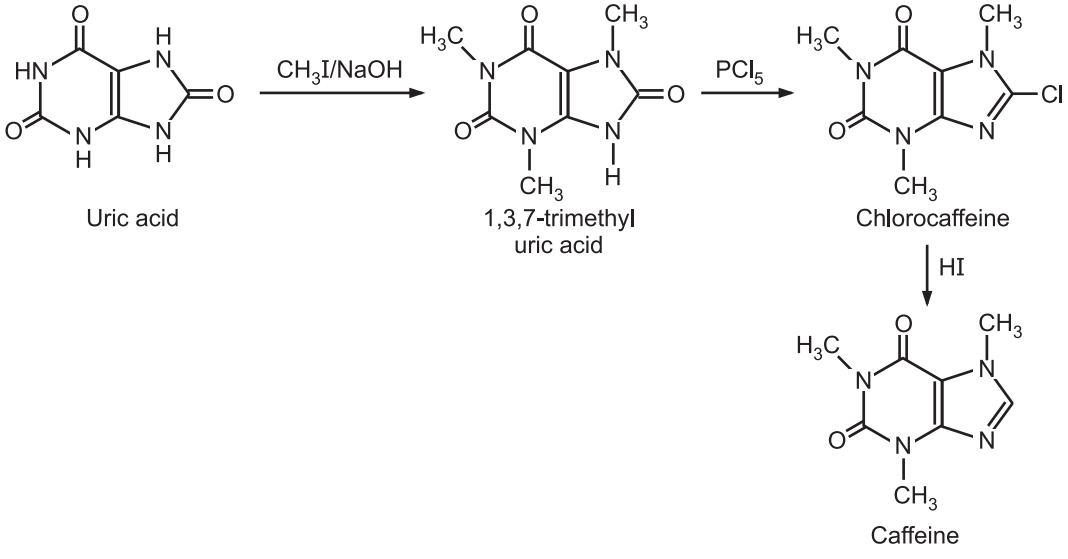


Uric acid — 2, 6, 8-trichloropurine — 2, 6-Di-iodopurine — Purine

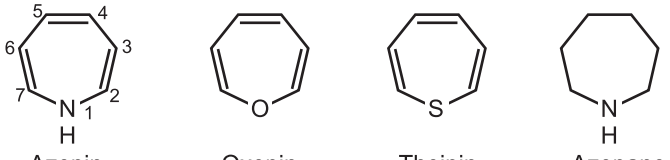
(2) Traube Synthesis: It begins with 4-amino-6-hydroxy pyrimidine or 4, 5-diamino pyrimidine involving the nitrosation at 5-position, reduction of nitroso to amino group using ammonium sulfide, and ring closure with formic acid or chloro carbonic ester.



Caffeine synthesis:



Medicinal Uses: Purine analogs are having antibacterial, antifungal, antitumor, antiviral and anti HIV activity. Important drugs from purine category include caffline (CNS stimulant), 6-mercaptopurine (anti-cancer), aristeromycin. Drugs having isoster of purine include sildenafil (erectile dysfunction), allopurinol (anti-gout), tubercidin (anti-cancer).

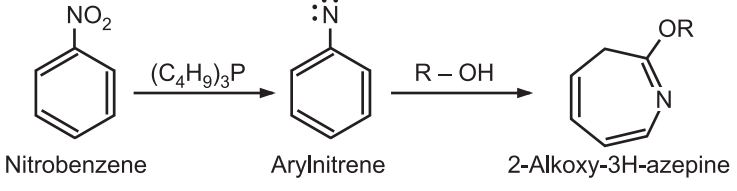


4.12.3 Azepines

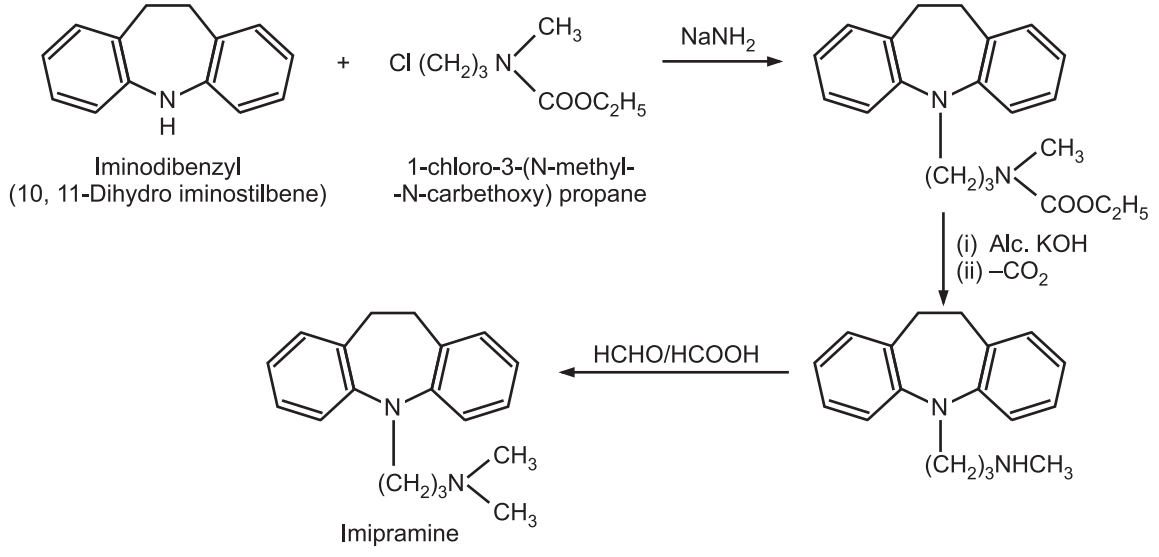
Azepines are poly-unsaturated non-aromatic seven membered heterocyclic ring, with a nitrogen replacing a carbon. The increase in ring size constrains these compounds to be non-polar in order to lessen the ring strain. This explains their non-aromatic nature. These heterocylics follow reactivity pattern of cyclic polyenes. The chemistry of azepines is dominated by their polyene character.

Synthesis:

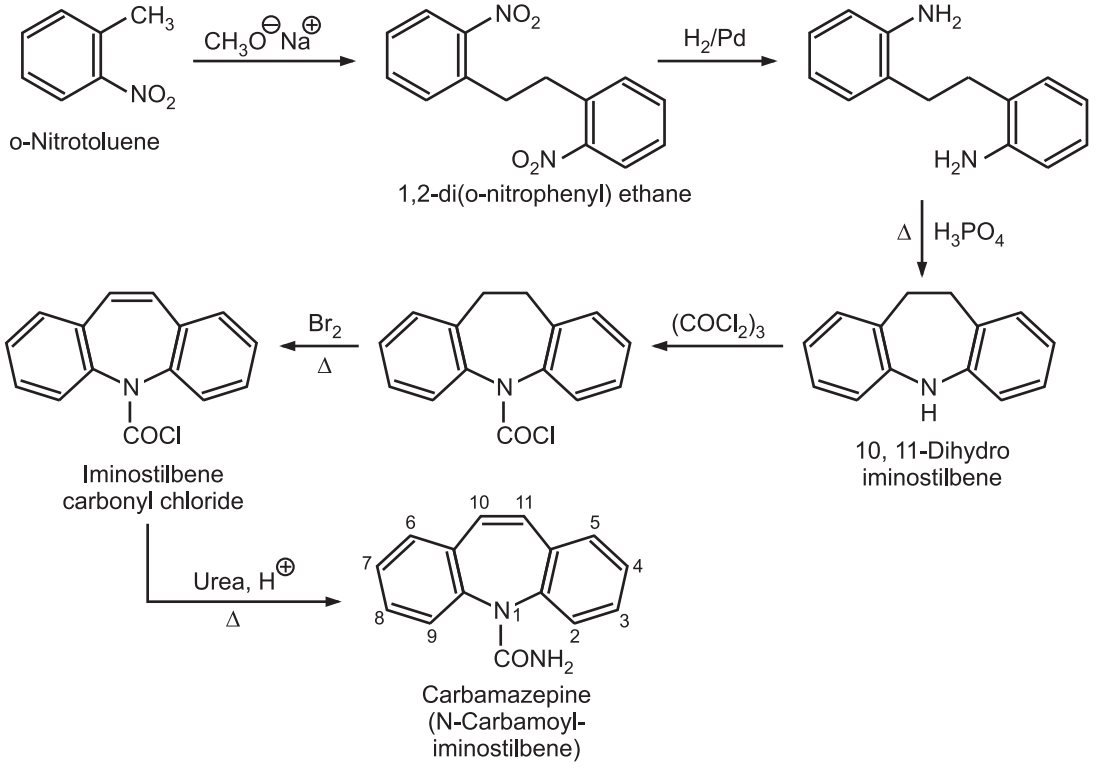
The nitrobenzene is deoxygenated using tributylphosphine. The resulting arylnitrene undergoes ring expansion through intramolecule rearrangement in the presence of primary/secondary alcohol to give 2-alkoxy -3H-azepines.



(a) Imipramine synthesis:



(b) Carbamazepine synthesis:

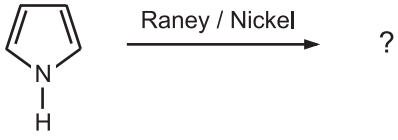


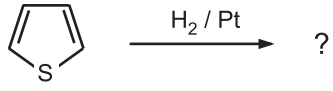
Medicinal Uses: Important drugs from azepine category include imipramine (antidepressant), diazepam (tranquillizer), temocapril (ACE-inhibitor/antihypertensive), omapatrilat (anti-hypertensive), quetiapine (anti-psychotic), tianeptine (anti-depressant), etc.

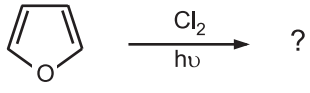
QUESTIONS

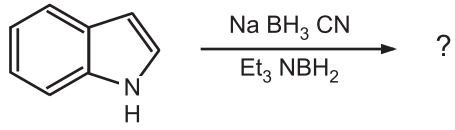
1. Discuss Skraup synthesis of quinoline with reaction mechanism.
2. Write down any four chemical properties of indole with reaction.
3. Give any two methods of preparation and two chemical reactions of pyridine.
4. Give any two methods of preparation and chemical reactions of imidazole.
5. Draw the structure of imidazole and indole.
6. Give any three reactions of indole.
7. Why is pyridine more reactive towards nucleophiles than benzene?
8. Draw structures of imidazole, 1,3 oxazole and isoquinoline with numbering.
9. Write examples of pharmaceutical drugs containing pyridine skeleton.
10. Explain Fisher indole synthesis.
11. Give structure, numbering and corresponding drug of 5-membered heterocycles containing two heteroatoms.
12. Explain synthesis and reaction of quinoline.
13. Write pharmaceutical applications of isoquinoline.
14. Write short notes on :
    a. Pyridine
    b. Indole
    c. Quinoline
    d. Thiazole
15. Give structures and numbering of following heterocycles
    i. 2-benzylthiazole
    ii. 6-aminoquinoline
16. Give structures of medicinal drugs that contain following heterocycles.
    i. Imidazole
    ii. Quinoline
17. Why nucleophilic substitution in pyridine takes place at β (beta) position?
18. Discuss chemistry of pyridine. Give hybridization resonating forms.
19. Give any two synthesis and any four reactions of isoquinoline.
20. Give any two synthesis and four reactions of indole.
21. Give any two synthesis and any four reactions of imidazole.
22. Give any four reactions of thiazoles.
23. Give structure and name of medicinally used drugs containing isoquinoline ring.

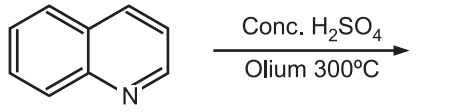
24. Predict the product

(i) 

(ii) 

(iii) 

(iv) 

(v) 

25. Give detail account of methods of synthesis and reactions of pyridine.
26. Why quinoline gives electrophilic aromatic substitution at C-5 and C-8 ?
27. Explain acidic and basic characters of imidazole.
28. Why pyridine is basic in nature.
29. Give properties of imidazole.
30. Draw resonance structures of
    a. Imidazole
    b. Pyridine
31. Explain electrophilic substitution reaction of quinoline.
32. Explain method of synthesis of indole.
33. Why nucleophilic substitution in pyridine take place preferably at 2 position than 4 position?
34. Write following reactions of pyridine
    a. Nitration
    b. Sulfonation
35. Define heterocyclic chemistry. Write any three synthetic methods and any three chemical reactions of pyridine or indole ?
36. Write note on Pall-Knorr synthesis and Skraup quinoline synthesis.

❖❖❖

Unit...V

REACTIONS OF SYNTHETIC IMPORTANCE

♦ **SYNOPSIS** ♦

5.1 WOLF KISHNER REDUCTION

By heating the hydrazone of a carbonyl compound in a sealed tube with sodium ethoxide or sodium hydroxide as a catalyst, nitrogen is evolved and the corresponding methylene compound is formed. This method of reduction is called Wolff-Kishner reduction.

$$\rangle CO \xrightarrow{N_2H_4} \rangle C = N - NH_2 \xrightarrow[NaOEt]{NaOH} \rangle CH_2 + N_2$$

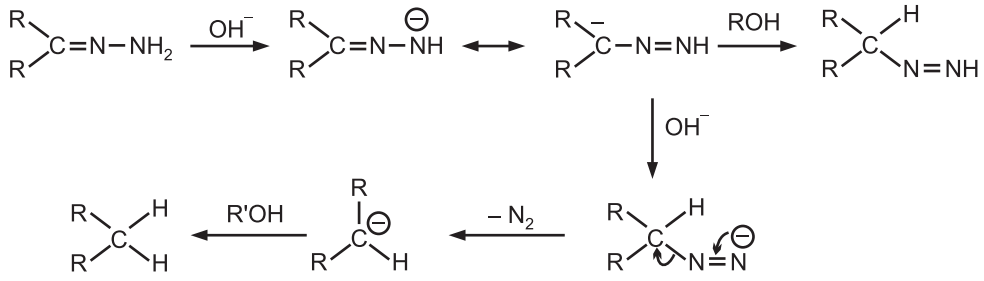
The semicarbazone and ozine derivatives have also been employed. In both cases, conversion to the hydrazone is essential before reduction occurs.

This method is suitable for reduction of high molecular weight carbonyl compounds as well as those sensitive to acid. The Clemmenson reduction which is more commonly employed for reduction of aldehydes and ketones is not satisfactory for these types of compounds. Furthermore, it has been shown with some α amino ketones, the expected product is obtained by Wolff-Kishner reduction whereas anomalous products are formed via the Clemmenson's method.

The reaction as originally carried out by Wolff consists of heating the hydrazone with sodium ethoxide in a sealed tube at about 180^{o}C for several hours.

Mechanism:

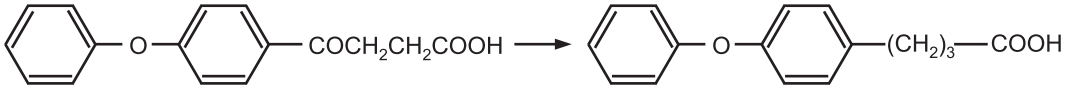
The classical Wolff-Kishner decomposition of the hydrazones of aldehydes and ketones in alkaline medium at high temperatures to give hydrocarbons involves anion formation followed by isomerization to an azo compound and loss of nitrogen as showed below.



The severity of the reaction condition can be brought down to room temperature if a strong base is used in a highly polar medium.

Modifications of Wolff-Kishner Reduction:

Huang Minlon Procedure: The ketone to be reduced (1 mole) and 3 moles of hydrazine hydrate are added to a solution of KOH, 3 moles in diethylene glycol, which has been cooled below 100°C. This mixture is heated cautiously until the initial exothermic reaction is complete and is then gently refluxed for 1 hr. At this stage, water and hydrazine are distilled from the reaction mixture until the temperature of the liquid reaches 200 – 210°C. Refluxing for 3 – 5 hrs. is continued at 200°C. This appears to be the most satisfactory modification of Wolff-Kishner reduction. By this procedure, phenoxy benzoyl propionic acid was reduced in 95% yield to phenoxy phenyl butyric acid. This reduction by Clemmenson gave 54% yield.



The Huang Minlon modification is applicable to large as well as small-scale reductions. With aryl methyl ethers, demethylation usually occurs with Huang Minlon modification. Oxidation of resulting phenol is avoided by using an atmosphere of nitrogen and a shortened reaction period. The reducing power of the reaction is increased considerably by using strictly anhydrous condition. Sterically hindered carbonyl compounds may be reduced in this manner.

Lower Temperature Modification: Gates and Tschudi have pointed out that reduction will often proceed well at temperatures lower than those employed in Huang Minlon. Veratraldehyde has been reduced to 4-methyl veratrole in excellent yield by heating a DEG solution of the reactants for 3 hours at 135°C.

Two Step (Lock modification): The Huang Minlon is often improved (particularly if base sensitive carbonyl compounds are to be reduced) by reacting the substrate with hydrazine hydrate for a short period before the base is added.

Barton modification: Sterically hindered ketones are resistant to Huang Minlon reduction but will often respond to vigorous treatment with anhydrous hydrazine.

Nagata Itazaki: A reduction procedure that appears to be more vigorous than Barton and which avoids use of anhydrous hydrazine.

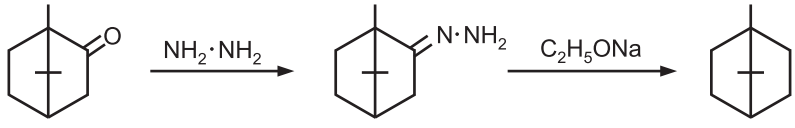
Two variations are:

1. A mixture of 0.01 moles of substrate, 0.66 moles of hydrazine hydrate, 0.08 moles of hydrazine dihydrochloride and 1.5 moles of triethylene glycol are heated at 130°C for 2.5 hours. After adding 0.2 moles of KOH pellets, the temperature was raised to 210°C. While the low boiling materials are distilled, heating was continued at 210°C for 3 – 4 hours.
2. A mixture of 0.01 moles of substrate, 4.0 moles of hydrazine, 0.3 moles of hydrazine dihydrochloride and 1.5 moles of triethylene glycol is heated at 130°C for 7 hours. After adding 0.7 moles of KOH, temperature was raised to 220°C as before.

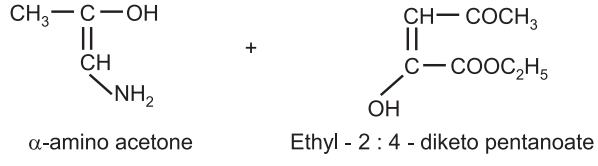
Gram modification: Studies of anion reactions in Dimethyl sulfoxide solution have shown a remarkable rate enhancement when the Wolff-Kishner reduction is carried out in that solvent.

Applications of Wolff-Kishner Reduction:

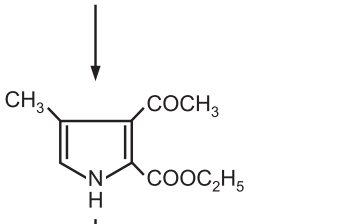
(i) Reduction of camphor to camphane:



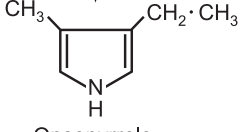
(ii) Synthesis of pyrroles: Structures of pyrroles (degraded products of haemin and chlorophyll) can be proved by their synthesis which involve Wolff-Kishner reduction. e.g. synthesis of opsopyrrole.



α-amino acetone Ethyl - 2 : 4 - diketo pentanoate

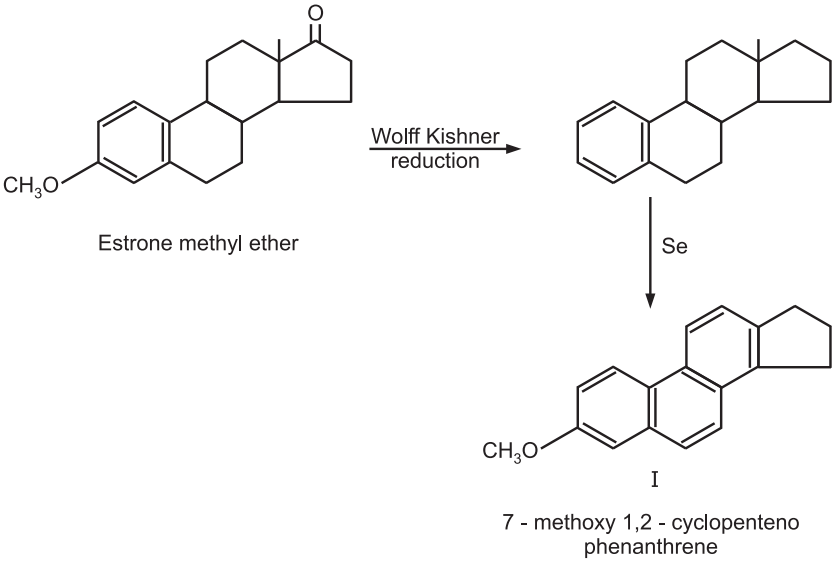


Wolff Kishner reduction



Opsopyrrole

(iii) Elucidating the structure of estrone: Estrone methyl ether on Wolff-Kishner reduction followed by selenium dehydrogenation gives a compound 7 methoxy – 1, 2-cyclopentenophenanthrene of known structure.



Estrone methyl ether

I

7 - methoxy 1,2 - cyclopenteno phenanthrene

The structure of degraded product (I) clearly indicates the carbon skeleton of estrone. Moreover it also establishes the position of phenolic group in estrone.

Reduction:

Reduction involves:

(i) the removal of oxygen,

(ii) the addition of hydrogen, and

(iii) the gain of electrons.

The addition of hydrogen may be subdivided into

(a) Hydrogenation i.e. the addition of hydrogen to an unsaturated system

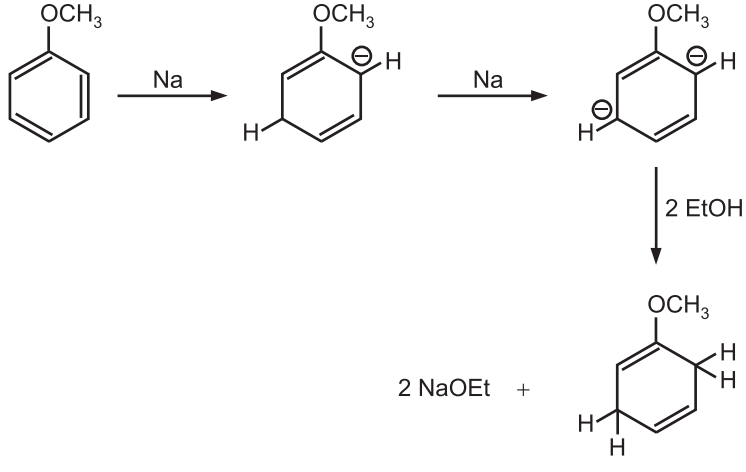
$$CH_2 = CH_2 + H_2 \xrightarrow{\text{catalyst}} CH_3 - CH_3$$

(b) Hydrogenolysis is the addition of hydrogen with concomitant bond repture

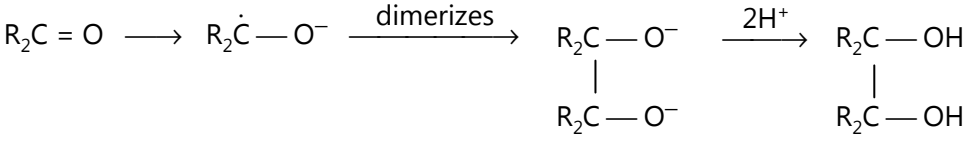
$$Ar\,CH_2 - NMe_2 + H_2 \xrightarrow{\text{catalyst}} ArCH_3 + HNMe_2$$

5.2 GENERAL MECHANISM OF REDUCTION

1. By the addition of electrons, followed by the uptake of protons, as in the reduction of anisole by sodium in liquid ammonia containing ethanol (Birch Reduction).

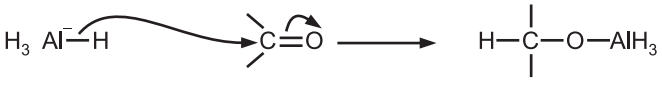


Or by coupling as in the reduction of ketones to pinacols.



Electron transfer reduction can also be brought about electrolytically at the cathode.

2. By the transfer of hydride ion as in the reduction of the carbonyl group by $LiAlH_4$



Such transfer may occur intramolecularly as in Meerwein Jonndorf Verley reduction.

3. By the catalysed addition of molecular hydrogen as in the reduction of olefins on metals.

Methods of Reduction:

1. Catalytic reduction:
   (a) Homogeneous catalytic reduction.
   (b) Heterogeneous catalytic reduction.
2. Di-imide reduction.
3. Reduction by hydrazide anion.
4. Reduction by metal hydride and alkoxide.
5. Dissolving metal reduction.

Catalytic Hydrogenation:

Catalytic hydrogenation is widely applicable technique for the reduction of organic compounds especially olefins.

The reaction is carried out by stirring or shaking a solution of the compound in presence of heterogeneous catalyst, under an atmosphere of hydrogen.

The reaction is carried out at various pressures and is therefore categorised as:

(i) Low pressure hydrogenation: It uses the pressure of hydrogen in the range of 1 – H atm. at 0 – 100°C.

(ii) High pressure hydrogenation: It uses the pressure of 100 – 300 atm. pressure at upto 300°C.

Catalysts Used:

Catalysts are broadly classified into two categories, both of which consist of transition metals and their compound.

(i) Heterogeneous Catalysts: Catalyst insoluble in the reaction medium.

e.g. Raney nickel, palladium on charcoal, sodium borohydride-reduced nickel, platinum metal or its oxide, rhodium, ruthenium, zinc oxide etc.

(ii) Catalyst soluble in the reaction medium: Homogeneous Catalyst.

e.g. (a) Chlorotris (triphenyl phosphine) rhodium (Wilkinson's Catalyst) which catalyses the hydrogenation of many olefinic compounds without disturbing such groups as – COOR, NO_2, CN, COR present in the same molecule.

(b) Chlorotris (triphenyl phosphine) hydrido rutheium. (II) $[(Ph_3P)_3RuClH]$ which is specific for terminal double bonds.

(c) Penta cyanocobaltate (II) $Co(CN)_5^{3-}$ which is effective for double and triple bonds on which they are part of conjugated systems.

Homogeneous catalyses in advantageous because of better catalyst reproducibility and better selectivity.

Heterogeneous catalysts are usually easier to separate from the reaction mixture.

Heterogeneous Catalysts used are: The most active catalysts are specially prepared platinum and palladium.

1. **Adam's Catalyst:** Chlorplatinic acid is fused with sodium nitrate to give a brown platinum oxide which can be treated with hydrogen to give a very finely divided black suspension of the metal.

   The solvents used are acetic acid, ethyl acetate and ethanol. About 0.2 g of platinum oxide is employed per 10 g of reactant.

2. **Palladium:** Active form of palladium is obtained from palladium chloride. Palladium chloride is most commonly reduced in the presence of a suspension of charcoal or other solid support on which the metal is deposited in a very finely divided state.

   Another reactive catalyst is obtained by the reduction of platinum oxide *in-situ* with sodium borohydride in the presence of carbon. The molecular hydrogen is generated by the addition of acid to the excess of borohydride.

   The olefinic bonds are reduced on these catalysts at temperature below 100°C and at atmospheric or slightly increased pressure.

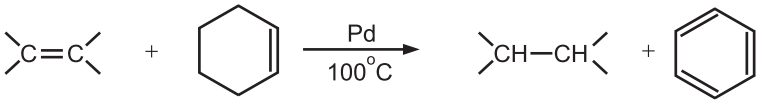
3. **Raney Nickel:** This is slightly less active catalyst, prepared by treating a nickel aluminium alloy with caustic soda and washing away the sodium aluminate to leave the nickel as black suspension saturated with hydrogen (50 – 100 cm^3) which is pyrophoric when dry. Alkenes are hydrogenated over Raney nickel at about 100°C and pressure upto 3 atm.

$$Ni - Al + NaOH \longrightarrow Ni + Na^+ AlO_2^- + \frac{3}{2} H_2$$

4. **Copper Chromite:** Adkin's catalyst. This is made from copper nitrate and sodium dichromate and corresponds to CuO. $CuCr_2O_4$. It is cheaper than palladium or platinum and hence more preferentially used.

5. **Transfer hydrogenation:** The hydrogen is supplied by a donor such as cyclohexene or hydrazine.

Example:

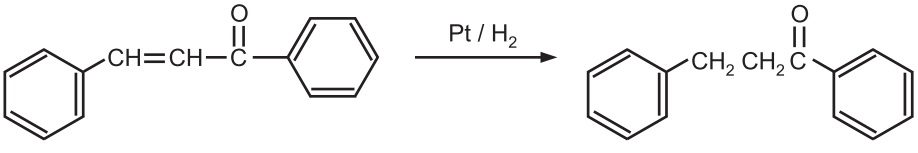


The driving force in the case of cyclohexene is the gain in aromatic stabilization energy when benzene is formed while with hydrazine, the strongly bonded N_2 molecule is formed.

Selectivity: Acetylenic bonds are reduced more readily than olefinic bonds, but other unsaturated groupings with the exception of nitro group and acid chlorides are reduced less readily.

Catalytic hydrogenation is used for the selective reduction of C = C in the presence of aromatic rings and carboxyl groups, whether or not the unsaturated functions are conjugated.

Example: Benzylidene acetophenone is reduced over platinum at 20°C to phenyl phenethyl ketone in 90% yield.



5.3 MECHANISM FOR CATALYTIC REDUCTIONS

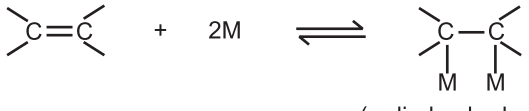
The hydrogen molecule undergoes homolysis into atoms which are chemisorbed on the surface of the catalyst.

$$H_2 + 2M \rightleftharpoons 2\ \underset{M}{H}$$

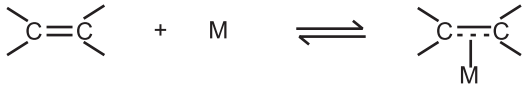
M = site of catalyst

The substrate is also chemisorbed on the surface of the catalyst.

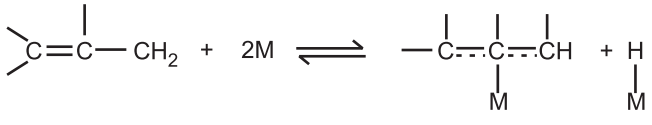
An olefin is chemisorbed in one of the following three ways:

(a) 

(σ diadsorbed species)

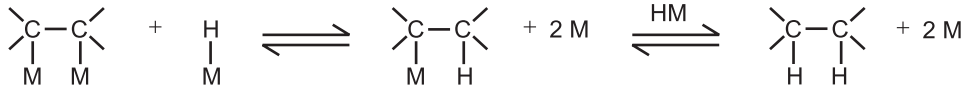
(b) 

(π adsorbed species)

(c) 

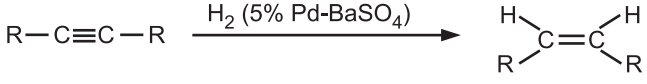
(π allyl complex)

The next step is the union of one adsorbed hydrogen atom with the adsorbed species to form a half hydrogenated state which then reacts with another chemisorbed hydrogen atom to give the saturated compound, resulting in the net cis addition of 2 hydrogen atoms.



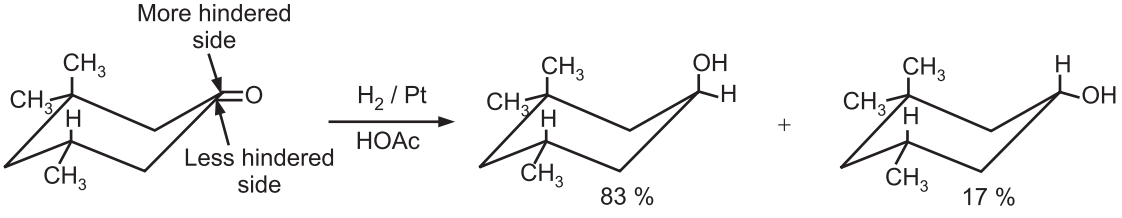
Stereochemistry:

A molecule approaches the catalyst through its less hindered side and the hydrogens are added cis to that side,



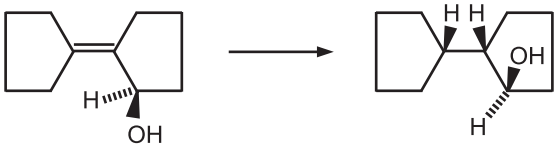
Cis 97%

The reduction of the following cyclohexanone derivative predominantly to the axial hydroxyl epimer illustrates that the catalyst approaches from the less hindered side avoiding 1, 3 diaxial interaction by the axial methyl group.



The presence of a polar group sometimes decides on which side the molecule is to be adsorbed and thus hydrogenated.

Example: Cyclopentylidene cyclopentanol gives trans alcohol.

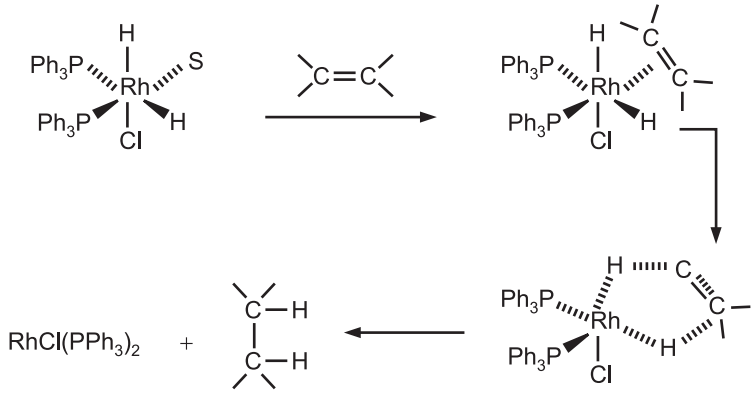


This attack from the sterically more hindered side is attributed to the interaction of both the π electrons of the double bond and one of the lone pairs on the oxygen atom with the catalyst surface for chemisorption so that hydrogen addition takes place on the same side as the hydroxyl group.

(A) Homogeneous Reduction:

Since reduction by heterogeneous catalyst leads to isomerization of the substrate, this may be minimized by use of a homogeneous catalyst like Wilkinson's catalyst. This is because the intermediate complex is less susceptible to rearrangement than its counterpart in the heterogeneous reaction.

Mechanism: The hydrogen is activated by the incorporation of hydrogen into the coordination sphere around a metal atom, usually of the group VIII. The complex which promises to be of the greatest utility is the cis-dihydrido rhodium species $Rh(ClH_2)$ $(PPh_3)_2$ formed when a solution of this (priphenyl phosphine) chloro rhodium is exposed to gaseous hydrogen.



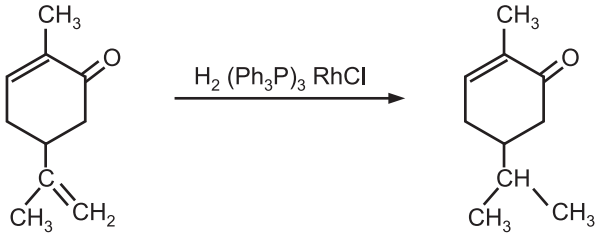
The unsaturated substrate displaces the solvent molecule. Then a stereospecific cis transfer of both hydrogen takes place via a cyclic transition state as in di-imide reduction.

Steric influences operate in this reduction; unsymmetrically disubstituted double bonds being reduced before a trisubstituted ones.

Advantages:

1. Only olefins and acetylenes are reduced, other groups such as C = O, C + N, NO_2 are unaffected. This helps in selective reduction.

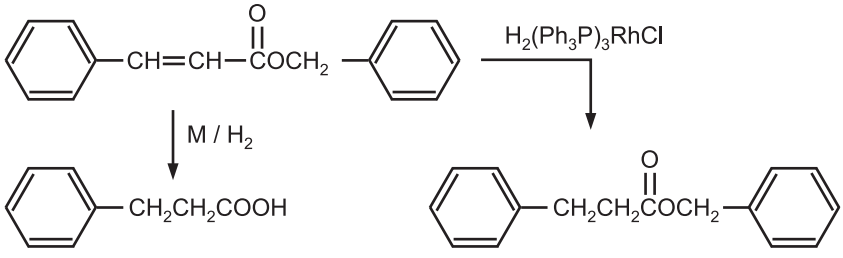
2. Mono and disubstituted olefins are reduced much more rapidly than tri or tetra-substituted ones.



Carvone Dihydrocarvone

3. Hydrogenolysis does not occur.

Example: Benzyl cinnamate gives the dihydro derivative.



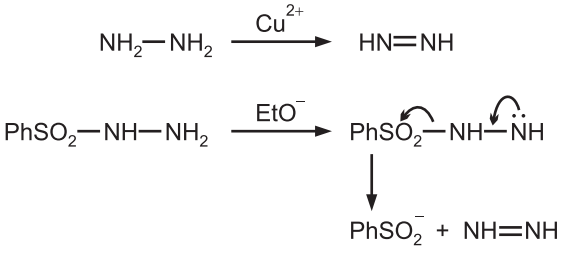
Whereas, hydrogenation on a metal catalyst results in cleavage of the O-benzyl bond to give phenyl propionic acid.

Disadvantage: There is strong affinity of the rhodium complex for carbon monoxide, aldehydes are degraded.

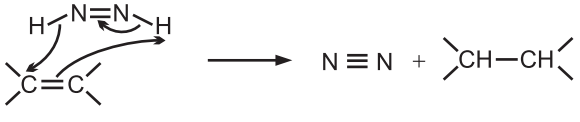
Example: Cinnamaldehyde gives styrene.

(B) Di-Imide Reduction:

Di-imide is an unstable compound which is obtained by the oxidation of hydrazine with copper (II) ion or by the treatment of sulphonyl hydrazides with base.



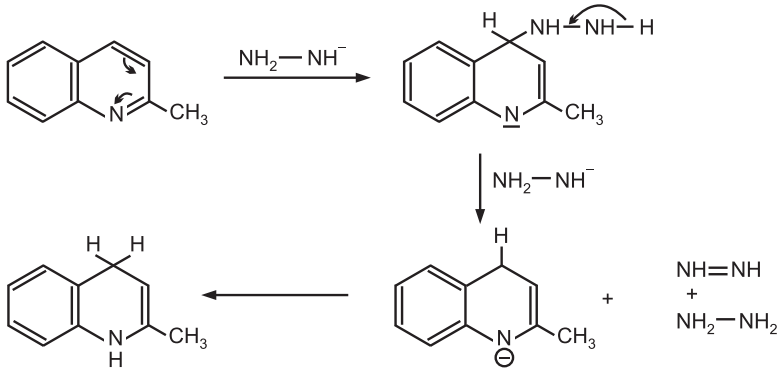
In the absence of additives, it decomposes to nitrogen and hydrogen, but when generated in the presence of an alkene rapid cis-stereospecific reduction occurs, the driving force is the great stability of the nitrogen molecule compared with the – N = N– system.



Homopolar unsaturated bonds such as those in acetylenes and azo compounds are also reduced but carbonyl containing groups, nitro groups, sulphoxides and S–S bonds are not affected.

(C) Reduction by Hydrazide Anion:

Sodium hydrazide is used in reducing olefinic polynuclear aromatic hydrocarbons and nitrogen heterocyclic aromatic compounds. Reduction involves anionic attack by the hydrazide anion, NH_2 NH^-, subsequent loss of a proton to give a dianion and expulsion of di-imide. The dianion can acquire two protons from the solvent.



(D) Reduction by Metal Hydride and Alkoxide:

Certain metal hydrides are synthetic equivalents of the hydride ion synthon and as such are powerful reducing agents which react preferentially at electron deficient centres.

Metal hydrides include nucleophilic substances like $LiAlH_4$, lithium aluminium deuteride, the borohydride of Na, Li, K and sodium borodeuteride as well as electrophilic reagents like diborane, alane (AlH_3) and their derivatives.

The hydrides react violently with water and readily with alcohols and so the reaction must be carried out in anhydrous ethereal or hydrocarbon solvents.

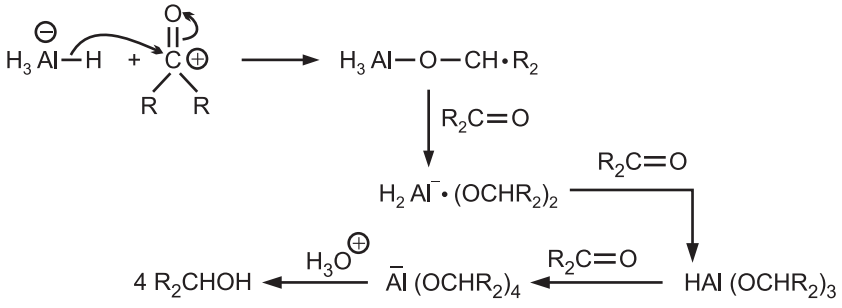
$LiAlH_4$, $NaAlH_2$ $(OCH_2CH_2OCH_3)_2$ [RED-Al] and alane are non-selective reagents. The more selective reagents DIBAL–H (AlH $[CH_2CH_2(CH_3)_2]_2$) is probably a better choice.

$$Ph(CH_2)_3OH \xleftarrow{LiAlH_4} PhCH = CHCHO \xrightarrow{AlH_3} PhCH = CH\ CH_2OH$$

(a) $LiAlH_4$:

$$LiH + AlH_3 \longrightarrow Li^+Al^-H_4$$

The anion is a nucleophilic agent and attacks the polarized multiple bond such as C = O, C = N, C + N, N = O at the more positive atom. All the four hydrogen atoms in the anion are used successively in reduction.



The first step is the fastest and the rate decreases in the successive steps since the electron withdrawing inductive effect of the alkoxy group opposes loss of hydride ion.

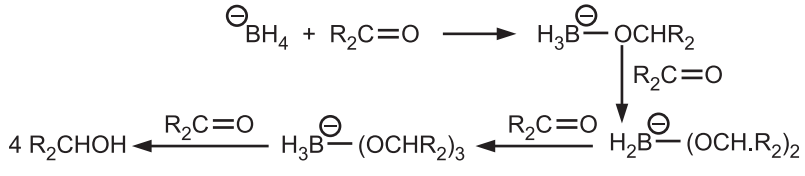
$LiAlH_4$ is a versatile reagent reducing a large number of functional groups like acids, esters, amides. It does not reduce olefinic double bond, exception are there.

e.g. Cinnamaldehyde when treated with excess of LAH gives an excellent yield of 3-phenyl propanol.

(b) Sodium borohydride ($NaBH_4$): It is more specific and reduces only ketones and aldehydes to corresponding alcohols without affecting other functional group.

The mechanism is same for $NaBH_4$ except that the first step here is slowest and rate determining.

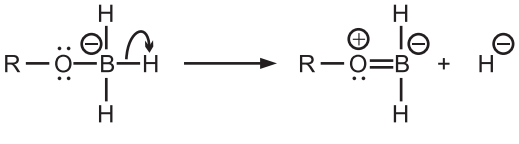
Mechanism:



The difference in the mechanism and rate of reaction is due to two opposing factors.

The mesomeric effect of the two unshared pairs of electrons on oxygen of the alkoxy group would assist the loss of hydride ion while as stated the electron - withdrawing inductive effect of the alkoxy group would retard the process.

For the small boron atom, substantial p-orbital overlap of the type depicted below is possible whereas in the case of larger aluminium atom this type of overlap is less effective so that the rate retarding inductive effect of the alkoxyl group becomes more dominant in the latter case.

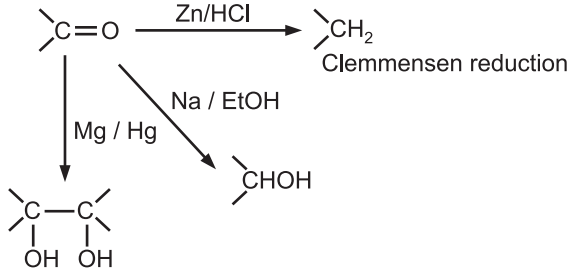


$NaBH_4$ is less powerful but is advantageous as it can be used in protic solvent. However, it produces more highly reduced compounds than are possible by $LiAlH_4$ or $NaBH_4$ in a protic solvent.

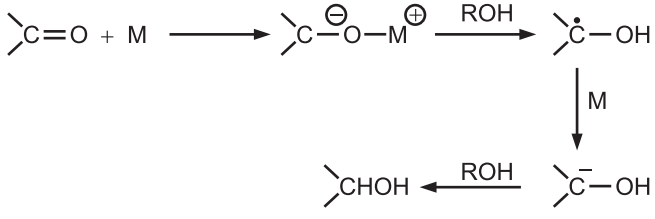
(E) Dissolving Metal Reductions:

The reaction involves electron transfer to the substrate from a metal such as lithium, iron, Na, K, Mg, Zn, tin. A proton donor (H_2O/EtOH) may either be present during electron transfer or be added at a later stage.

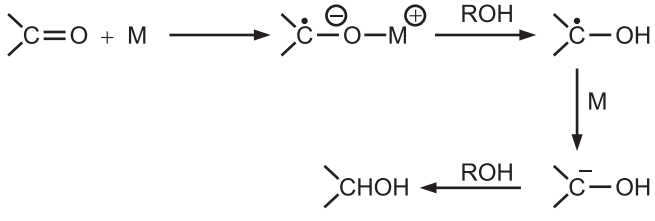
Reduction of the carbonyl group leads to formation of three types of products depending on the reaction conditions used.



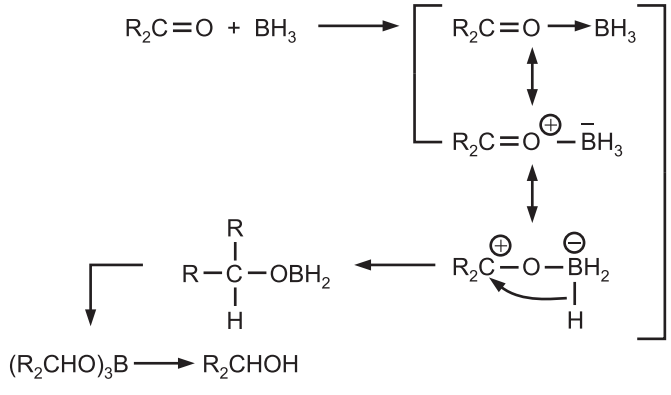
Reduction to alcohol takes place in presence of a proton donor, when the initially formed radical anion is first protonated and then converted into the carbanion by a second electron transfer.



In the absence of proton donor, the radical anion dimerizes to the pinacolate dianion.



Hydroboration: Aldehydes and ketones are reduced by ketones to the primary and secondary alcohols.



Stereochemistry: Dialkyl borane though less reactive are more selective reagents than borane. By increasing the bulk of the alkyl substituents, the dialkyl boranes can be made sensitive to steric control in order to give stereospecific reduction.

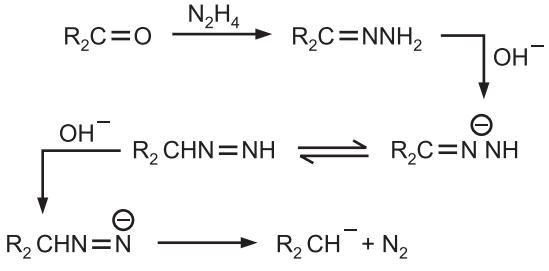
Example: Bis isopinocamphenyl borane obtained from α–pinene and diborane reduces camphor to isoborneal by approaching from the less hindered end side.

5.4 REDUCTION OF SPECIFIC FUNCTIONAL GROUPS

Reactions involving Replacement of Oxygen by Hydrogen:

(A) Reduction of Carbonyl to Methylene in Aldehydes and Ketones:

(i) Clemmensen Reduction: Wolff-Kishner Reduction: The hydrazones of aldehydes and ketones are reduced in vigorously basic conditions (NaOH and KOH) with the evolution of N_2.



(ii) Huang-Minlon Modification: In this the carbonyl compound, hydrazine hydrate and KOH are heated together in a high boiling solvent.

The reaction is carried out under more moderate temperature in dimethyl sulphoxide with potassium t-butoxide as a base.

Other reagents used to reduce C = O of aldehydes and ketones to CH_2 are catalytic hydrogenation at 180° – 250°C, $LiAlH_4$ – $AlCl_3$, Li–NH_3 or trialkyl silane in trifluoro acetic acid.

Aliphatic aldehydes are reduced to RCH_3 with titanocene dichloride. $(C_5H_5)_2TiCl_2$.

(B) Reduction of Carboxylic Acid to Alcohols:

$$RCOOH \xrightarrow{LiAlH_2} RCH_2OH$$

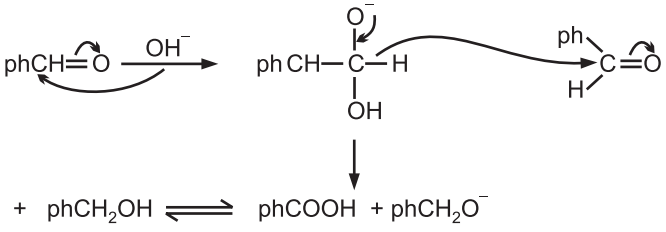
Reduction to alcohol is done by hydride transfer and electron transfer reaction.

1. Hydride transfer:

(i) The alkali metal hydrides such as Na hydride are unsuitable because of their insolubility in organic solvents and their powerful effects as catalyst for base catalysed condensation.

Commonly used hydride reducing agents are $LiAlH_4$, $NaBH_4$ and $LiBH_4$.

(ii) Cannizzaro's reaction: Aldehydes which do not have α – methyl group cannot undergo base catalysed condensation. But they react with bases by disproportionation involving transfer of hydride ion.



(iii) Meerwein Pondorff Verley reaction.

2. Electron transfer reagents: These reagents are less selective than Na borohydride For example, they reduce the olifinic double bond in α – β unsaturated carbonyl compounds. The reduction is stereoselective.

(C) Reduction of Amides to Amines:

Amides are reduced to amines using $LiAlH_4$ or by catalytic hydrogen though high temperature and pressure are required in the latter case.

$NaBH_4$ cannot reduce the amides but it does so in presence of $COCl_2$.

$$RCONH\ R' \longrightarrow RCH_2\ NHR'$$

Borane is a good reducing agent for all three types of amides.

Mono and disubstituted amides are reduced by triethyl oxonium fluoroborate $EtO_3^-\ BF_4^-$ to give the amino ether fluoroborate $RC(OEt) = NR_2^+\ BF_4^-$ followed by reduction of this with $NaBH_4$ in ethanol.

Substituted amides are reduced to amines with trichlorosilane. Thioamides are reduced using H_2 and Raney Nickel.

(D) Reduction of Esters to Ethers:

$$RCOOR' \xrightarrow[LiAlH_4]{BF_3 - Etherate} RCH_2\ OR'$$

$LiAlH_4$, $LiBH_4$, $NaBH_4$, trichlorosilane with UV light and with catalytic hydrogenation.

(E) Reduction of Esters to Alcohols:

$$RCOOR' \xrightarrow{LiAlH_4} RCH_2OH + R'OH$$

Two moles of alcohol are obtained. $NaBH_4$ reduces phenolic esters especially those containing electron withdrawing groups.

Esters are also reduced to alcohols by hydrogenation over copper chromite catalyst though high temperature and pressure are required.

(F) Reduction of Nitro Compounds to Amines:

$$RNO_2 \xrightarrow{Zn/HCl} RNH_2$$

Aliphatic and aromatic compounds undergo this reduction.

Reducing agents like Zn, Sn or Fe and acids are used, while for catalytic hydrogenation $AlH_3 - AlCH_3$, hydrazine and catalyst, like $TiCl_3$, dodecacarbonyl tri iron $[Fe_3(CO_2)]$ methanol and sulphides like NaHS, $(NH_4)_2$ S or polysulphides may be used.

The reaction with sulphides or polysulphides is called as zinin reduction. Sodium dihydro (trithio) borate $NaBH_2S_3$ reduces aromatic nitro compound giving azo compounds. Aromatic nitro compounds are reduced to cyclohexane rings by using $NaBH_4$ alone.

With polysulphides more than one nitro group can be reduced. With some reducing agents, reaction can be stopped at an intermediate stage to give compounds like azo benzene, hydroxyl amine, hydrazo benzene etc.

(G) Reduction of Nitro Compound to Nitroso Compound:

This is done by irradiation of the nitro compound in 0.1 M aq, KCN with UV light.

(H) Reduction of Miscellaneous Nitrogen Compounds:

Isocyanates, isothiocyanates are reduced to methyl amines and azides to primary amines on treatment with $LiAlH_4$.

$$R - N = C = O \xrightarrow{LiAlH_4} RNHCH_3$$

$$R - N = C = S \xrightarrow{LiAlH_4} RNHCH_3$$

General Reaction Conditions:

Catalytic reduction can be carried out in batches or in continuous processes in the liquid phase or in the vapour phase.

Temperature – 20°C – 300°C

Pressure - atm. pressure to several thousand pounds.

Catalysts have included nickel, Cu, Co, chromium, iron, tin etc. They are used as free metals in finely divided form for enhanced activity or as compounds of oxides or sulphides.

Catalyst may be used singly and in combination with alumina magnesia, silica, barium sulfate or in unsupported form.

Reactions have been carried out with organic solvents, without solvents and in water dispersion.

Na acetate, NaOH, sulfuric acid, ammonia, Co are used for special purpose. Vapour phase reduction of nitrobenzene, nitroxylene and other relatively low boiling mononitro compounds by H_2 and hydrogen containing gases in the presence of metal catalyst.

The advantages of vapour phase reduction are:

1. Continuous conversion of reactants to finished amine.
2. Minimum operating labour requirement.
3. Low steam and power costs as the heat in vapour leaving the chamber is utilized.

Drawbacks:

1. Limited per pass conversion.
2. Sensitivity of catalytic operation which may result in over reduction and relatively low yields of amine compared with competitive processes.

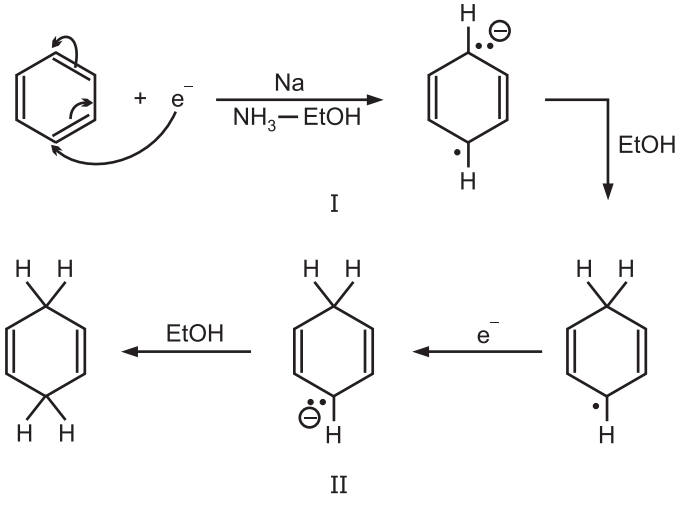
Liquid Phase Reduction: High boiling mono and poly nitro compounds, nitro compounds which decompose at high temperature or where undesirable side reaction occur at high temperature, liquid phase reduction is used.

Water soluble and water insoluble solvents may be used, the pH is adjusted whenever needed. The reduction is carried out at low temperature and high pressure using Ni catalyst generally.

5.5 BIRCH REDUCTIONS

Definition: When aromatic rings are partially reduced by sodium or K or Li in liquid ammonia, usually in the presence of an alcohol like ethyl alcohol, isopropyl or tertiary butyl alcohol, 1 - 4 addition of hydrogen takes place and non-conjugated cyclohexadienes are produced. This reaction is called Birch Reduction.

Mechanism: It involves the direct transfer of electrons from the metal.



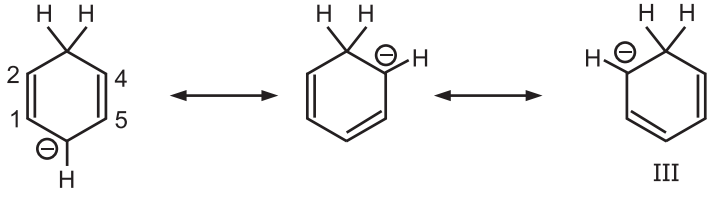
The Na transfers an electron to the ring becoming oxidised to Na^+ and creating a radical ion. The radical ion accepts a proton from the alcohol to give a radical, which is reduced to a carbanion by another Na atom which finally accepts another proton.

Alcohol supplies proton as in presence of most substrates ammonia is not acidic enough for the supply of protons.

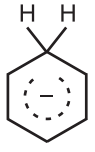
In the absence of alcohol, products arising from dimerization of (I) are frequently obtained.

In some substrates like biphenyl, the radical ion (I) is converted to the carbanion (II) by a different pathway, where the order of steps is reversed. In this case, first a second electron is gained to give a dianion which then acquires a proton producing the intermediate corresponding to (II).

Carbanion (II) is a resonance hybrid having two canonical forms.



III

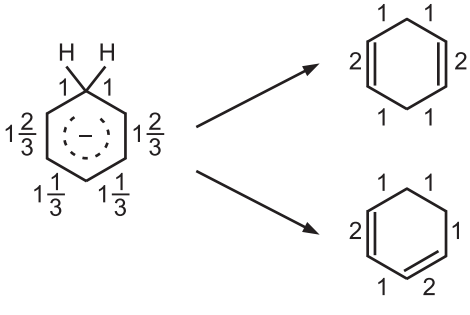


The carbanion ion picks up a proton at the 6 position to give 1, 4-diene but not at the 2 position to give 1, 3-diene due to the operation of the 'Principle of Least Motion'.

Bond Order: It is the sum of the weights of those canonical forms in which the bond 5 is double plus 1 for the single bond which is present in all of them.

According to this principle, those elementary reactions will be favoured that involve the least change in atomic position and electronic configuration.

In other words, the valence bond order for the 6C – C bonds are $1\frac{2}{3}$, 1, 1, $1\frac{2}{3}$, $1\frac{1}{3}$, $1\frac{1}{3}$.



When the carbanion is converted to the diene, these bond orders change as above.

The 2 bonds whose bond order is 1 are unchanged in the 2 products, but for the 4 bonds there is a change. If the 1, 4 diene is formed, the change is 1/3 + 1/3 + 1/3 + 1/3, while formation of the 1, 3 diene requires a change of 1/3 + 2/3 + 2/3 + 1/3.

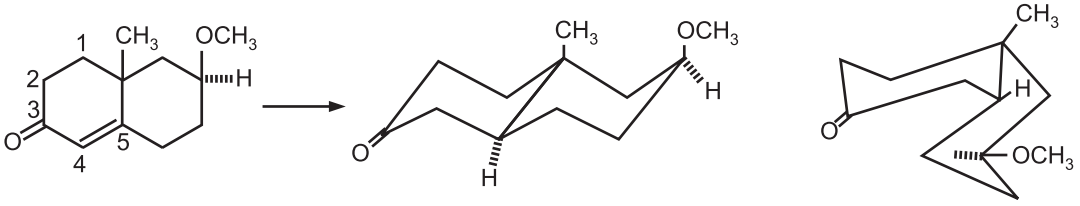
Since a greater change is required to form 1, 3-diene, the principle of least motion predicts formation of 1, 4-diene.

Another factor is that the C^{13} NMR spectrum of (II) shows that the 6^{th} position has somewhat greater electron density than the 2 position, which presumably would make the former more attractive to a proton.

Stereochemistry:

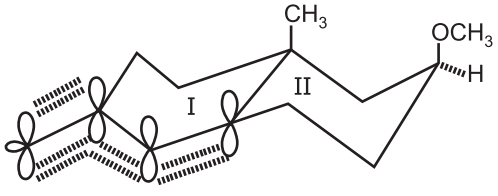
The mechanism of this reduction does not depend on the stability of the product but on both steric and electronic factors involved in the radical anion transition state.

The radical anion will have the lowest energy and will therefore be favoured in which the 4p-orbitals can best overlap, even though it may give rise to the thermodynamically less stable product.

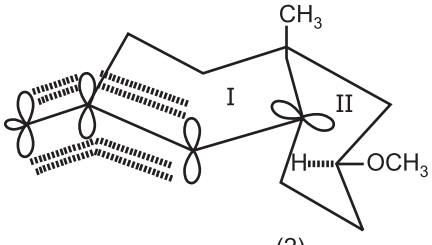


(a) **(b) Less stable** **(c) More stable**

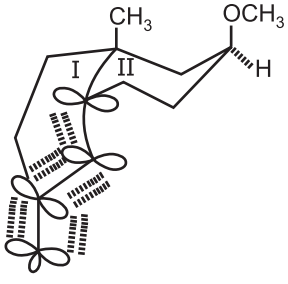
On the metal ammonia reduction of A there are three structural possibilities of the radical anion i.e. 1, 2, 3.



(1)



(2)



(3)

Between (1) and (3), (1) would be energetically preferred since it represents the thermodynamically more stable trans form of decalin, the overlap of the four p-orbitals and 1, 3-diaxial interactions between the two substituents being the same in both.

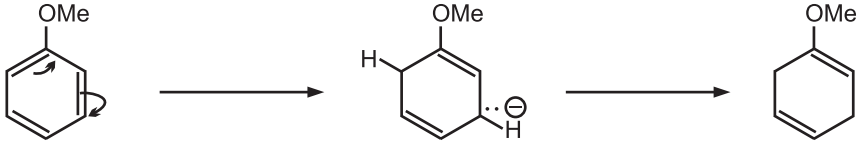
In (2), the quasi equatorially disposed filled p-orbital at C_5 is incapable of overlap with the other 3-axil p-orbitals of the conjugated radical system and therefore it may be a higher energy species even though 1, 3 diaxial intermediate of the substituents both being equatorially disposed with reference to ring (II) are absent.

It appears that the electronic factors are dominant over the steric factors in (1) which explains the formation of (B) through (1) in preference to (C) through (2). Conceivably, much larger substituents in place of CH_3 and OCH_3 may tilt the balance in favour of the products of cis decalin type (C).

The regioselectivity and rate of reduction are crucially dependent on the electron donating or electron withdrawing characteristics of the substituents.

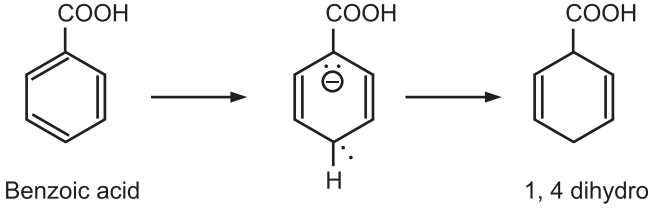
The electron donating groups such as alkyl or alkoxyl decrease the rate of reaction because they increase the electron density in the aromatic ring and thus hinder the acceptance of electron.

The groups are present on the non-reduced position of the product.



1 methoxy cyclo hexa 1,4 - diene

While electron withdrawing groups such as –COOH, $–CONH_2$ increase the rate of reaction and are found on the reduced position of the product.

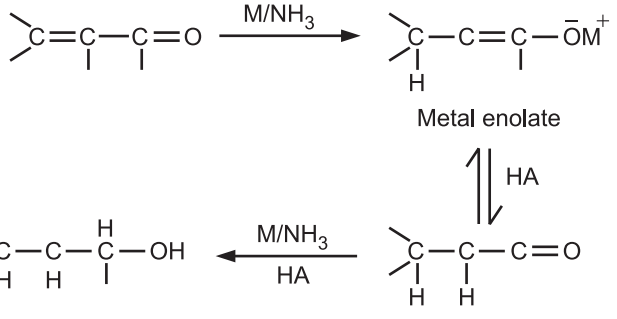


Benzoic acid

1, 4 dihydro benzoic acid

The regioselectivity of the reduction is explained from the consideration of the relative stabilities of the possible mesomeric intermediates.

α – β unsaturated acids, esters and aldehydes are also reduced by metals in liquid ammonia.

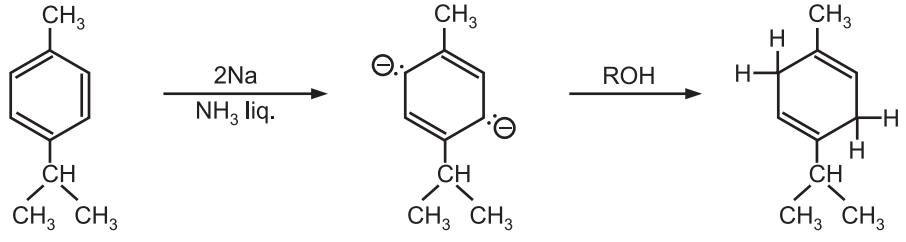


Ordinary olefins are usually unaffected by Birch reduction condition and double bonds may be present in the molecule if they are not conjugated with the ring.

But phenylated olefins, internal alkynes and conjugated olefins (C = C, C = O) are reduced under these conditions.

Applications:

(i) Synthesis of γ-terpinene.



(ii) The reduction of steroids and terpenoids enone in which the β carbon atom was located at the fusion of two six-membered rings showed that the reaction gives thermodynamically stable isomer.

5.6 CLEMMENSEN REDUCTION

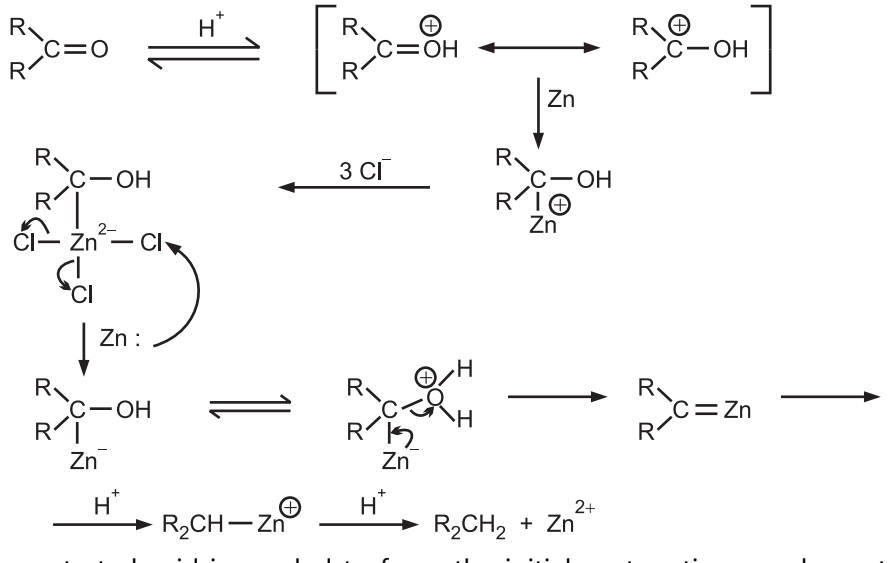
Definition: The conversion of a carbonyl group to a methylene group is done by Clemmensen reduction.

It consists of heating the aldehyde or ketone with zinc amalgam and aq HCl. Ketones are more preferentially reduced than aldehydes.

The reaction is highly specific for aldehydes and ketones and can be carried out with many other functional groups present.

Mechanism:

The probable mechanism for Clemmensen reduction is



The concentrated acid is needed to force the initial protonation, amalgamation of zinc raises its hydrogen over voltage so that hydrogen is not produced.

Only haloacids are effective probably because by complexing the initial Zn species, they provide a medium for the reduction of this species by a second atom of Zn.

Drawbacks of Clemmensen Reduction:

1. Purely aromatic ketones do not give satisfactory results. Pinacols and resinous products often predominate.
2. The reduction of ketonic compounds of high molecular weight and very slight solubility is facilitated by the addition of a solvent such as EtOH, CH_3COOH or dioxane which is miscible with aq. HCl.
3. Keto acids in presence of EtOH give lower yields.

Meerwein - Pondorf Verley Reduction:

Definition: The conversion of a carbonyl compound into an alcohol by the action of aluminium isopropoxide in isopropyl alcohol medium is called the Meerwein-Pondorf-Verley Reduction.

$$3\ R-\overset{\overset{O}{\|}}{C}-R' + (Me_2CHO)_3\ Al \rightleftharpoons 3Me_2CO + (RR'\ CHO)_3Al$$

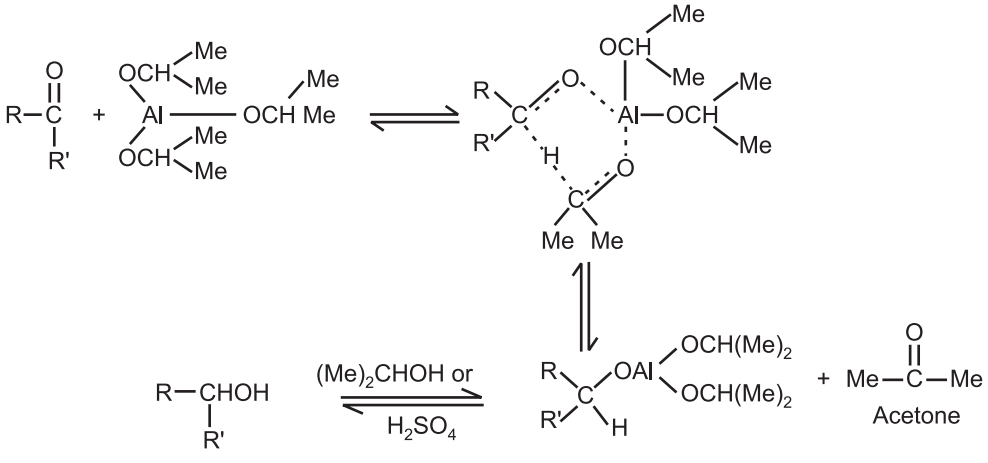
$$(RR'CHO)_3\ Al + 3CH_3CHOHCH_3 \rightleftharpoons 3RR'\ CHOH + [(CH_3)_2CHO]_3\ Al$$

$$2\ (RR'CHO)_3\ Al + 3H_2SO_4\ (dil.) \rightleftharpoons 6\ RR'CHOH + Al_2(SO_4)_3$$

This is a reversible reaction. The equilibrium is shifted by removal of the acetone by distillation.

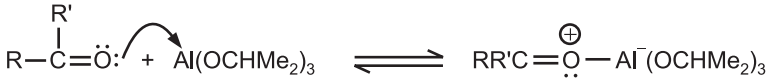
The reaction takes place under very mild conditions and is highly specific for aldehydes and ketones so that C = C bonds and others like C + C, OR, $-NO_2$, etc. do not get reduced by this reagent.

Mechanism: It involves the direct transfer of hydride from the α – C of aluminium isopropoxide to the carbonyl carbon reversibly.



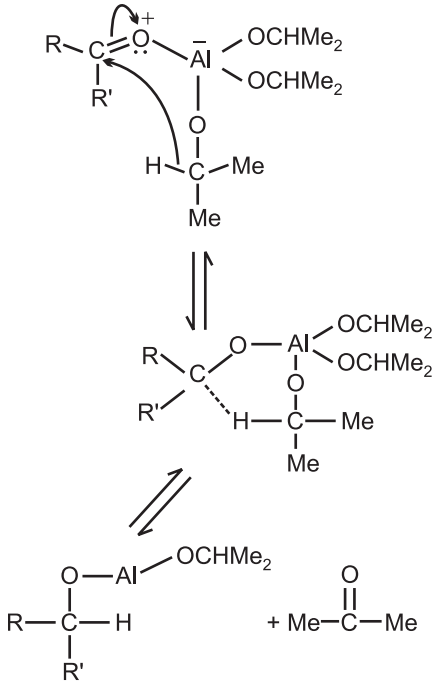
This is a three step mechanism.

(i) Coordination of the ketone with the aluminium isopropoxide.

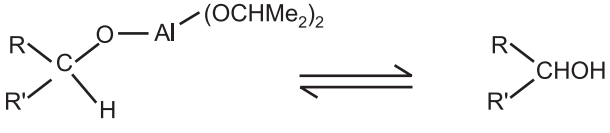


(ii) The hydride transfer from the α – H of the aluminium isopropoxide to the carbonyl carbon atom of the carbonyl compound.

(iii) Separation of the new complex.



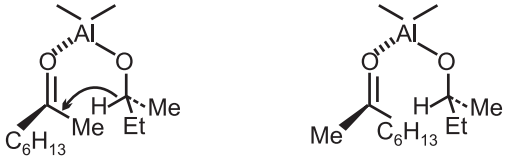
Final Step: Generation of the alcohol from the computer



Stereochemistry:

The product is the racemic [R/S] alcohol since the free energies of the two diastereoisomeric transition states, resulting from hydride attack on the si-face of the ketone or re-face, are identical.

Aluminium alkoxide derived from an optically pure secondary alcohol was used to effect a stereoselective reaction s – (+) – butan–2–ol in the form of aluminium alkoxide, with 6-methyl heptan-2-one gave rise to two diastereoisomeric transition states which lead to an excess of s-6-methyl heptan-2-ol derived from transition state (b) as expected from a consideration of the relative steric interactions.



Transition state (a) has a less favourable Me – Me and Et – Hex interaction and hence requires a higher free energy of activation; it therefore represents the less favourable reaction pathway.

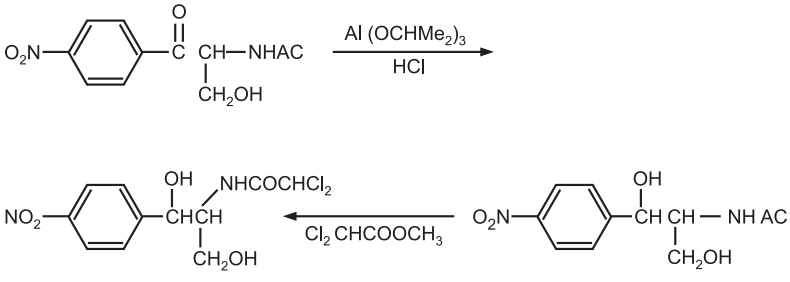
Applications:

Since the reduction is specific for aldehydic and ketonic group, the reaction is specially useful for the reduction of carbonyl compounds containing other reducible groups.

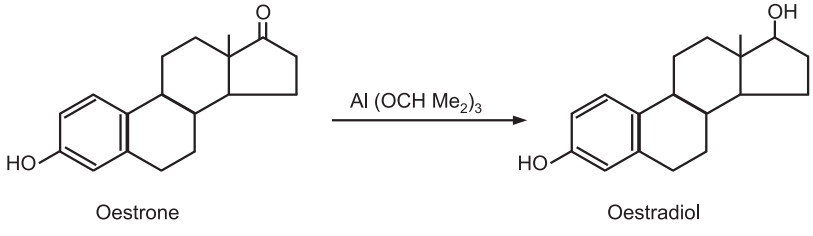
$$CH_2 = CH.CHO \xrightarrow{Al(OCHMe_2)_2} CH_2 = CH.CH_2OH$$

Acraldehyde — Allyl alcohol

(a) Synthesis of chloromycetin

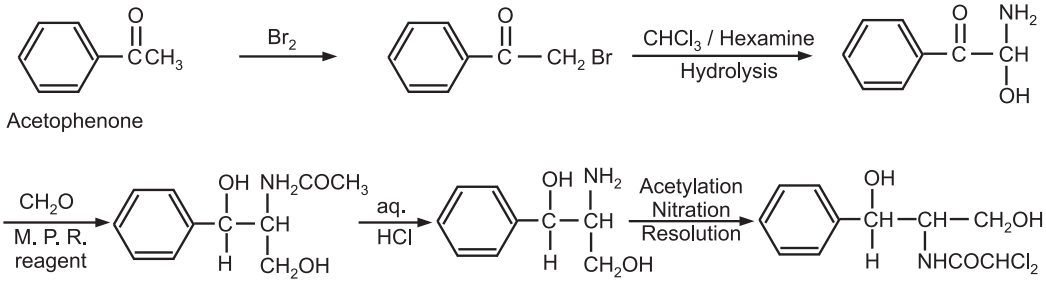


(b) Synthesis of oestradiol



Oestrone — Oestradiol

(c) Synthesis of chloramphenicol

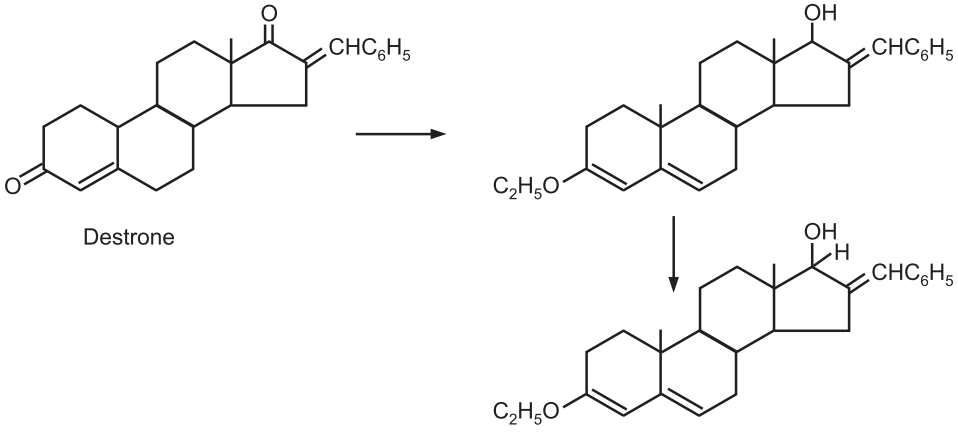


Advantages of Alisopropoxide over other Alkoxides:

Although a number of metals are used as their alkoxides for the reduction reaction, like Mg ethoxide, chloromagnesium ethoxide etc. the aluminium derivatives have been the best reagents. They are weaker condensing agents than Na or Mg alkoxides and are soluble in alcohol and hydrocarbon.

Applications:

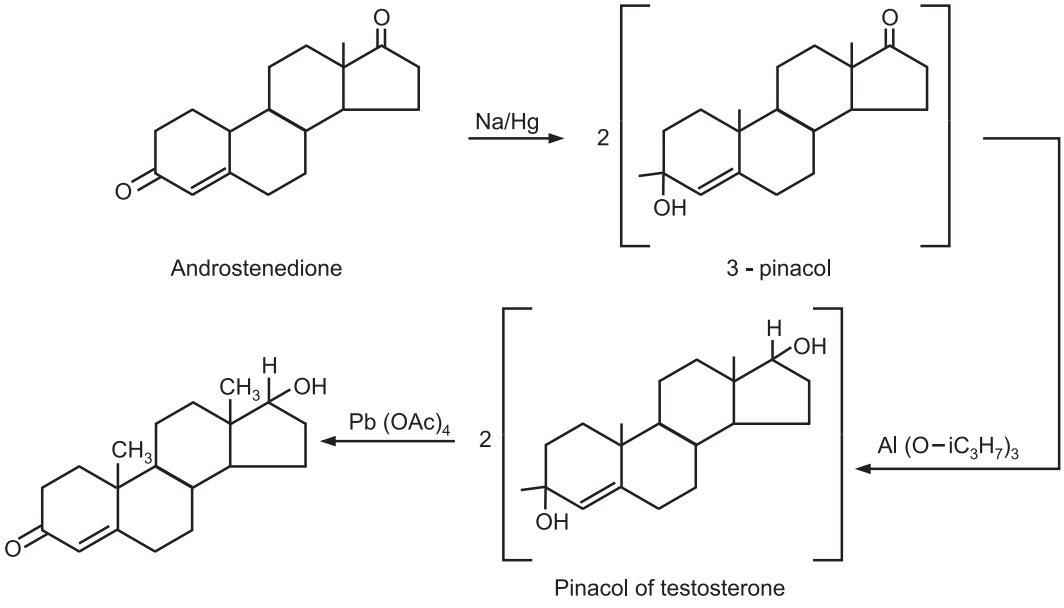
1. 16-benzalandrostenedione is reduced selectively to carbinol.



Destrone

Carbinol

2. Androstenedione is converted into 3-pinacol with sodium amalgam and then reduced by aluminium isopro poxide in 81% yield to the pinacol of testosterone. Treatment of the latter 1, 25 glycol with lead tetracetate regenerated the ketone group with cleavage of the molecule to give testosterone.



Androstenedione

3 - pinacol

Pinacol of testosterone

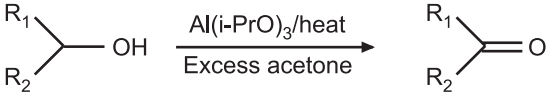
Limitations:

β-keto esters and β-diketones which are capable of enolization form the aluminium salt of the enolic form and are not reduced.

5.7 OPPENAUER OXIDATION

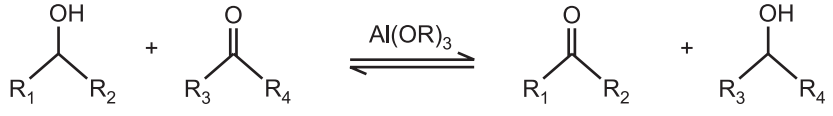
This reaction is named after Rupert Viktor Oppenauer. This method is used for selectively oxidizing secondary alcohols to ketones, using aluminium isopropoxide in excess acetone. The reaction is the opposite of Meerwein-Ponndorf-Verley reduction.

(i)



2º alcohol Ketone

(ii)



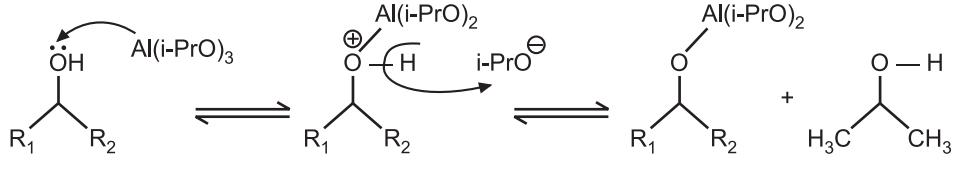
2º alcohol Ketone Ketone 2º alcohol

Oppenauer oxidation, is an important reaction used in the synthesis of alkaloids, hormones, steroids, and terpenes. The low reactivity of aluminium alkoxide used in this reaction can be improved by tert-Bu-CHO and excess of acetone as the powerful hydride acceptor. Excess of acetone shifts the equilibrium toward the product side.

In Oppenauer oxidation, the aluminium-catalysed hydride shift occurs from the α-carbon of an alcohol component to the carbonyl carbon of a second component.

Reaction Mechanism:

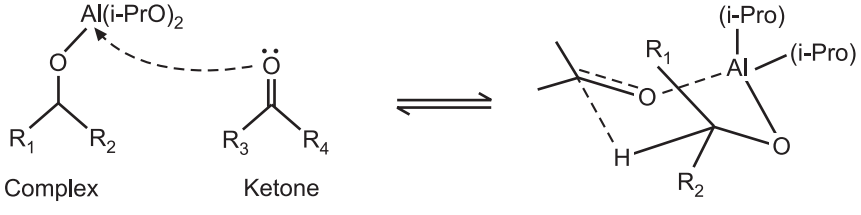
(i)



2º alcohol Complex Isopropyl alcohol

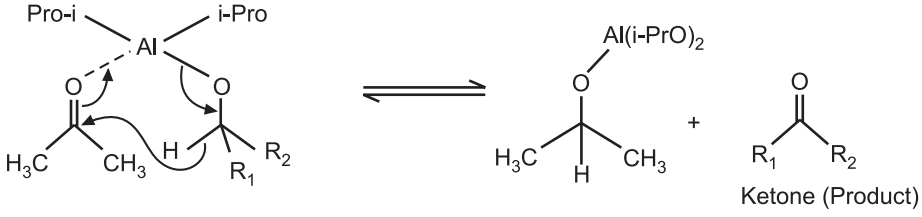
In the first step, alcohol co-ordinates with aluminium isopropoxide to form a complex and isopropyl alcohol. The reaction begins with the alcohol (starting material) replacing one of the isopropoxide groups on the aluminium to generate isopropyl alcohol.

(ii)



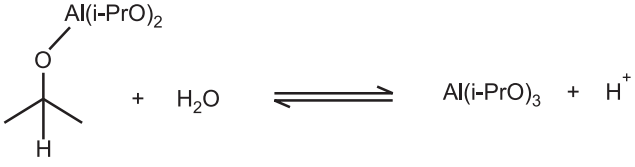
Complex Ketone

The complex reacts with a ketone (acetone) to form a six membered transition complex.



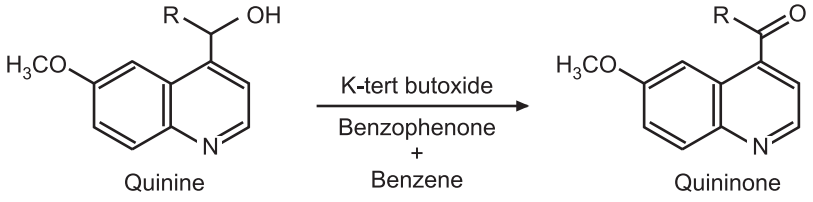
The α-carbon of the alcohol (starting material) is converted to the carbonyl carbon (product) from the aluminium catalysed hydride shift. The desired ketone is formed after the hydride transfer.

(iv)



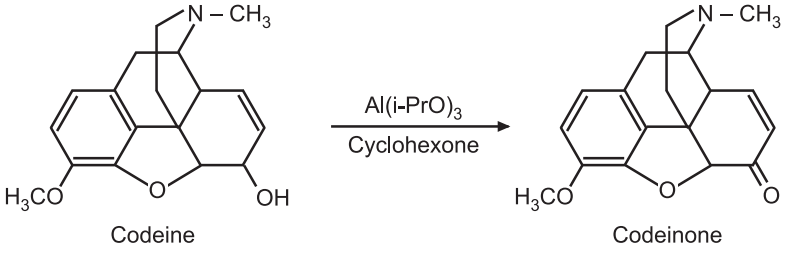
The last step thus results in the formation of the final ketone product and regeneration of the aluminium isopropoxide catalyst.

Woodward Modification: In the Woodward modification, potassium tert-butoxide is used in place of aluminium alkoxide. He used potassium tert-butoxide and benzophenone for the oxidation of quinine to quininone.

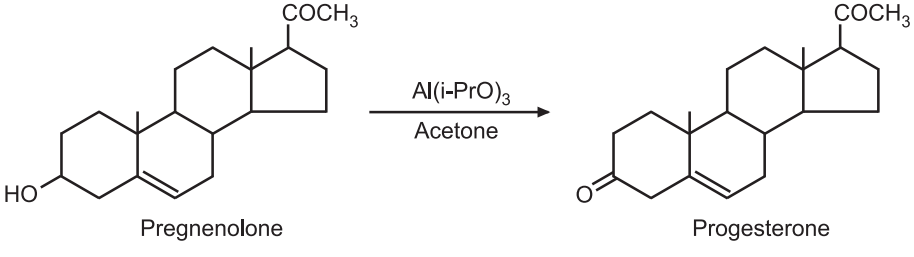


Applications in Drug synthesis:

(i) The analgesic drug codeine is converted to codeinone by Oppenaure oxidation.

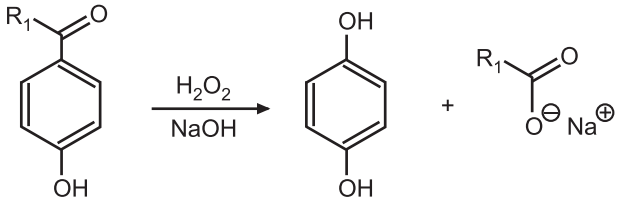


(ii) The female sex hormone progesterone is prepared by the Oppenauer oxidation of pregnenolone.



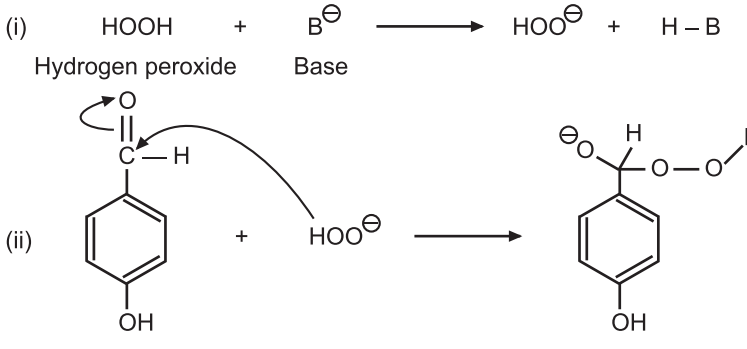
5.8 DAKIN REACTION

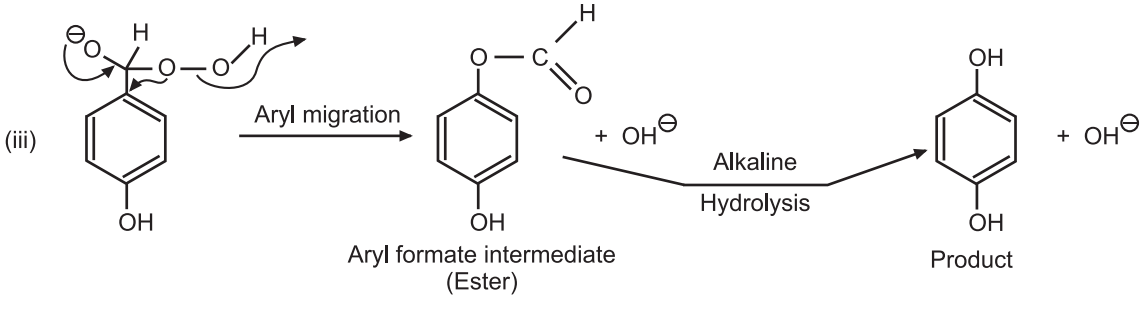
It is a redox reaction in which an ortho or para-hydroxylated benzaldehyde or ketone reacts with hydrogen peroxide in alkaline condition to form a benzenediol and a carboxylate ion.



In short, the oxidation of aldehydes or ketones to the corresponding phenol is known as Dakin reaction.

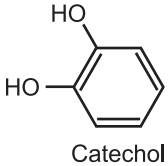
Reaction Mechanism:





Applications of Dakin reaction:

(i) Dakin reaction is used to synthesize catechol. Catechol is used as the starting material for the synthesis of several catecholamines, catecholamine derivatives and 1, 4-tertbutyl catechol, a common antioxidant and polymerization inhibitor.

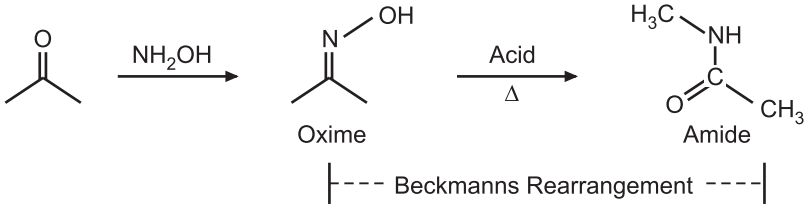


Catechol

(ii) Dakin's solution is a dilute hypochlorite solution. Chlorine, the active ingredient in Dakin's solution, is a strong antiseptic that kills most forms of bacteria and viruses that may lead to skin and tissue infections.

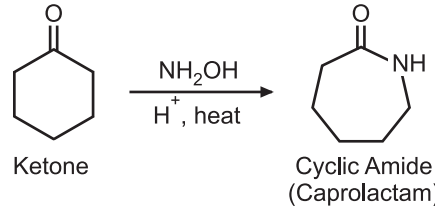
5.9 BECKMANN REARRANGEMENT

It is an acid catalysed rearrangement of an oxime to an amide. It is named after the German Chemist, Ernst Otto Beckmann (1853-1923).

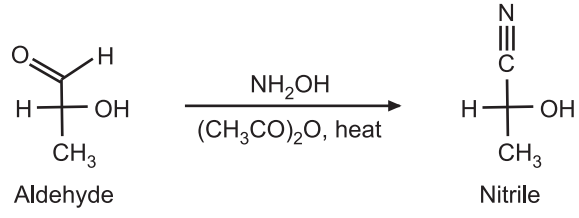


Oximes derived from ketones form amides while oximes derived from aldehydes form nitriles. e.g.,

(i)



(ii)



Open chain oxime gives an open chain amide while cyclic oximes give lactam. The Beckmann rearrangement is often catalysed by acid. The Beckmann solution, acetic acid, hydrochloric acid and acetic anhydride is widely used to catalyze the rearrangement. Other acids like polyphosphoric acid, sulfuric acid or phosphorous pentachloride can also be used. The Beckmann solution consists of acetic acid, hydrochloric acid and acetic anhydride and is widely used to catalyze the rearrangement. Besides the acids, other catalysts like tosylchloride, thionyl chloride, phosphorus pentachloride, sodium hydroxide, triethylamine, etc. may also be used.

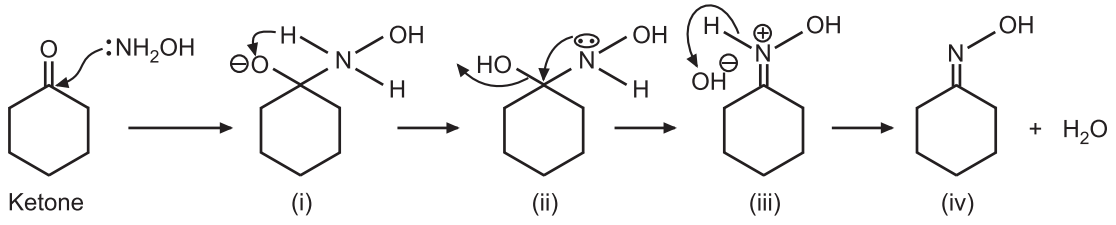
Reaction Mechanism:

(a) Formation of an oxime: In the first step the nitrogen adds to the carbonyl carbon

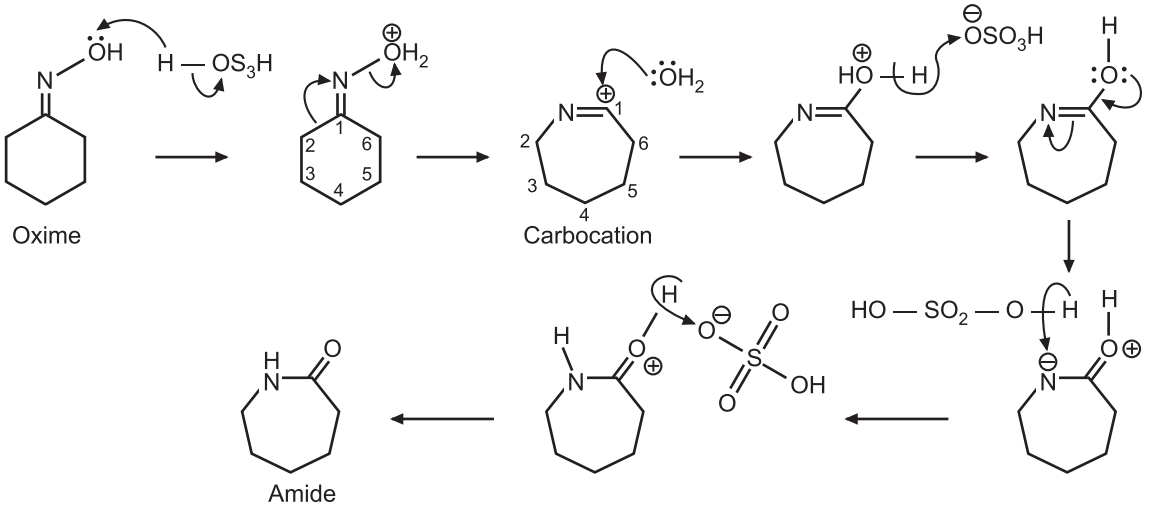
(i) followed by proton transfer,

(ii) then the lone pair of nitrogen displaces the hydroxide,

(iii) and finally oxime is generated by deprotonation of nitrogen.



(b) Beckmann rearrangement:

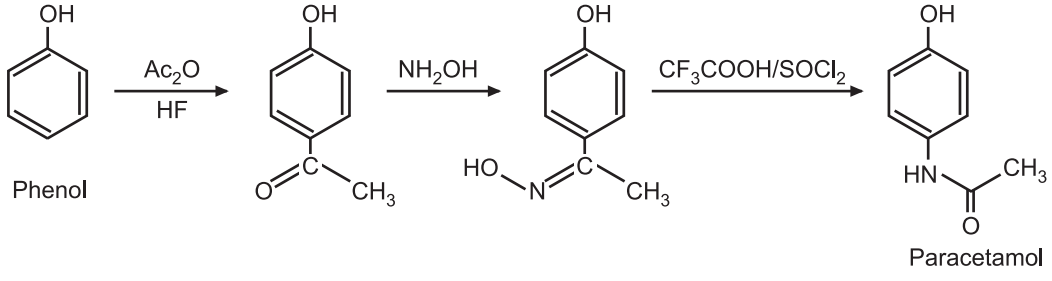


The reaction begins by protonation of the oxime oxygen group forming a better leaving group. The oxime can also be treated with acetic anhydride, $(CH_3CO)_2$ O (converting the oxime oxygen to an acetate, a better leaving group than OH). The R group trans to the leaving group then migrates to the nitrogen, resulting in a carbocation and the release of a water molecule (deprotonation).

The free carbocation is then attacked by water. The positively charged oxygen is deprotonated by base. Protonation of nitrogen followed by deprotonation of oxygen gives the final product, Amide.

Applications in drug synthesis:

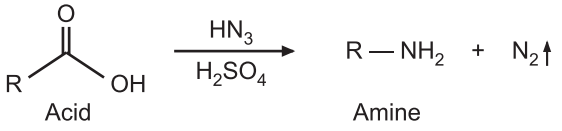
(i) One of the synthetic route of paracetamol (an analgesic antipyretic) involves the conversion of a methylketone to an acetanilide via a Beckmann rearrangement.

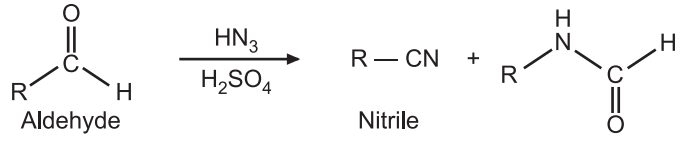


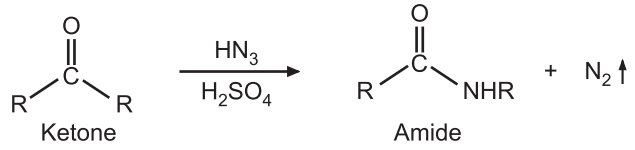
(ii) Beckmann rearrangement reaction is an excellent tool to prepare aza (ring containing nitrogen) derivatives of steroidal (anti-inflammatory) drugs.

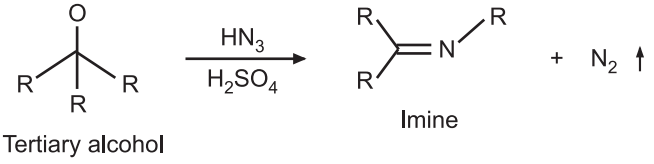
5.10 SCHMIDT REARRANGEMENT

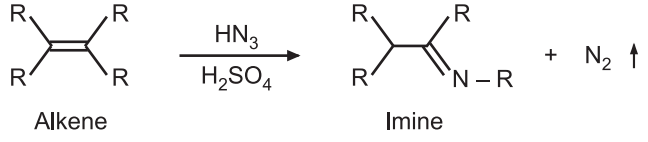
This reaction was discovered by Karl Friedrich Schmidt in 1924. Azides (RN_3) are nucleophilic at their terminal nitrogen atoms and may add to suitably activated electrophiles, such as carbonyl compounds, tertiary alcohols or alkenes to give amines, nitriles, amides or imines. It is an acid catalyzed reaction. For example:

(i) 

(ii) 

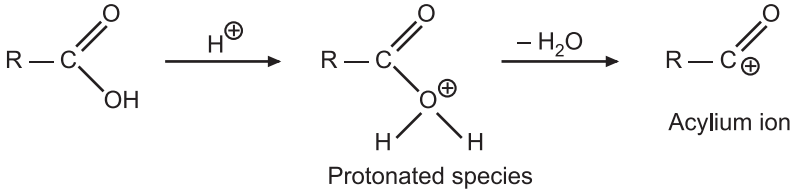
(iii) 

(iv) 

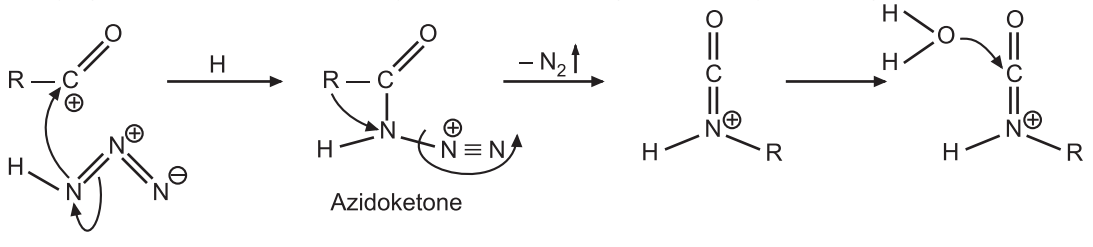
(v) 

Reaction mechanism:

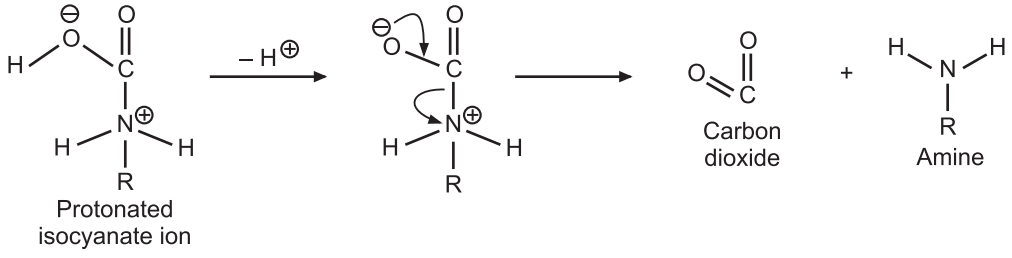
(i) Initially, protonation reaction takes place and water molecule is lost forming an acylium ion.



(ii) The acylium ion then reacts with hydrazoic acid to form protonated azido ketone. The alkyl group shifts from carbonyl carbon to nitrogen atom by rearrangement reaction.

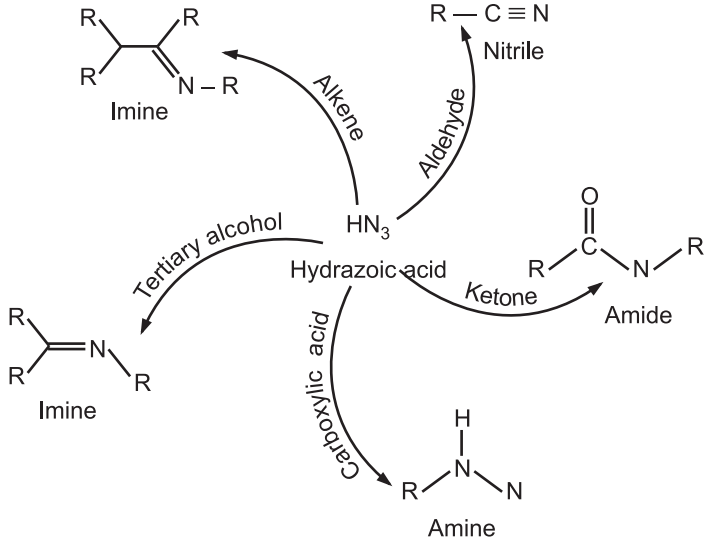


(iii) A protonated isocyanate ion is formed due to addition of a water molecule. It undergoes deprotonations to give amine and carbon dioxide.



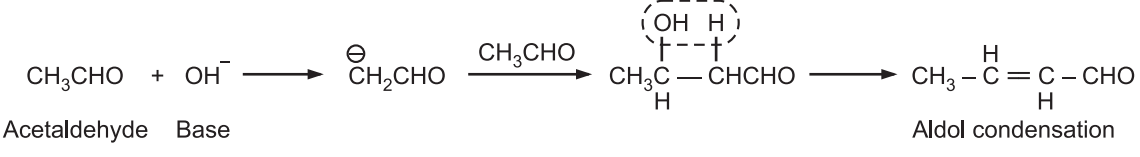
Applications of Schmidt Rearrangement:

It is used to introduce amine, nitrile, amide or imine functional group.

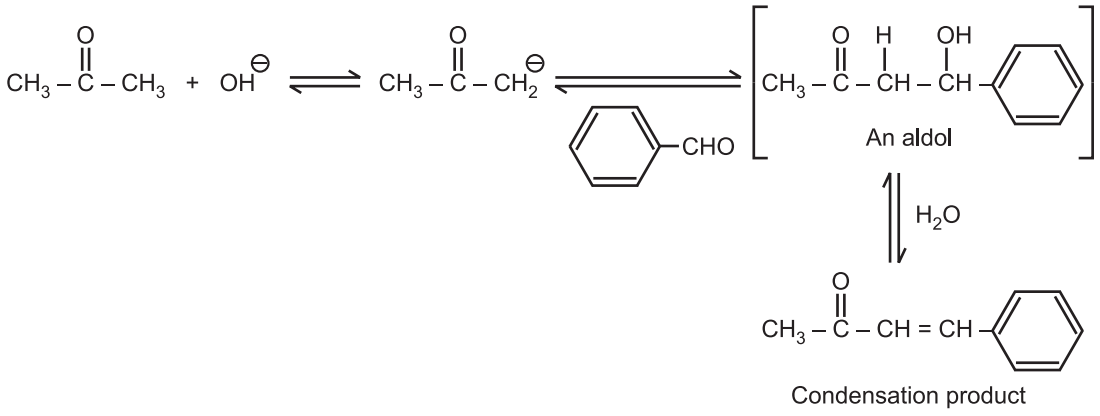


5.11 CLAISEN-SCHMIDT CONDENSATION

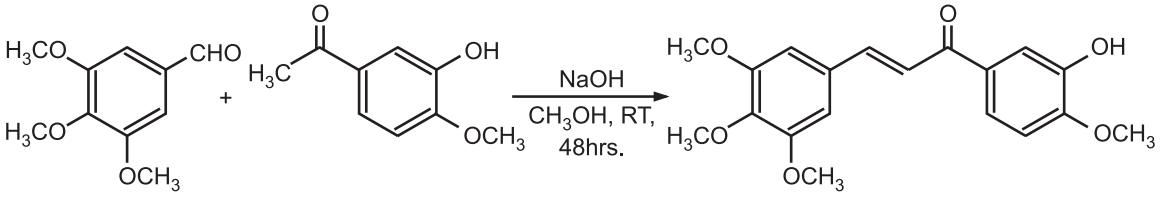
The condensation of an aromatic aldehyde with an aliphatic aldehyde or ketone in the presence of a base or an acid to form an α, β-unsaturated aldehyde or ketone is known as Claisen-Schmidt Condensation. When an enolate obtained from an aldehyde, normally react with unreacted aldehyde, the reaction is known as **Aldol condensation reaction**.



When an enolate from a ketone reacts with an aldehyade, it is called Claisen-Schmidt condensation or crossed aldol condensation. In this, the product still has a reactive alpha hydrogen and a hydroxide adjacent to it. Dehydration quickly occurs leading to the condensation product. The reaction is named after Rainer Ludwig Clasien in 1887.

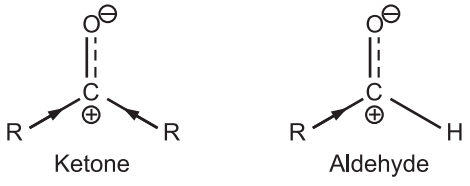


Sample reaction:



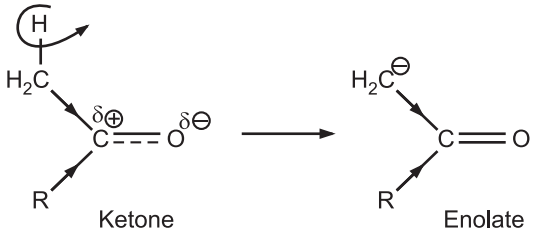
In above crossed aldol condensation:

(a) Aldehyde carbonyl group is always more reactive towards nucleophilic addition than ketone carbonyl group.



Alkyl groups are electron releasing in nature. The δ ⊕ (delta positive) charge developed on carbon of ketone is greatly neutralized due to more electron release by both alkyl groups. Hence, carbonyl carbon of ketone is less reactive. While aldehyde has more reactive carbonyl carbon.

(b) Ketones form enolate ions more quickly than aldehydes.

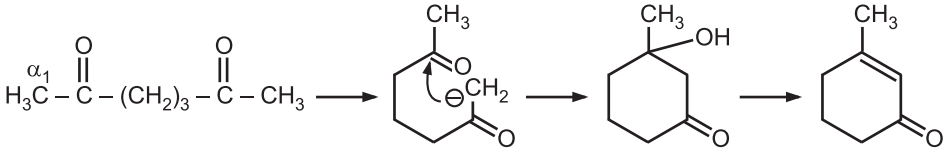


The ketone forms the lower energy enolate (nucleophile) at much faster rate than aldehyde.

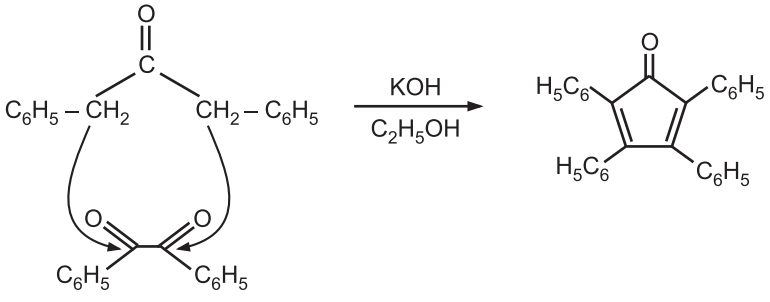
(c) Thus ketone generates enolates (nucleophile) while aldehyde has highly carbonyl carbon (electrophile). Hence in the "crossed/mixed" reaction, the ketone enolate usually adds to the aldehyde.

(d) When the reaction contains an enolizable aldehyde and a ketone, one product does predominate. This reaction may also be used in the formation of ring structure. e.g.,

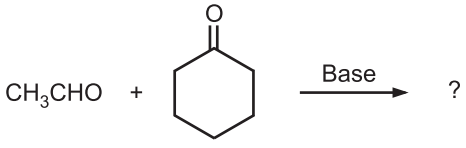
(i)



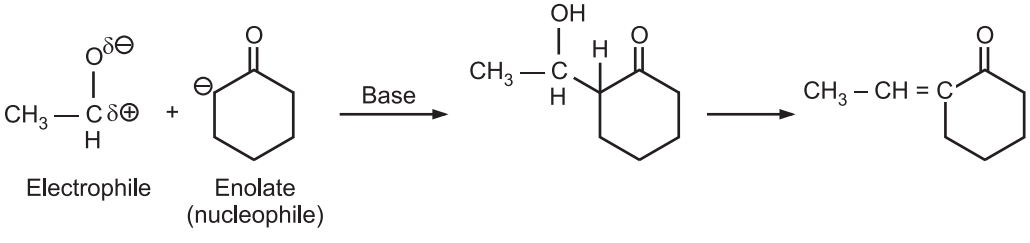
(ii)



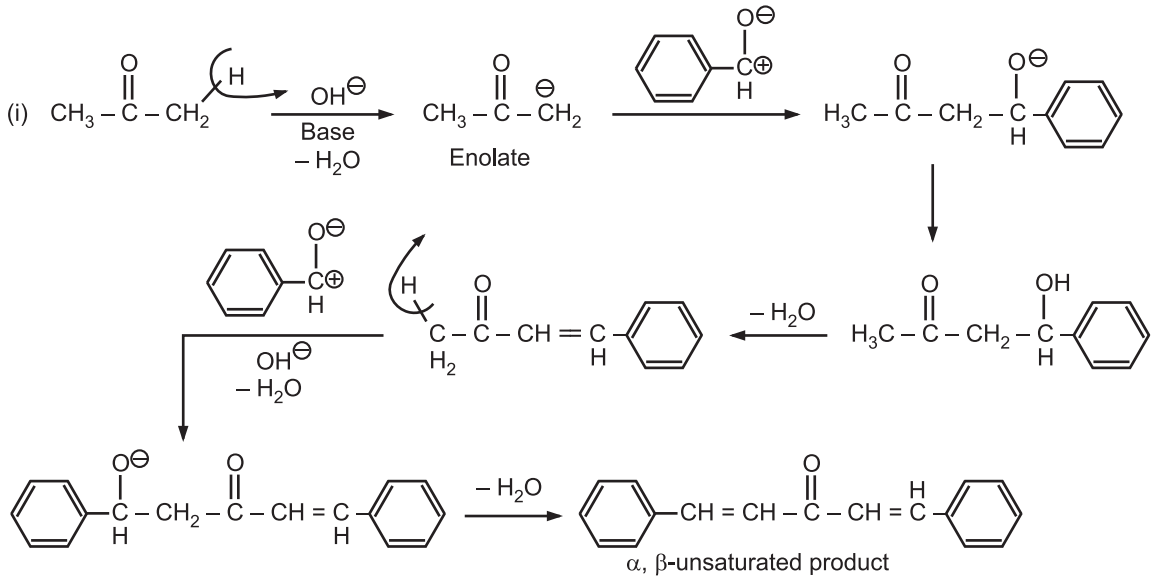
Example: Predict the major product of the following condensation



Ans.: Ketone generates enolate (nucleophile) that attacks on highly reactive electrophile (carbonyl carbon) of aldehyde.

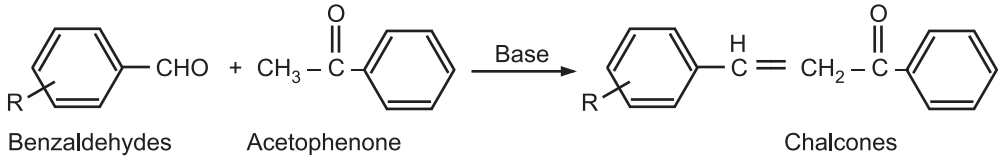


Reaction Mechanism:



Applications in Drug Synthesis:

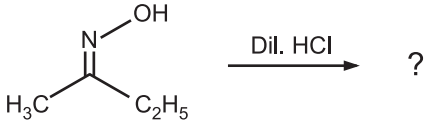
(i) The Claisen – Schmidt condensation between acetophenone and benzaldehyde derivatives allows unsaturated ketone such as chalcones to be obtained.



(ii) This reaction is also used to synthesize flavanone and 1.3-diaryl propane derivatives.

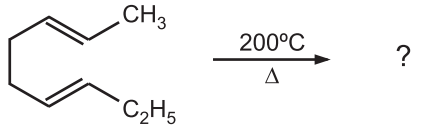
QUESTIONS

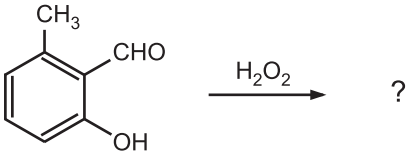
1. Define and classify molecular rearrangement reactions.
2. Explain any two nucleophilic rearrangements of electron deficit nitrogen atom.
3. Write note on Dakin oxidation.
4. Write note on Beckmann rearrangement.
5. Write down two rearrangements of aromatic nucleus.
6. Write down any two rearrangements of electron rich system.
7. Identify rearrangement

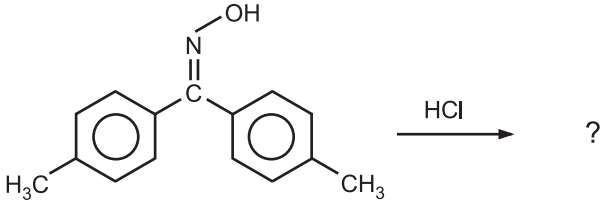


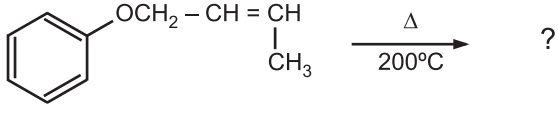
8. How Beckmann rearrangement helps to distinguish between syn and anti-isomerism in oxime?

9. Identify rearrangement and predict products and mechanism.

(i) 

(ii) 

(iii) 

(iv) 

10. Write synthetic reaction for synthesis of aniline using Hoffmann rearrangement and anthranilic acid using Bayer villiger oxidation. Write mechanism of each reaction.

11. Explain rearrangement reaction which go through isocyanate as an intermediate and give their side product.

12. Give mechanism involved in Schmidt rearrangement.

13. Explain with mechanism Birch reduction and Wolf Kishner reduction.

14. Write short note on: Oppenaur-oxidation.