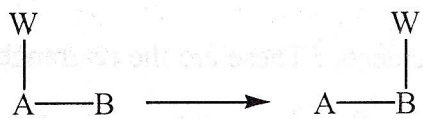
4.6.1 General mechanistic considerations

In a rearrangement reactions a group moves from one atom to another in the same molecule. In most rearrangement reaction in migratory groups the migration from an atom to an adjacent one and it is called 1,2-shift. However, in some rearrangement reactions migration to longer distances can also be observed. The migratory group (W) may move with its electron pair, without its electron pair (or) with just one electron, thus, the migratory group may act as an necleophile, electrophile or a free radical. The atom 'A' is called 'migration origin' and 'B' is the migration terminus.



All above reactions have been grouped together under the name rearrangement reactions or molecular rearrangements. Thus, molecular rearrangement may be defined as follows.

"It is the electron which involves reshifting of the sequence of the atoms to form

Molecular rearrangement may be grouped under the following two headings.

1. Intramolecular molecular-rearrangement : If rearrangement occur within the same molecule, they are said to be intramolecular. In these rearragneemtns the migrating group does not get detached completely from the system in which rearrangement is taking place.
2. Intermolecular molecular rearrangement : If rearrangements involve the migration of the group between two molecules, they are said to be intermolecular. In these rearrangements, the migrating group is first detached and reattached at another site.

4.6.2 Types of molecular rearrangements : The molecular rearrangements can be conveniently classified into the following types.

1. Nucleophilic rearrangement : These are the rearrangement reactions in which the migrating group (nucleophile) gets migrated to electron deficient centre
2. Electrophilic rearrangements : these are the rearrangement reactions in which the migrating group (electrophile) gets migrated to electron-rich catre (atom).
3. Free radical rearrangements : These are the rearrangement reactions in which the migrating group moves to a free radical catre
4. Aromatic rearrangements : These are the rearrangement reactions in which the migrating moves to aromatic nucleus.

The just three types of molecular rearrangements are intro molecular while the fourth type of molecular rearrangement may be intramolecular, intermolecular or both.

4.6.3 Rearrangements to electron deficient atom or nucleophilic rearrangements : These rearrangements are much more common than electrophilic or free radical 1,2-shift rearrangements. These are the rearrangement reactions in which the migrating group moves from a carbon atom to an adjacent electron deficient atom which has only six electrons in its valency shell. The electron deficient atom arises due to the loss of some electronegative group (:Y) with its bonding electrons during the migration. The rearrangements are also known as 1,2-shifts. The electron deficient atom may be carbon, nitrogen or oxygen. The group which migrates is most often hydrogen, alkyl or aryl group. The other group containing oxygen, nitrogen or sulphur atoms may also migrate. The important types of 1,2-shifts can be represented as follows.

These rearrangements may proceed through a classical or a nonclassical (bridged) carbonium ion intermediate or both. The whole process may be depicted as follows.

In some cases, a pair of unshared electrons on the migrating group gets facilitated by the formation of the intermediate. In other cases, such as carbon or hydrogen (R = - C – or H), one pair of electrons is able to bind three atoms momentarily together. The formation of the bridged carbonium ions in 1,2-shifts is regarded as an example of neighbouring group participation, and when the rate is increased because of this effect the rearrangement is termed as anchimerically assisted.

The arrangements of this group have been further divided into three types on the basis of the nature of the atom where the migrating group gets moved. The three types are as follows :

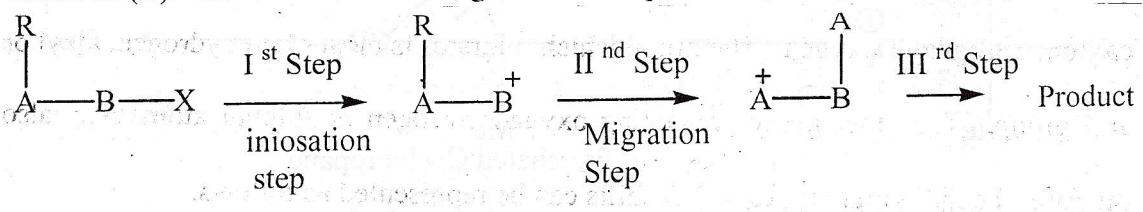
a) rearrangements to electron deficient carbon

b) rearrangements to electron deficient nitrogen and

c) rearrangements to electron deficient oxygen

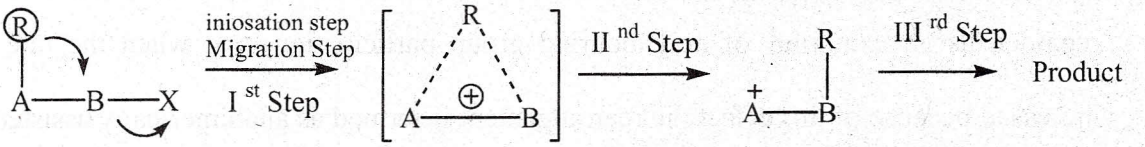
4.6.4 Nature of migration

Most nucleophilic 1,2-shifts are intramolecular. The migratory group (W) does not become free but always remains connected in some where to the substrate. Depending on the nature of the migration the reaction may ends with inversion of configuration or recemisation with respect to the migration origin (A) or migration terminus (B). the molecular rearrangement takes place in the steps. They may be



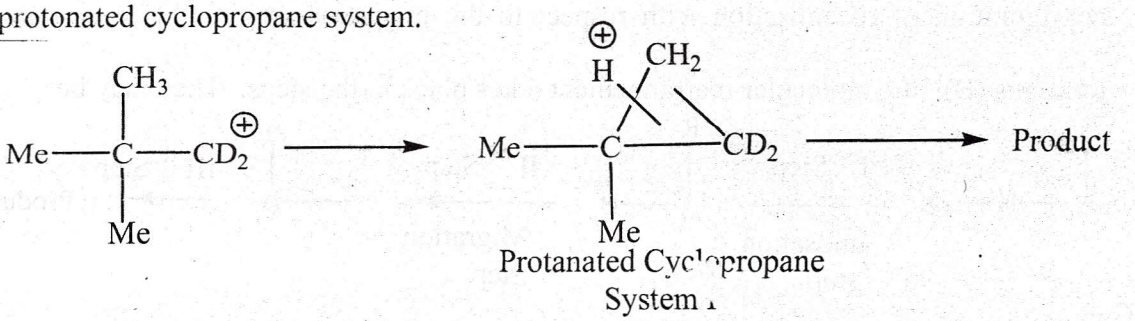
If recemisation is foundent at migration terminus (B), then it is probable the inversation step takes place before the second step and that a positively charge carbon is present at 'B'. These rearrangement reaction is an SN^1 type process with respective 'B'.

If inversion occurs at B, then the inversation step (first step) and migration step (second step) takes place by converted mechanism, the rearrangement reaction is an SN^2 type process with respective B.

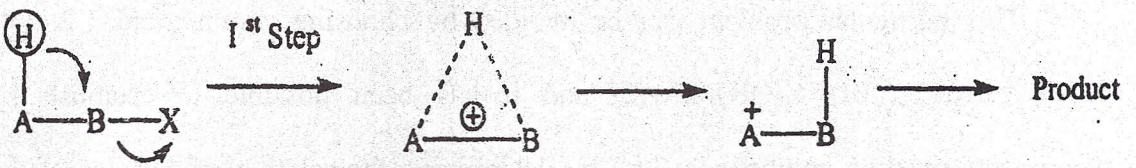


In these case participation by R assist in removal of X which is similar to neighbouring group participation reactions. In the intermolecular rearrangement reaction the bond between R and A is broken, on other hand in the intramolecular rearrangement reactions the migrating group does not get detached completely from the system in which rearrangement taking place.

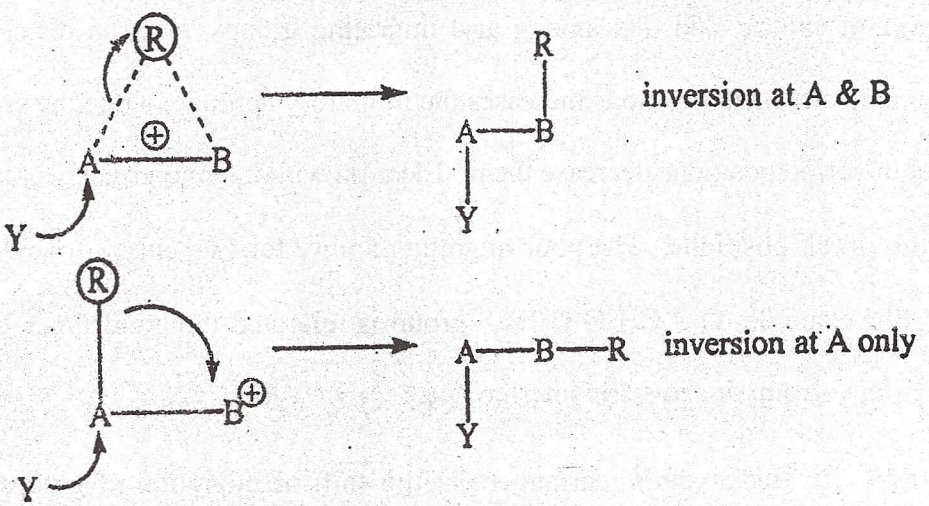
The rearrangement reactions may proceed through an intermediate formation or hypothetical transition state formation (I). When R is aryl or vinyl groups, then (I) is probability on intermediate the rearrangement results with increasing rate of reaction due to achim ric assistance of migratory group when R is alkyl group, then, I is protonated cyclopropane system.



When R is hydrogen atom migrated from migration origin (A) to migration terminus (B), then I is transform state or intermediate.



The stereochemistry at migration origin (A) is less often involved there is because that in most cases it does not end up as a tetrahydral atom. On some rearrangement reactions inversion of conformation at migration origin (A) is noticed. In such cases the reaction proceeds through an SN^2 type process.



4.6.5 Migratory aptitude

All groups do not migrate with equal ease in 1,2-nucleophilic rearrangements. A number of experiments have been carried out to determine the relative migratory aptitude of groups in these types of rearrangements and in general the relative ease of migration is found to be

$pH > Me_3C > MeCh_2 > Me$

This is the rearrangement of the 1,2-diol, Ph_2 C(OH) C(OH), it is the Me that is found to migrate and not C_6H_5 as might have been expected from the sequence above. However, the reaction here is controlled by preferential protonation on that OH group

which will lead to the more stable carbocation (1a rather than 1b) and the migration of Me rather than Ph is there by predetermined.

This particular problem can be avoided by choosing symmetrical 1,2-diols suchas PhArC (OH) C(OH)PhAr(2) and it has been possible to establish by experiments on such compounds (i.e.) by determining the relative proportions of the two ketones 2a and 2b that are produced, the relative migratory aptitude sequence is

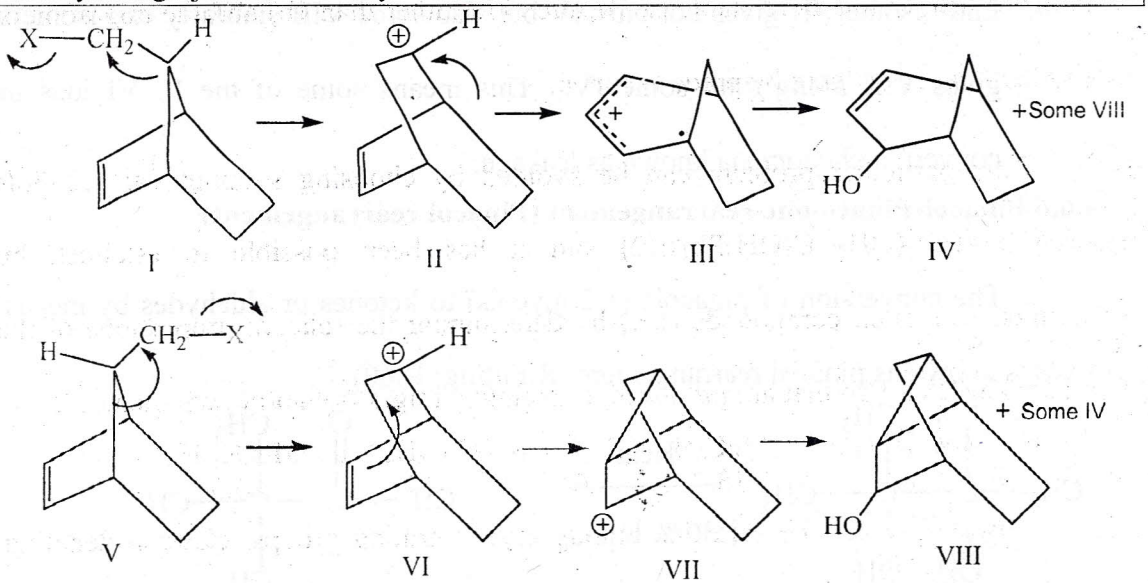
$$P - MeOC_6H_4 > P - MeC_6H_4 > C_6H_5 > p - ClC_6H_4 > o - MeOC_6H_4$$
$$500 \qquad 15.7 \qquad 1.0 \qquad 0.7 \qquad 0.3$$

However, it can be said that among aryl migrating groups, electron denoting substituents in para and meta positions increases the migratory aptitude, while the same substituents in the ortho positions decrease them. Electron withdrawing group decrease migrating ability in all positions. The poor migrating ability for O – anisyl group has steric cause. For example; O – $CH_3O\ C_6H_4$ – group is migrated thousand times less than P-$CH_3OC_6H_4$ – group due to setric interference.

Trans migration : In Backmann's rearrangement the shift of migration of groups is always trans to the leaving – OH group. The pinacole rearrangement occurs in such a manner that the migrating group is always trans to the leaving hydroxyl group. It is an important consequence in alicyclic system.

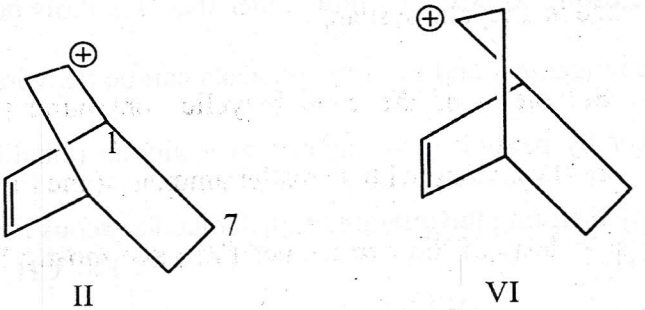
Memory effects : Solvolesis of the endo bicyclic compound (I) gave mostly the bicyclic allylic alcohol (IV), along with a smaller amount of the tricyclic alcohol (VIII) on the other hand solvolesis of the exo isomer (V) gave mostly the tricyclic alcohol (VIII), with a smaller amounts of (IV).

The two isomers gave entirely different ratios of the products, though the carbo cation initially formed (II, VI) seems to be the same for each rearrangement.



In the case of I, a second rearrangement (a shift of1,7 bond) follows, while with V it is an intramolecular addition of the positive carbon to the double bond that follows. "The formation of carbocations (II, VI), how they were formed before the go on to the second step is known as memory effect". It is attributed to the following reasons.

1. The twisted carbocation II positive charge is nearer to the 1,7 bonds in the molecule
2. The twisted carbocation VI positive charge is nearer to the double bond of the molecule



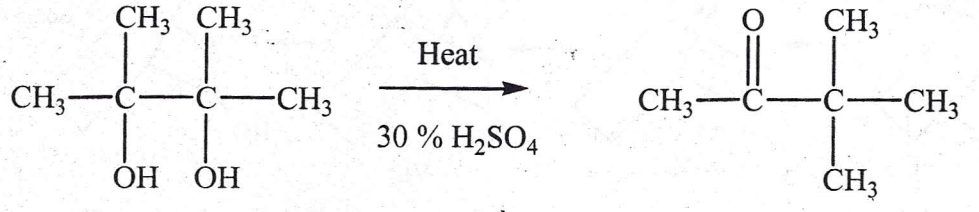
II VI

3. The rearrangement involves non classical carbocations and the reactions proceeds in step wise mechanism but not concerted mechanism

4. Endo isomer (I) gives not only IV but also some VIII similarly exo isomers V gives VIII along with some IV. This means some of the II, VI ions inter convert, a phenomena known as leakage.

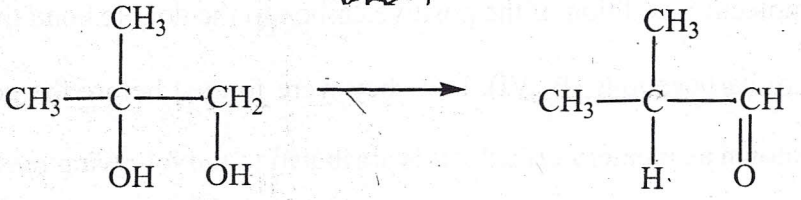
4.6.6 Pinacol-Pinacolone rearrangement (Pinacol rearrangement)

The conversion of pinacols (1,2 glycols) to ketones or aldehydes by means of acids is known as pinacol rearrangement (R.Fitting, 1860).



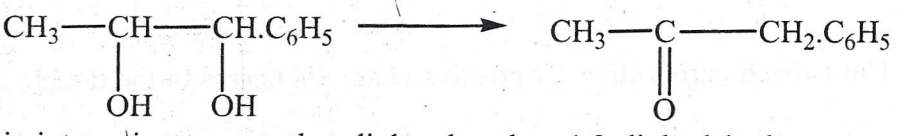
2, 3 - Dimethyl - 2, 3 - Butanediol (Pinacol)

Methyl *t* - butyl ketone (Pinacolone)

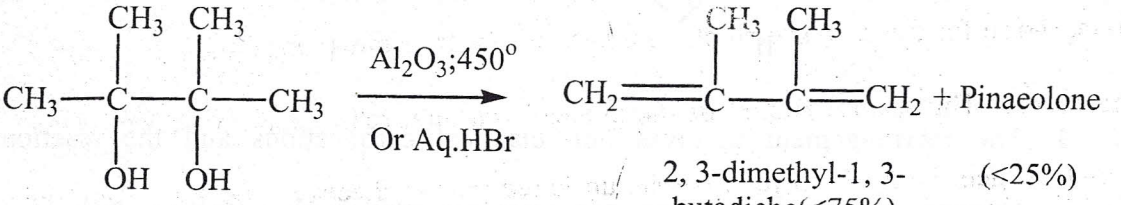


2 - Methyi propan - 1, 2 - Diol

Isobutyraldehyde



It is interesting to note that diols other than 1,2 diols dehydrate normally i.e., without any rearrangement and even the pinacols can be dehydrated to normal product i.e., olefins either by passing their vapours over alumia (alkaline conditions) at high temperature or by distilling the mixture of pinacoland aqueous HBr.

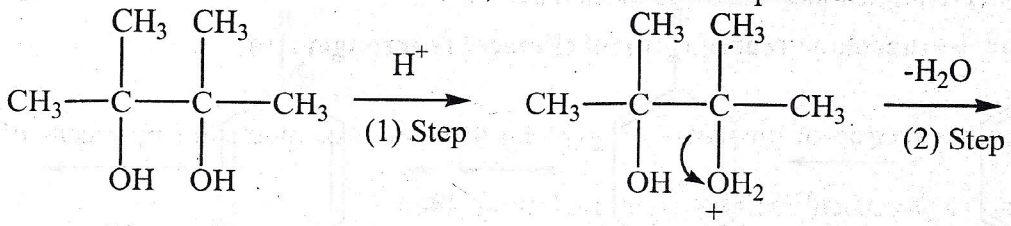


Pinacol

2, 3-dimethyl-1, 3-butadiehe(<75%) (<25%)

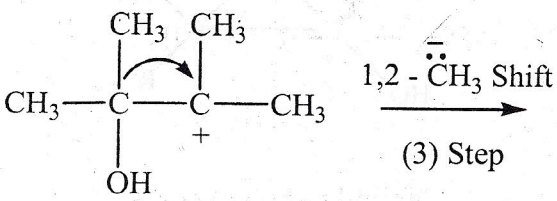
Mechanism : The reaction involves four steps

1) Protonation of an OH; 2) Loss of H_2O to form a carbocation; 3) 1,2 shift of H;R (or) Ar to form a more stable cation and 4) Loss of H^+ to form product

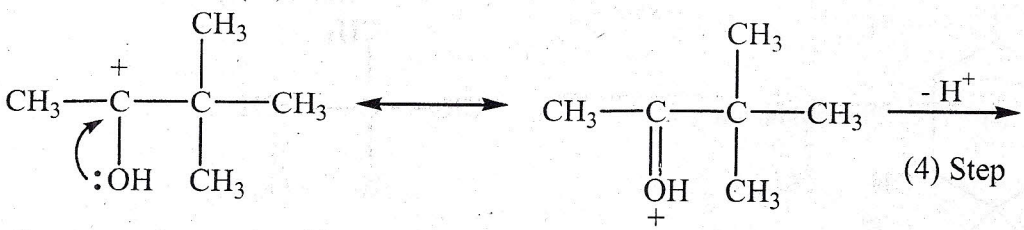


Pinancol

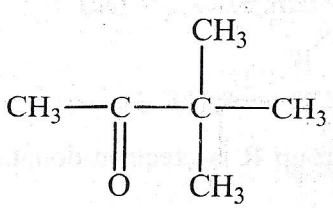
Oxonium ion



Carbocation (3^o)



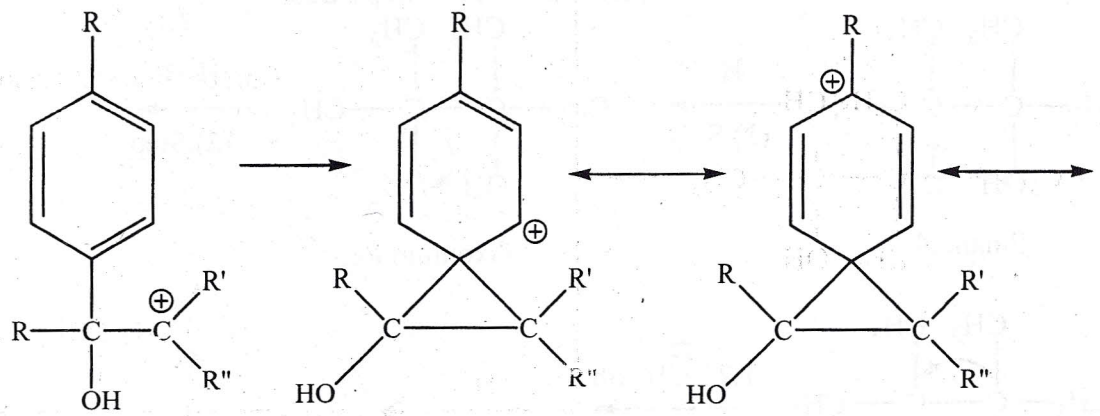
Rearranged protonated ketone (more stable cation)

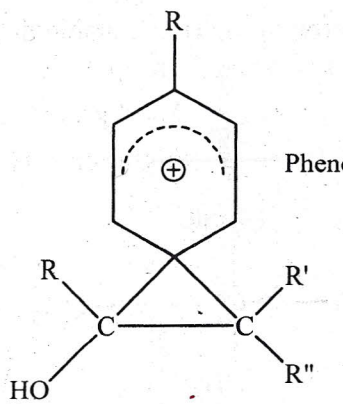


Pinacolone

It is important to note that although both the initial and the rearranged carbonium ions are tertiary, the rearranged cation is a resonance-stabilized oxonium ion (a protonated carbonyl). The resonance stabilization is undoubtedly an important driving force for the rearrangement. Loss of proton from the rearranged ion produces pinacolone. The special feature of the pinacol rearrangement is the presence of the second oxygen atom which provides its unshared pair of electrons needed during the rearrangement of the cation.

When an aryl group migrates an intermediate of structure I is obtained. The resonance hybrid of I is called the phenonium ion.



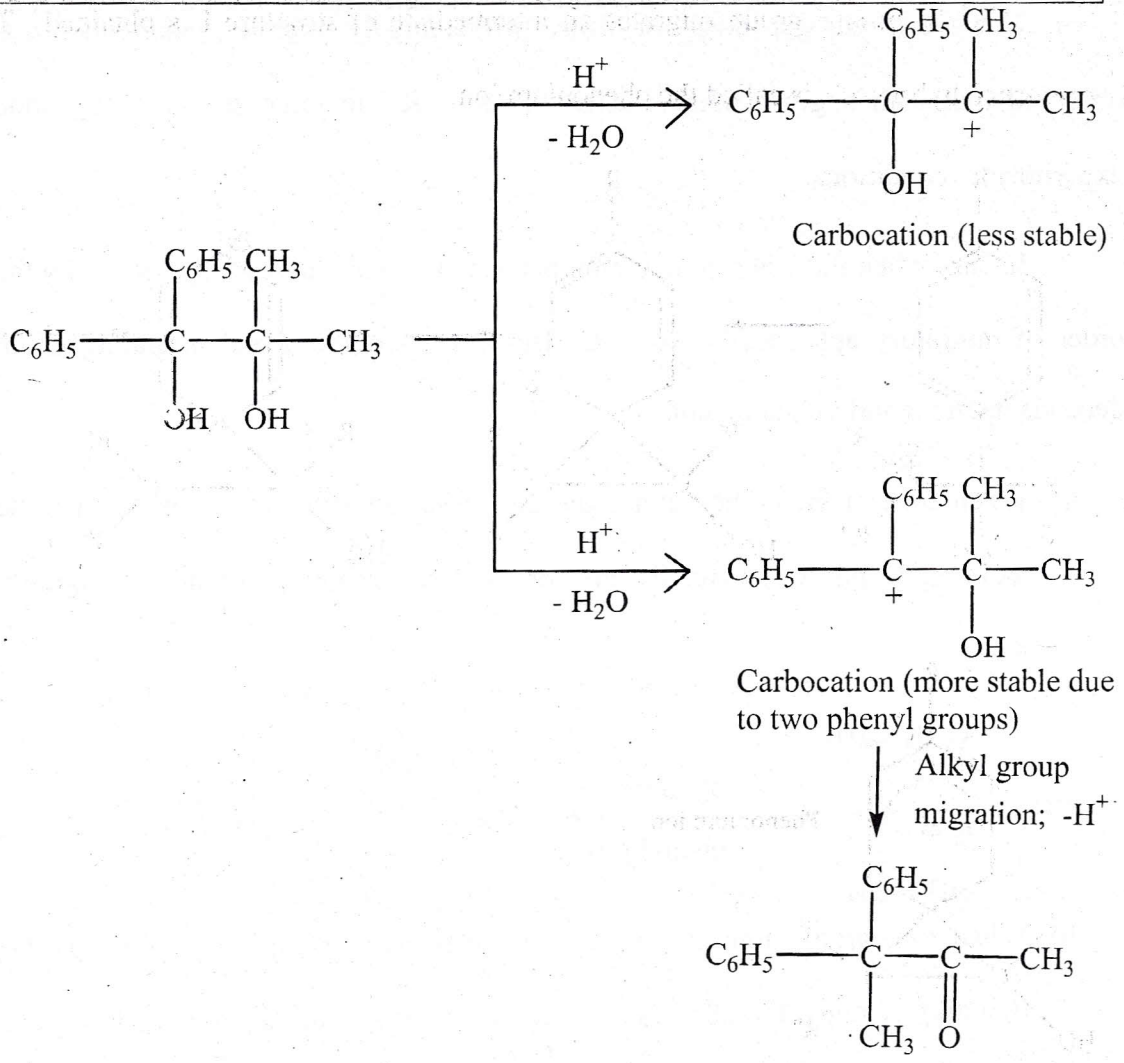


Phenonium ion

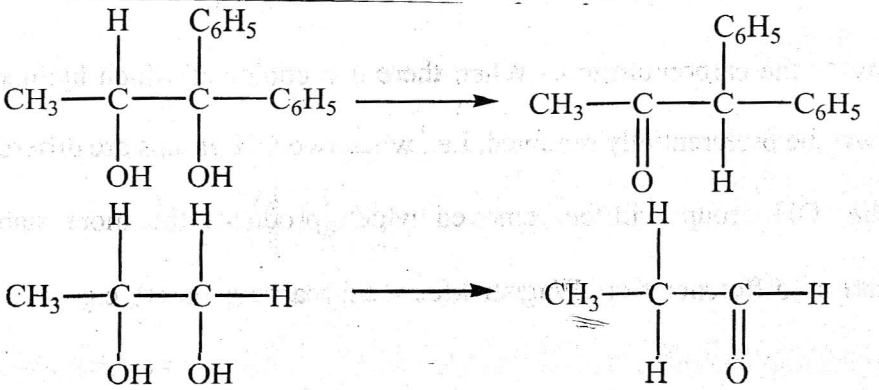
In case of group R is electron-donating (viz., R, OR etc) the migration of the aryl group is facilitated.

Features of pinacol rearrangement

i) Stability of the carbonium ion. When there is a choice as which hydroxyl group will be preferentially removed, i.e., when two OH groups are different then that OH group will be removed which produces the more stable carbocation (difference from Wagner-Meerwein rearrangement), e.g.



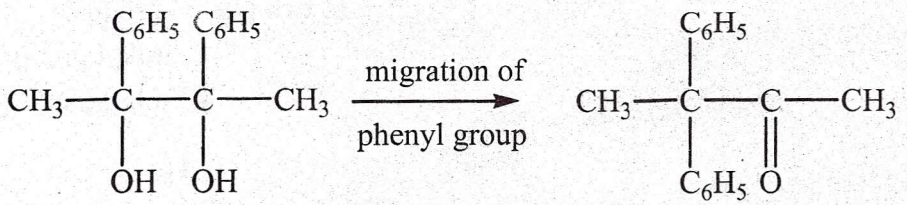
ii) Migratory aptitude of the group. The migrating group in the pinacols may be alkyl, aryl or even hydrogen atom. Hydrogen may migrate in preference to – R or –Ar, as in the following examples.



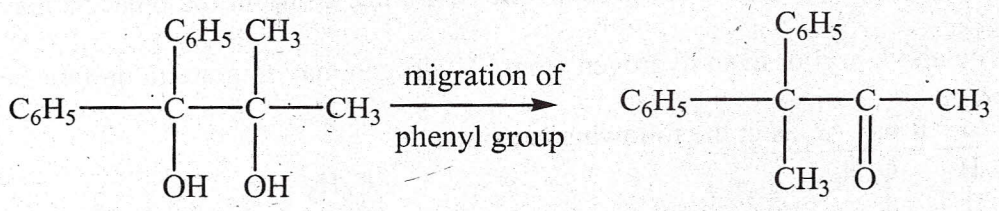
However, hydrogen does not always preferentially migrate. Sometimes it is observed that with a given pinacol either- H or – R can migrate, depending upon experimental conditions.

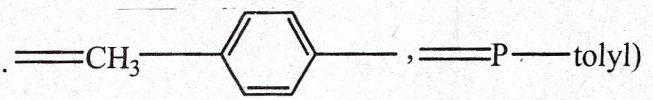
In case when there is a competition between alkyl and aryl groups generally the order of migratory aptitudes is Ar > R. But, however, the actual migrating group depends upon the individual glycol.

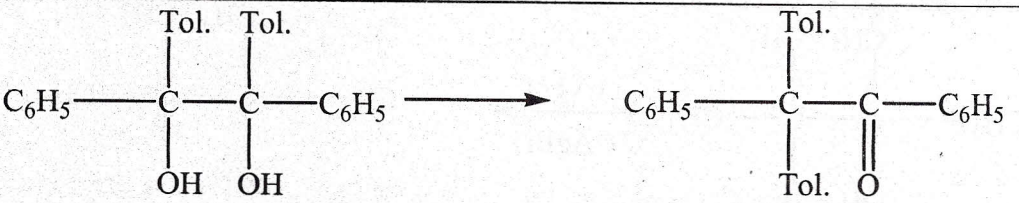
a) When each of the carbon atoms the glycol has an aryl and an alkyl group the more nucleophilic (potentially electron rich) aryl group preferentially migrates, e.g.



b) When one carbon atom of the glycol possesses two aryl groups while the other two alkyl groups, the alkyl group migrates owing to the greater stability of its carbonium ion.



Lastly, when the migratory competition is between two aryl groups, then the one which is a better nucleophile (more powerful electron donor towards carbon) migrates preferentially. Thus the migratory aptitude follows the order. P-anisyl > p-tolyl > phenyl > p-chlorophenyl > p-anisyl. This can be visualized by the following example (Where, Tol. 



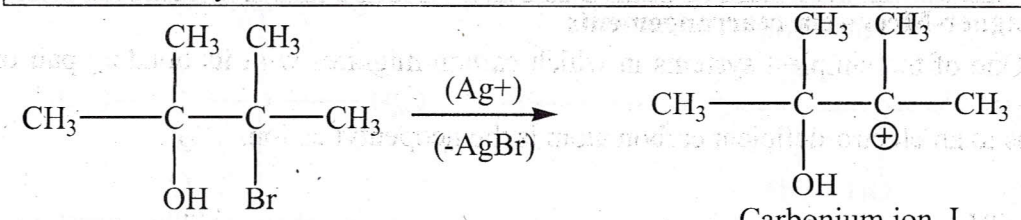
iii) Intramolecular migration : As mentioned in the mechanism, the migrating group migrates within molecule i.e., it never becomes free from the rest of the molecule as it retains its configuration in the product. Moreover, the intramolecular migration is further evidenced by the fact that when a mixture of two different pinacols is heated with H_2SO_4 no cross product is obtained. The intramolecular nature of the rearrangement is further indicated by the use of tracer technique. If rearrangement, in which there is a hydride shift, is carried out in deuteriated solvent (e.g., D_2O, MeOD, etc.) no deuterium incorporated into the new C-H (D) bond in the final rearranged product.

iv) Steric effect : The migration of the group is also effected by steric factor viz., MeO.C_6H_4-group migrates thousand times less than the p-MeO. C_6H_4-group.

v) Transmigration : The migrating group migrates to the opposite (trans) side of the leaving group (see mechanism) which has important consequences in alicylic system

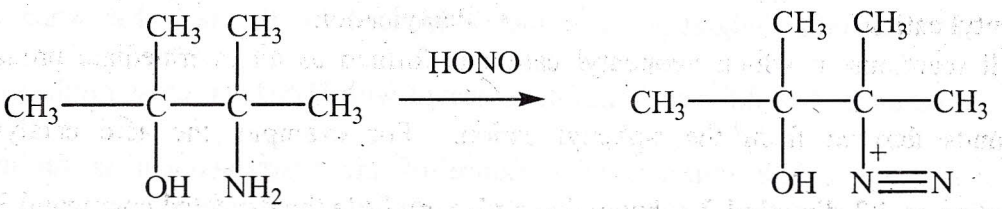
Extension and application

In addition to 1,2-diols, β-halohydrins undergo rearrangement in the presence of Lewis acid, and β- amino alcohols via the diazonium ion, on treatment with nitrous acid to pinacolone.



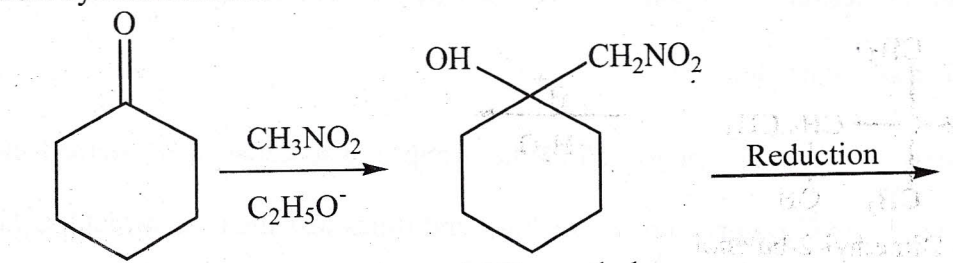
2,3 - Dimethyl - butene
β -bromohydrin

Carbonium ion, I



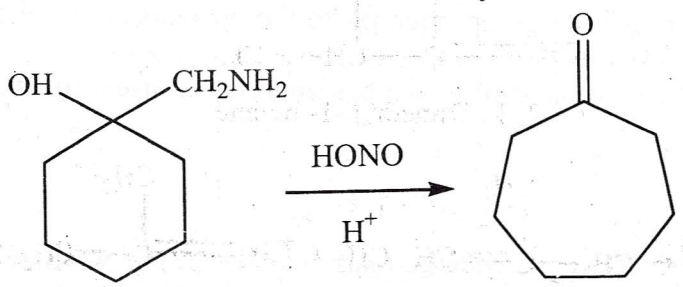
β -aminoalcohol

The latter extension of pinacol rearrangement has a synthetic application e.g. synthesis of cycloheptanone from aminomethyl cyclohexanol which in turn is obtained from cyclohexanone.



Cyclohexanone

1-Nitromethyl Cyclohexanol



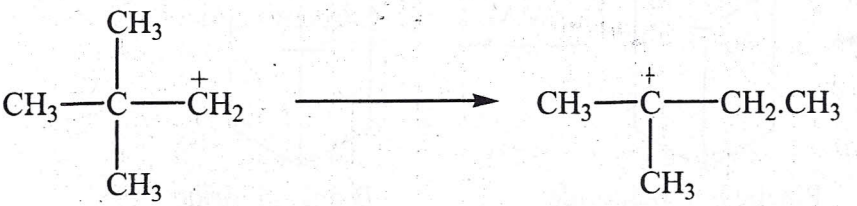
1-Aminomethyl Cyclohexanol

Cycloheptanone (40%)

The yield of cycloheptanone is considerably better than can be achieved from readily available compound via a ring closure reaction.

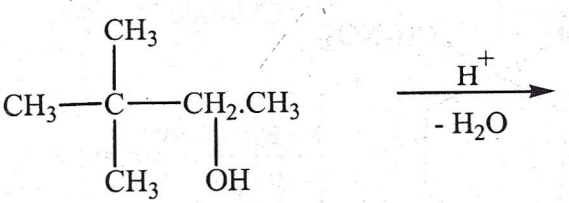
4.6.7 Wagner-Meerwein rearrangements

One of the simplest systems in which carbon migrates with its bonding pair of electrons to an electro-deficient carbon atom is the neopentyl cation.

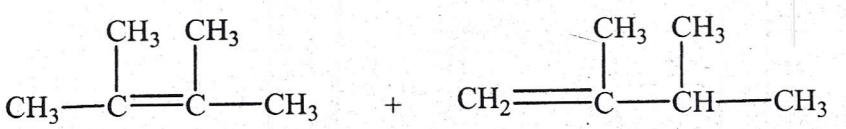


Neopentyl cation *t* - Pentylcation

Thus all reactions in which neopentyl cation is formed as an intermediate produce compounds derived from the t-phenyl cation. For example, the acid catalysed dehydration of 3,3-dimethyl-2-α-butanol affords very little the expected compound 3,3-dimethyl-1-butane, but yields mainly a mixture of 2,3-dimethyl-2-butene and 2,3-dimethyl-1-butene.

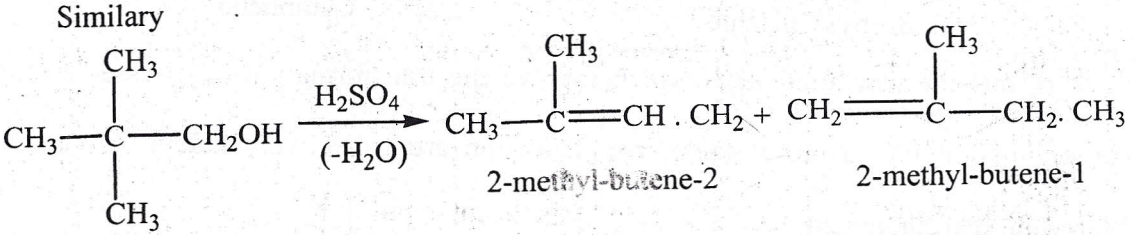


3, 3 - Dimethyl-2-butanol



2, 3 - Dimethyl - 2 - butene 2, 3 - Dimethyl -1- butene

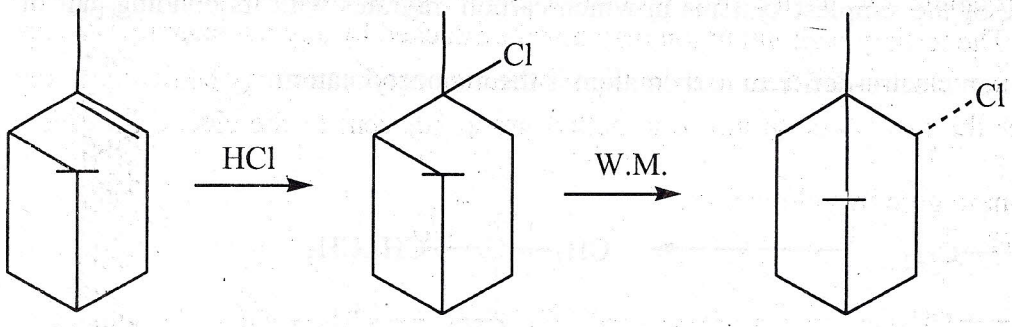
Similary



Neopentyl alcohol 2-methyl-butene-2 2-methyl-butene-1

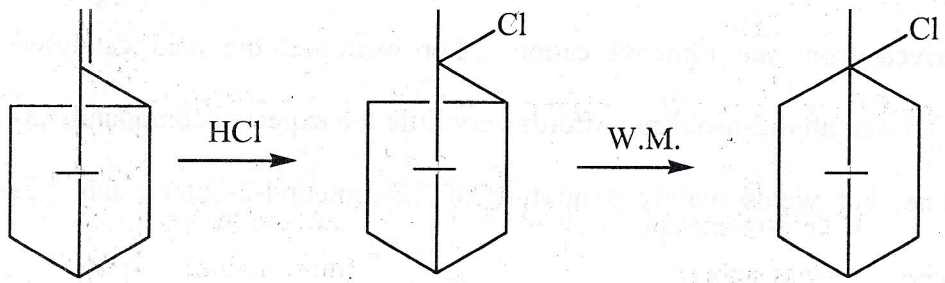
The rearrangement is also exhibited by alicyclic compounds, the important examples are given below.

a) Pinene hydrochloride to bornyl chloride



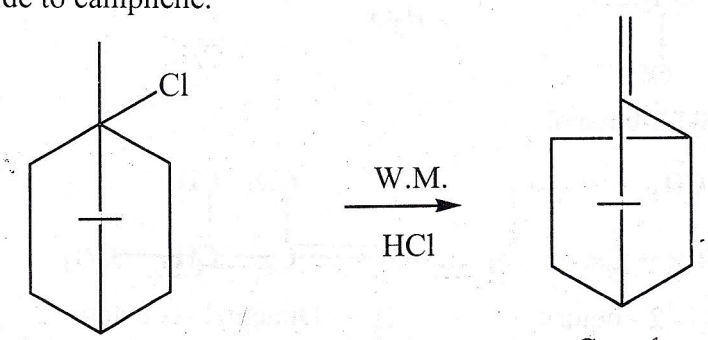
α-Pinene Pinene hydrochloride B only chloride

b) Camphene hydrochloride to isobornyl chloride.



Camphene Camphene hydrochloride Isobornyl Chloride

c) Bornyl chloride to camphene.

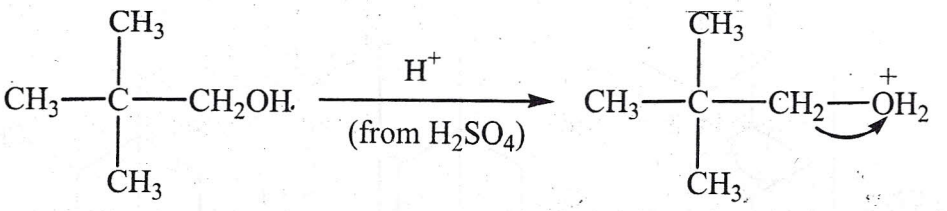


Bornyl Chloride Camphene

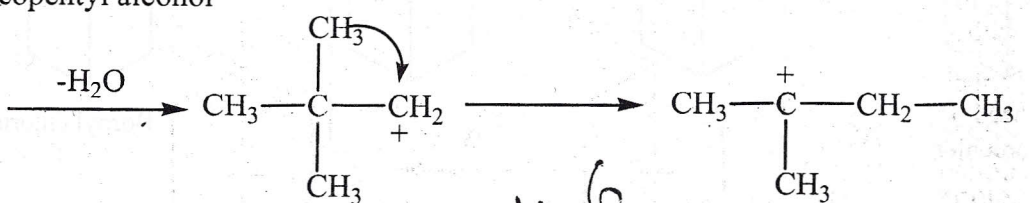
Thus the rearrangements which involve the transformation of a lesser stable carbonium ion into a more stable carb ium ion are collectively known asWagner Meerwein rearrangement.

Mechanism : The first stage of the reaction is the protonation of the hydroxyl group followed by the loss of water molecule to yield a carbonium ion. Now since the so

formed primary carbonium ion is relatively unstable, it rearranges itself to a more stable tertiary carbenium ion by the migration of a methyl group with its pair of bonding electrons. The tertiary carbonium ion may now be attacked by any nucleophilic species present in the reaction medium to form the substitution product or may be deprotonated form either the methylene group or a methyl group adjacent to the electron deficient carbon atom to give two olefins.

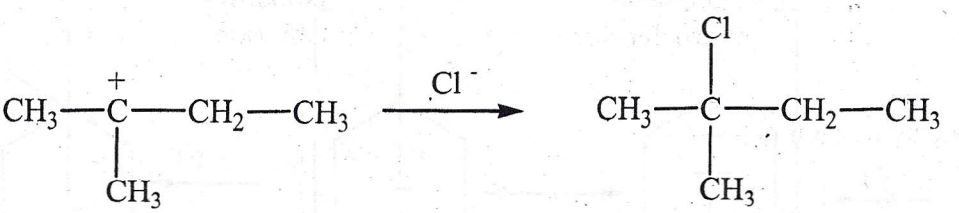


Neopentyl alcohol

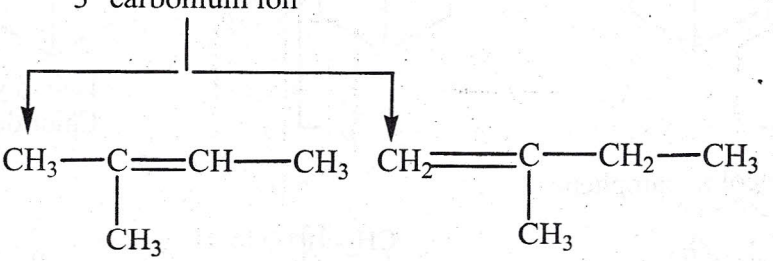


1° carbonium ion (less stable)

3° carbonium ion (more stable)



3° carbonium ion

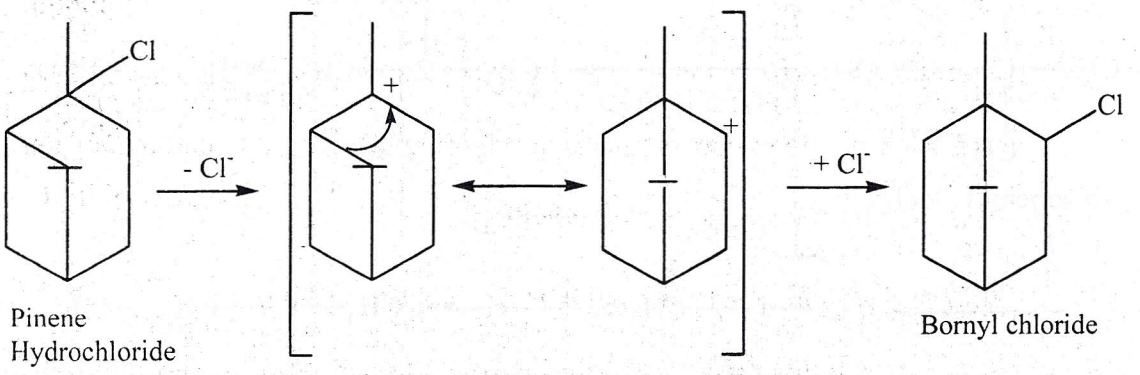


So in this case it is important to note that the driving force for the rearrangement resides in two factors viz., i) the greater stability of the resulting tertiary carbonium ion than a primary carbonium ion, and (ii) steric repulsion between the three methyl groups of the starting material which is reduced when one of the methyl groups moves to the

adjacent carbon. Rearrangement is especially favourable under these circumstances, and less so when a secondary carbonium ion is formed.

Mechanism in allcyclic system (bicyclic terpenoids)

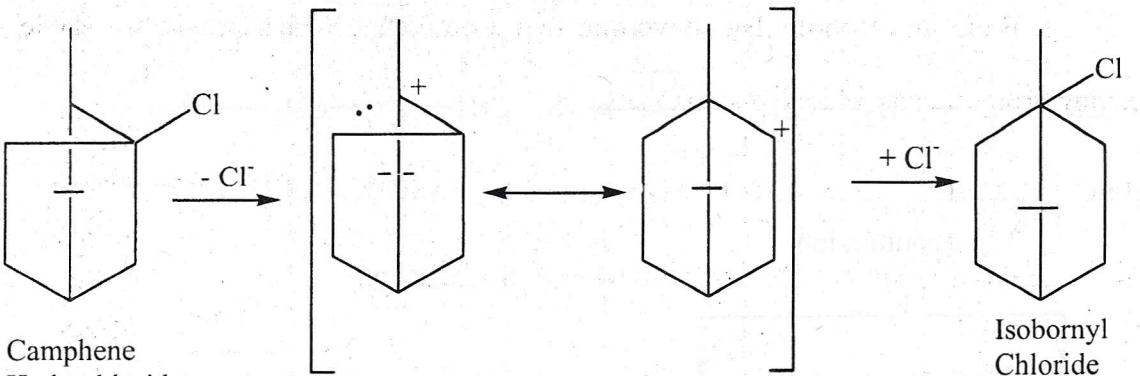
a) Pinene hydrochloride to bornyl chloride.



Pinene Hydrochloride

Bornyl chloride

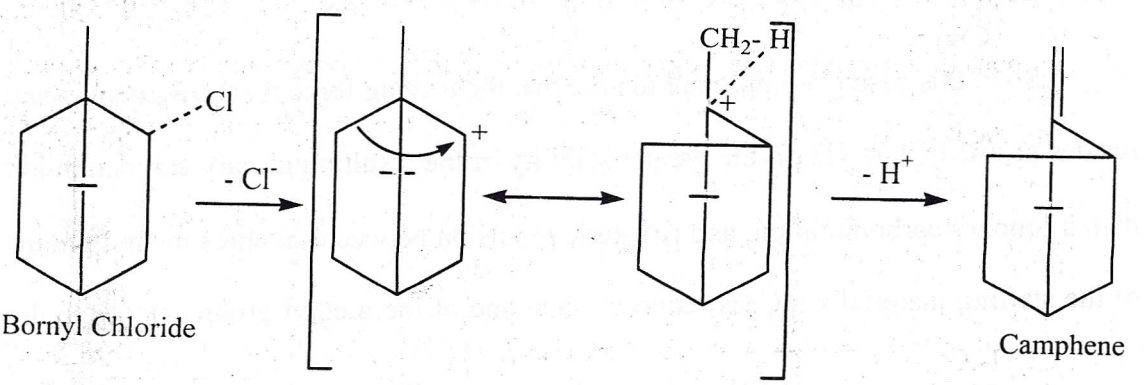
b) Camphene hydrochloride to isobornyl chloride.



Camphene Hydrochloride

Isobornyl Chloride

c) Bornyl chloride or borneol to camphene.



Bornyl Chloride

Camphene

Note that in the first example the relief of strain (i.e., the transformation of the strained four membered ring into the less strained five membered analogue) provides a powerful driving force for rearrangement.

Principle features of Wagner-Meerwein rearrangement.

1. The carbonium ion in general may be generated in a variety of ways.

   a. From a halide : By using a strongly ionizing solvent or by adding a Lewis acid such as silver ion or mercuric chloride which helps carbonium ion formation by abstracting the halide ion, e.g.

   $Me_3C - CH_2 - Cl + Ag^+ \rightarrow Me_3C - {}^+CH_2 + AgCl$

   b. From an alcohol : By treatment with acid to promote heterolysis, e.g.

   $$Me_3C - CH_2 - OH \underset{}{\overset{H^+}{\rightleftharpoons}} Me_3C - {}^+CH_2 + H_2O$$

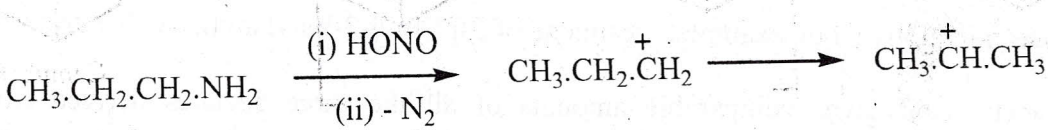
   c. From an alcohol : By converting into a derivative which provides a stable leaving group suchas toluene p-sulphonate, e.g.

$Me_3C - CH_2 - OSO_2.C_6H_4.CH_3\text{-}P \rightarrow Me_3C - {}^+CH_2 + O^-SO_2.C_6H_4.CH_3\text{-}P$

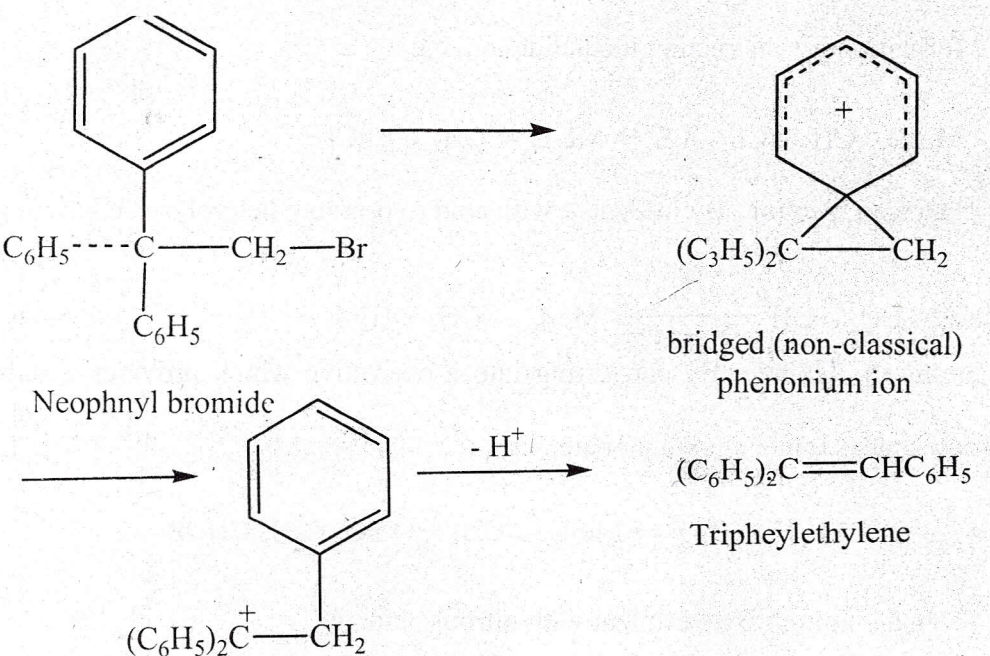
   d. From an amine : By treatment with nitrous acid., e..

$$Me_3C - CH_2 - NH_2 \xrightarrow{HONO} Me_3C - CH_2 + N^+ \equiv N \xrightarrow{-N_2} Me_3C - {}^+CH_2$$

2. The migratory group may be hydrogen atom, aryl or alkyl group. The two important examples of hydrogen migrations in the carbonium ion rearrangement are mentioned below.



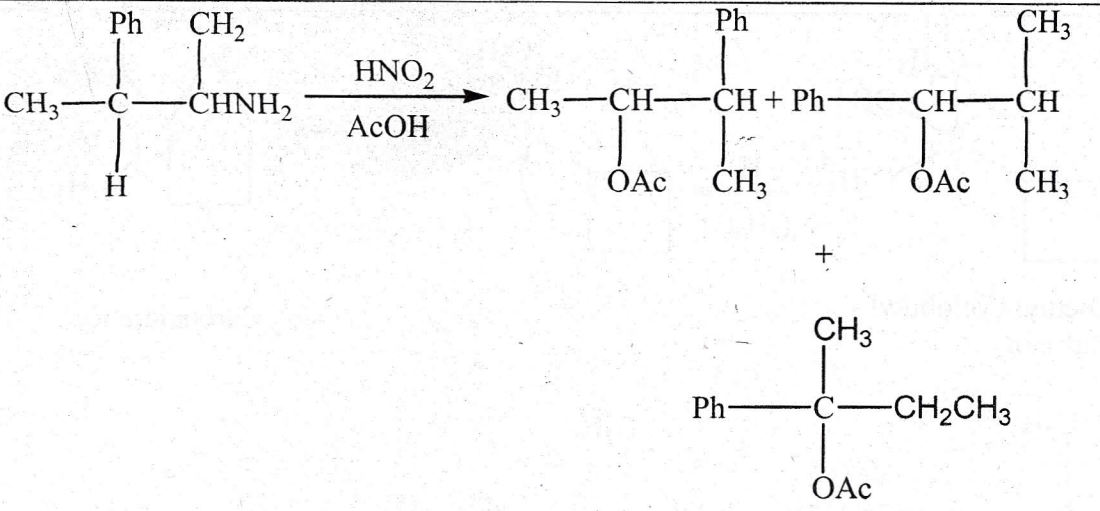
Among the aryl and alkyl groups,aryl groups have a far greater migratory aptitude than alkyl groups. For example, neophyl bromide undergoes solvolysis with rearrangement many thousand times faster than neopentyl bromide under the same conditions. This difference in the rate of reaction is due to the fact that the rate determining step in the reaction of neopentyl bromide involves the formation of the high energy primary carbonium ion, whereas the reaction of neophyl bromide involves the formation of a lower energy bridged carbonium ion.



The aryl group is said to provide anchimeric assistance to the reaction.

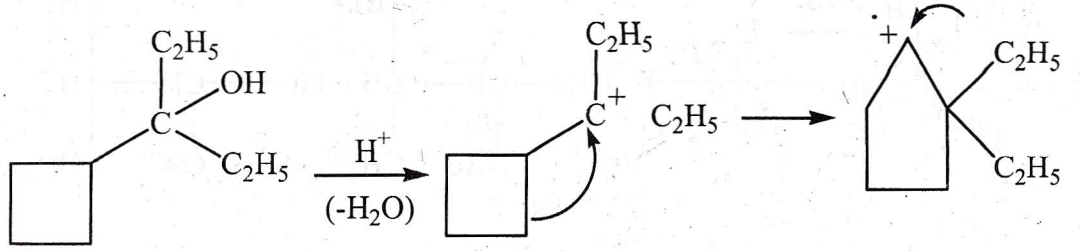
The presence of electron releasing group in the aromatic ring (e.g. P-OCH_3) increases the rate of migration of the aryl group while the electron-attracting (e.g., P-Cl) lowers the rate of migration.

However, it is important to note that the enormously greater tendency for rearrangement of aryl groups than of alkyl groups or hydrogen does not apply to deaminations. For example, treatment of 3-phenyl-2-butylamine with nitrous acid in acetic acid gives comparable amounts of all the three acetates derived from the with sodium alkoxide.



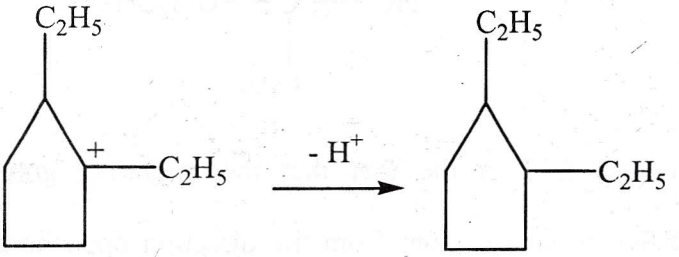
3. The rearrangement is stereospecific in the fact that the migrating group approaches the electron deficient carbon atom from the direction opposite to that in which the departing group is moving (cf S_N^2 reaction). Thus inversion of configuration occurs at the electron deficient carbon. The stereospecificity of the reaction has significant consequences in alicyclic chemistry

4. In some cases two or more rearrangements may occur successively. For example, the initial carbonium ion obtained by treating diethylcyclobutylcarbinol with acid rearranges by ring expansion (relief of strain) to a secondary carbonium ion which in turn undergoes a further rearrangement to yield a tertiary carbonium ion. The latter then undergoes deprotonation and forms the olefin.



Diethyl cyclobutyl - carbinol

sec - Carbonium ion

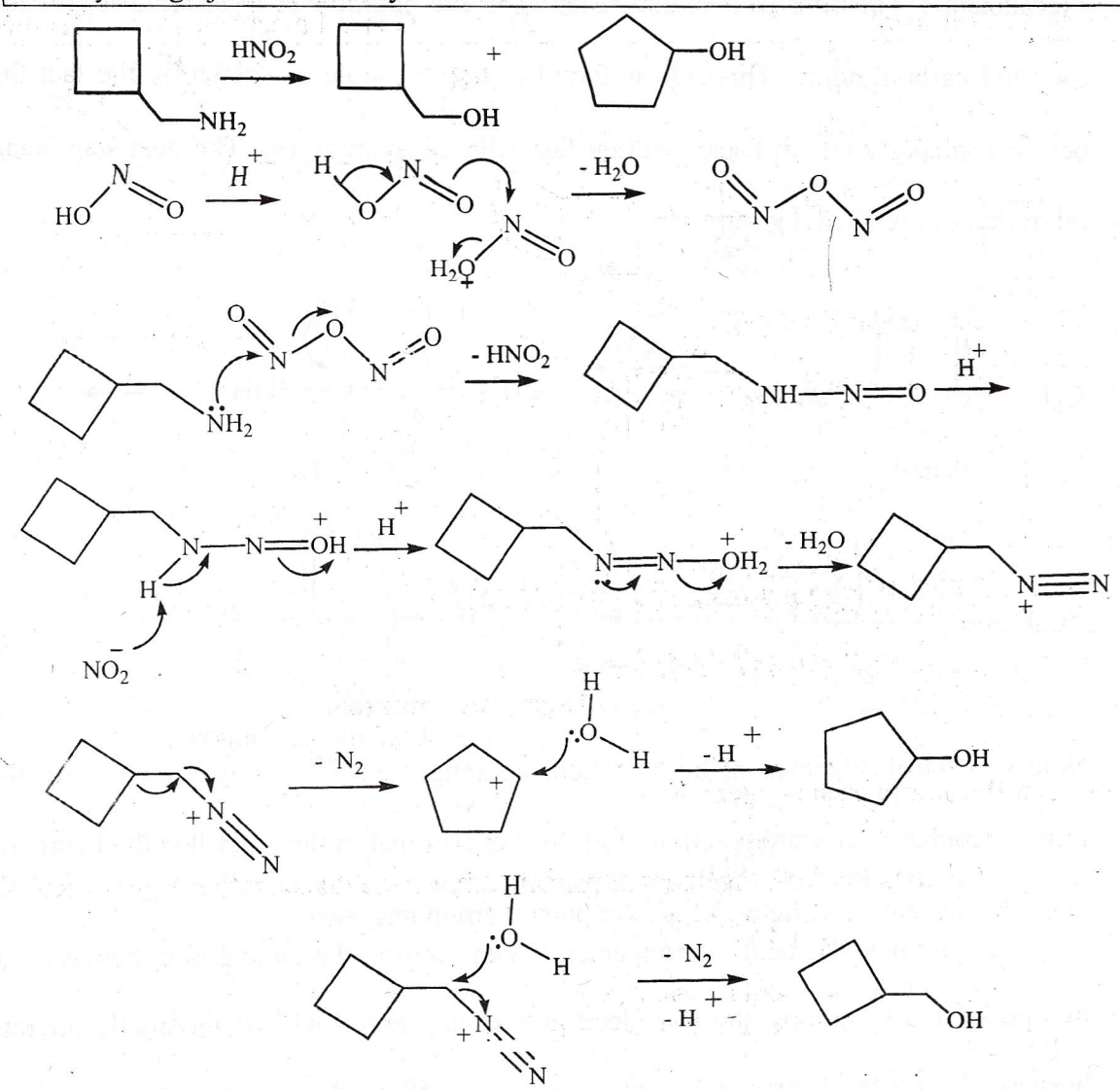


t - Carbonium ion

1, 2 - Diethyl cyclopentene

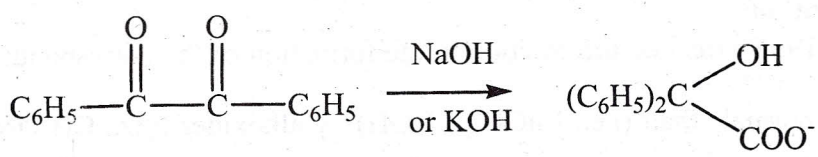
4.6.8 Demjanov rearrangement

Carbocation rearrangement of primary amines via diazotization to give alcohols.



4.6.9 Benzil-Benzilic acid rearrangement

The transformation of α-diketones (Benzil) to α-hydroxy acids by means of hydroxide ion is known as benzilic acid rearrangement. The best known example is the conversion of benzyl into benzilic anion.

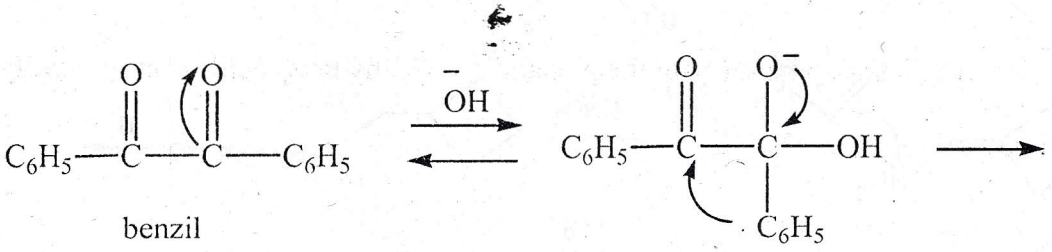


Benzil

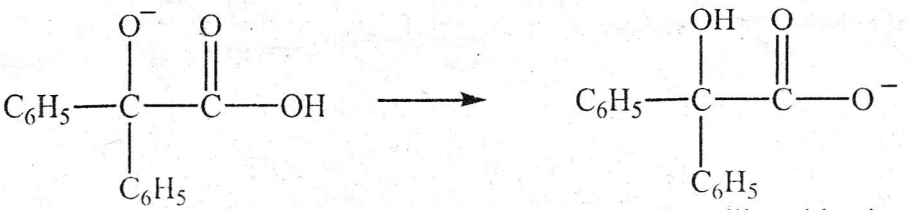
Benzitic acid anion

Pfeif in 1956 observed that barium and thallous hydroxides are more effective than the

Mechanism : The first step of the reaction is the addition of hydroxide ion to the carbonyl carbon atom. This step is found to be reversible as shown by the fact the benzyl exchanges O^{18} in basic solution faster than it rearranges. The next step being migration of the phenyl group.



benzil



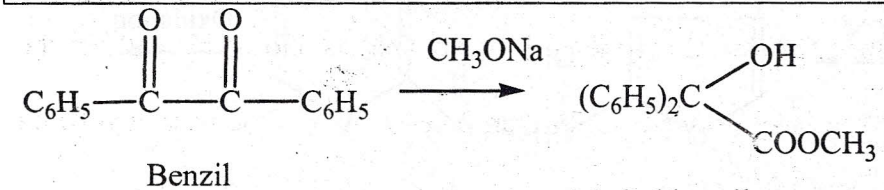
Benzilic acid anion

Note that the mechanism of benzilic acid rearrangement is exactly analog s to the intramolecular cannizzaro reaction of glyoxal except that in the latter it is the hydrogen atom that migrates, while in the former phenyl group migrates.

In the benzilic acid rearrangement when there is the competition between the two possible aryl groups, the less electron releasing group will preferentially migrate because the more electron releasing aryl group will tend to neutralize the positive charge on the carbonyl carbon atom to which it is attached by supplying the electrons and thus the hydroxide ion will attack carbon atom of the other carbonyl group. Since a phenyl group is involved, it is possible that during this 1,2-shift a phenonium ion is formed as an intermediate.

Extension and applications

Deoring et al. 1956 extended the reaction to the formation of the corresponding ester by replacing the normal alkali (i.e., NaOH or KOH) by alkoxides (viz., CH_3ONa, Me_3COK, etc.). thus benzyl may directly be converted into alkyl benzilate by treatment

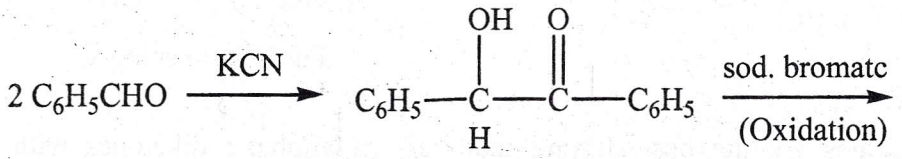


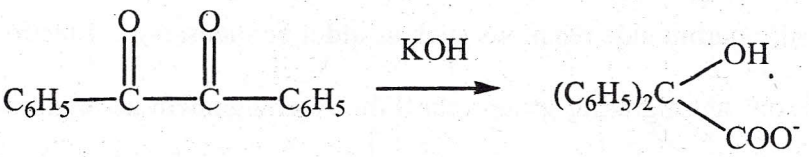
Benzil

Methyl benzilate

The reaction may be used for the preparation of α-hydroxy acids from the easily accessible starting materials, e.g.,

a)

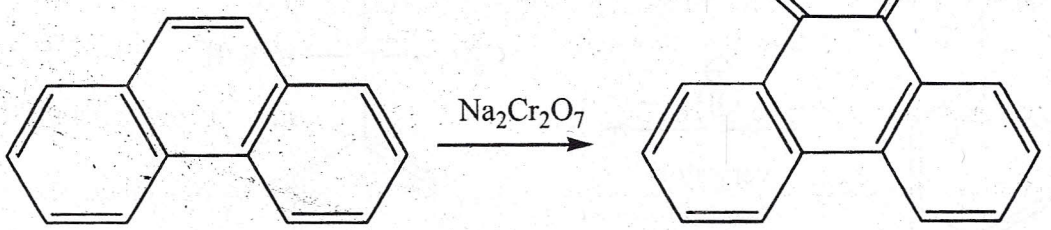




Benzil

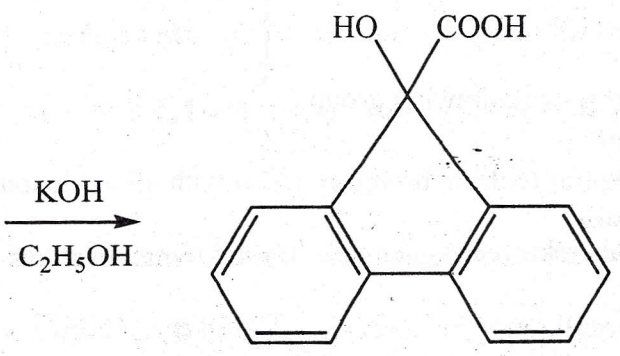
Benzitic acid anion

b)



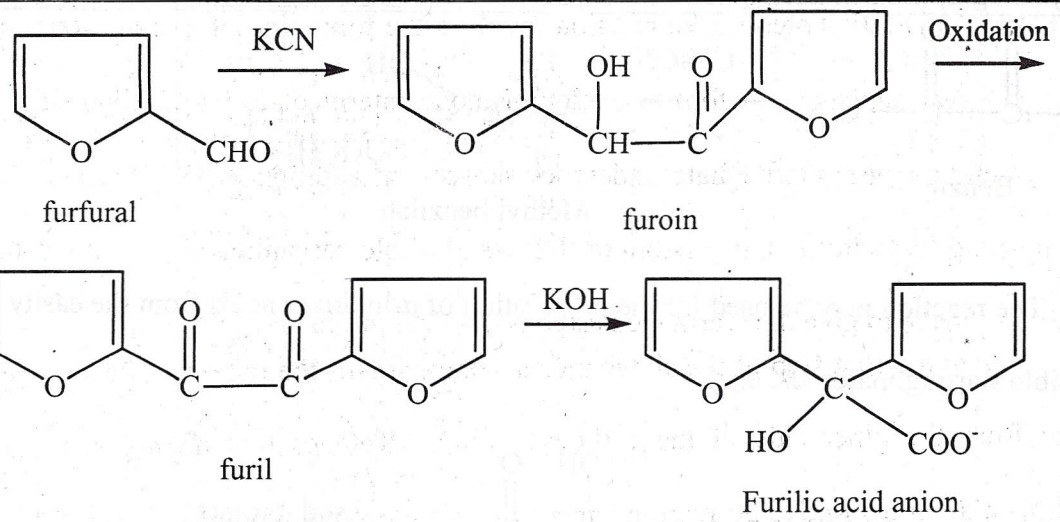
Phenanthrene

9, 10-phenathraquinone

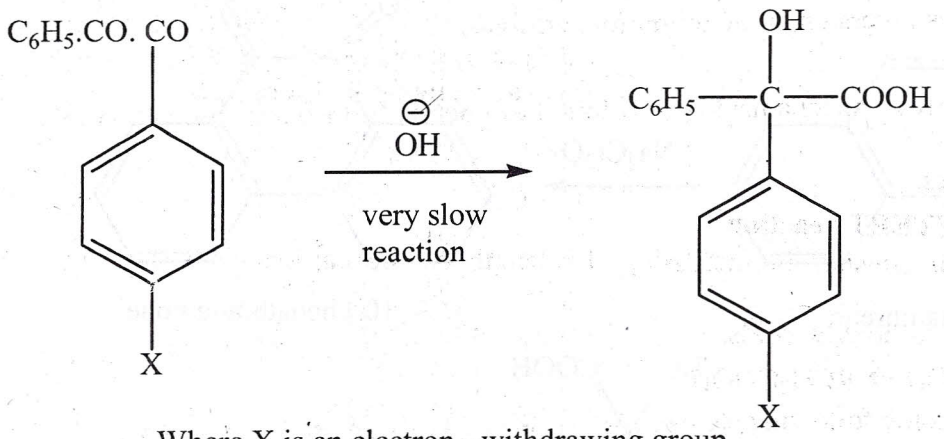


9-hydroxyfluorene-9-carboxylic acid

c)



Diaryl diketones are the best starting materials as aliphatic diketones with enolizable hydrogen usually permit side reactions such as aldol condensation. Electron withdrawing substituents on the migrating group retard the rearrangement as might be expected, since the migration is to an electron poor carbonyl carbon atom.



Where X is an electron - withdrawing group

4.6.10 Favarskii rearrangement

The reaction of α-haloketones (chloro, bromo or iodo) with alkoxide ion to give rearranged esters is called the favorskii rearrangement. Cyclic α—haloketones lead to ring contraction

In case, hydroxide ion (or) an amine is used as base in place of alkaxide ion, the final product is free acid (as salt) and amide respectively.

Mechanism : The first step of the reaction involves the formation of a carbanion with undergoes rearrangement to form a cyclopropanone intermediate I (1,3-elimination). The cyclopropanone intermediate undergoes subsequent addition of OH^- followed by ring opening to yield the more stable of the two possible carbanions followed by the proton exchange to give the rearranged ester as the final product.

Note the first step of the above mechanism involves the removal of α-hydrogen atom from the other side of the carbonyl group. Ketones that do not have such hydrogen atom also undergo rearrangement to give the same type of product. This is usually called the quasi-Favorskii rearrangement. An example is found in the preparation of demerol.

The mechanism of quasi Favorskii rearrangement does not involve the formation of cyclopropanone intermediate. The mechanism called semibenzillic mechanism involves inversion at the migration terminus.

The semibenzilic mechanism is also found to operate in the ring contraction of α-nalocylobutanones.

4.6.11 ARNDT-EISTERT reaction

The reaction consists in increasing the length of the carbon chain by one methylene group in carboxylic acids.

$$RCOOH \rightarrow RCH_2COOH$$

The reaction involves the following stems :

The acid is first converted to acid chloride which reacts with excess of diazomethane to form diazoketone. The latter on irradiation with light of heating with Ag_2O in the presence of water splits off nitrogen and rearranges to ketene (this rearrangement of diazoketone to ketene is known as Wolff rearrangement). The ketene then reacts with water to form a higher homologue of the starting acid.

$$RCOOH \xrightarrow{SOCl_2} RCOCl \xrightarrow[-CH_3Cl-N_2]{2CH_2N_2} RCOCHN_2 \xrightarrow{Ag_2O} R-CH=C=O \xrightarrow{H_2O} RCH_2COOH$$

Excess of diazomethane is used to consume the liberated hydrochloric acid

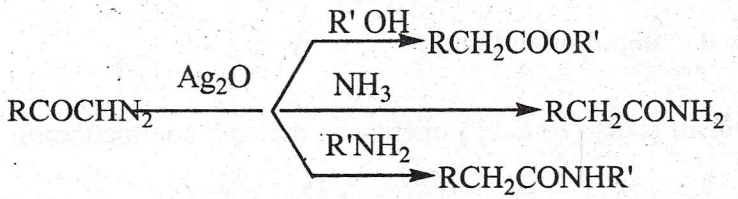
$$RCOCl + CH_2N_2 \rightarrow RCOCHN_2 + HCl$$

$$CH_2N_2 + HCl \rightarrow CH3Cl + N_2$$

In absence of excess diazomethane, diazoketone is lost in reacting with HCL to form chloromethyl ketone.

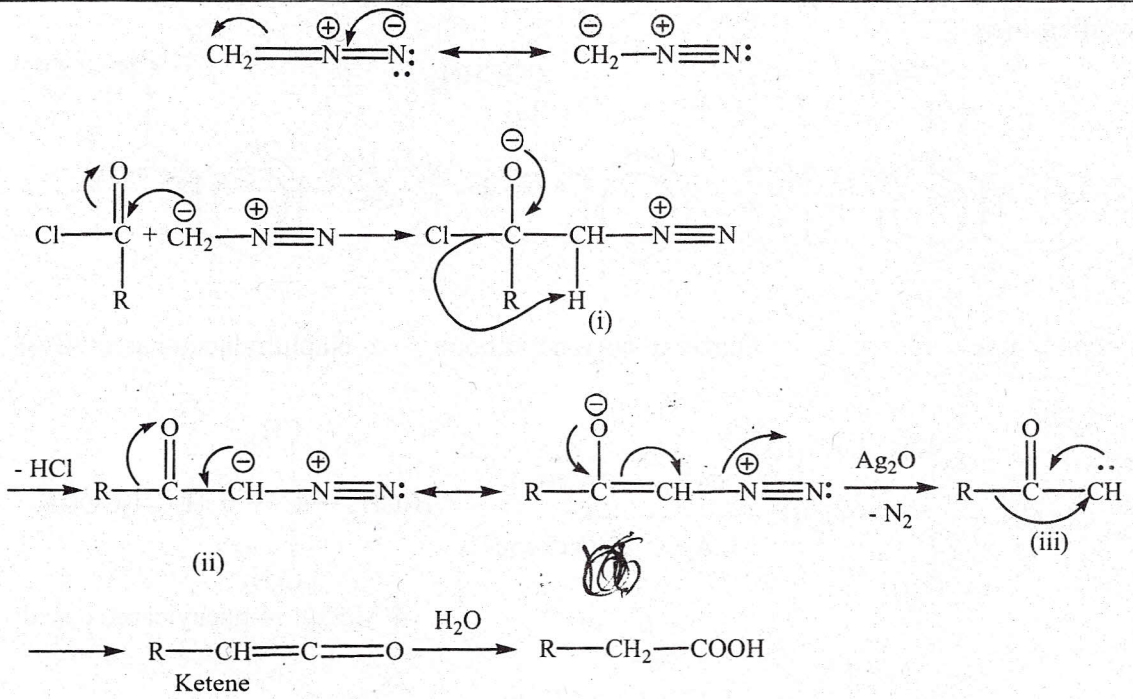
$$RCOCHN_2 + HCl \rightarrow RCOCH_2Cl + N_2$$

If alcohol, ammonia or amine is present in place of water then ester, amide or substituted amide respectively is formed



Besides Ag_2O, the reaction is catalysed by colloidal platinum, silver, copper, etc., and sometimes heat. The group R may be alkyl, aryl, heterocyclic or alicyclic and may contain reducible groups which remain unaffected. Acidic groups react with diazomethane and diazoketone.

Mechanism : Nucleophilic attack of diazomethane on the carbonyl carbon of the acid chloride gives an intermediate (i) which eliminates a molecule of HCl to give diazoketone (ii). Diazoketone then splits off a molecule of nitrogen to form a carbene (iii) which rearranges to ketene. The highly reactive ketene readily reacts with the nucleophile present (H_2O) to form the next higher acid.



The presence of carbine (iii) has not been detected and therefore the two steps – splitting of nitrogen and migration of R group – may be concerted.

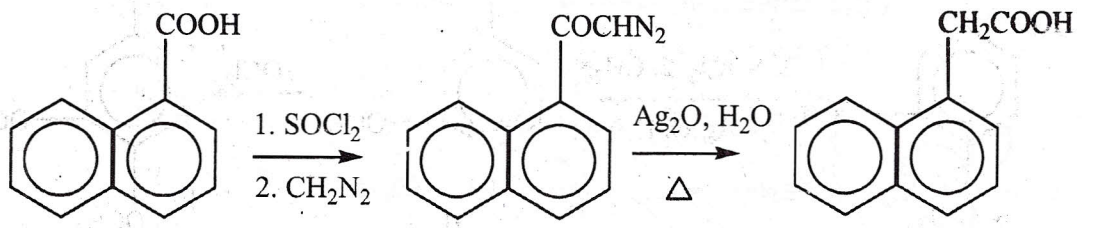
$$RCOCHN_2 \xrightarrow[H_2O]{Ag_2O} RCH_2COOH$$

The mechanism has been supported by the fact that ketones have been isolated or trapped. Further, isotopic labeling experiment has shown that the carbonyl carbon of diazoketone is present in the resulting acid as the carboxyl carbon.

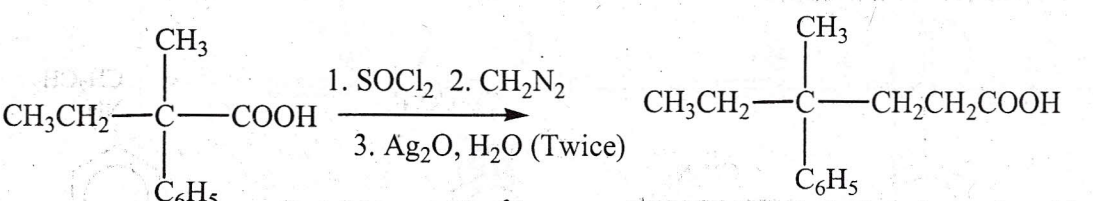
The group R migrates with retention of configuration, for an optically active acid on conversion to its higher homologue and subsequent Barbier-Weiland and degration gives the original acid with the same configuration.

Mild reaction conditions permit this synthesis without affecting complex or reducible groups in the substrate. The yield is high. It has, therefore, many synthetic applications, especially in the field of natural products.

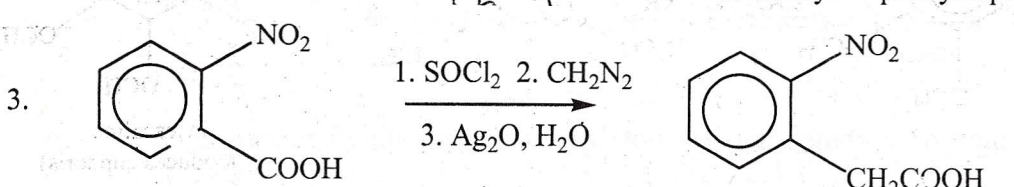
Applications

1. 

α - Naphthoic acid Diazo–α–acetonaphthone α–Naphthylacetic acid(80%)

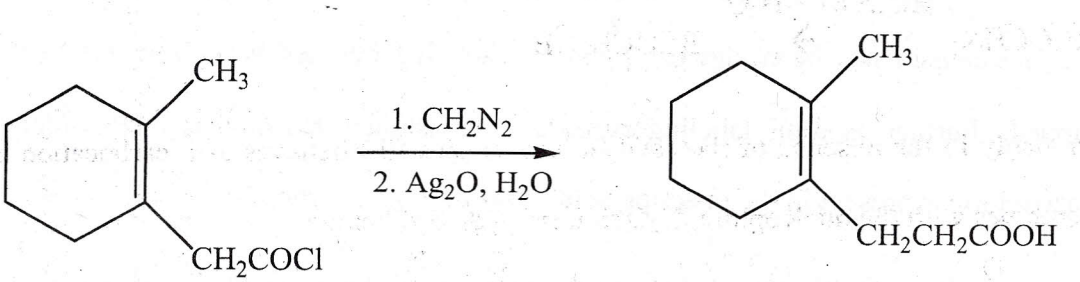
2. 

4-Methyl -4-phenylcaproic acid

3. 

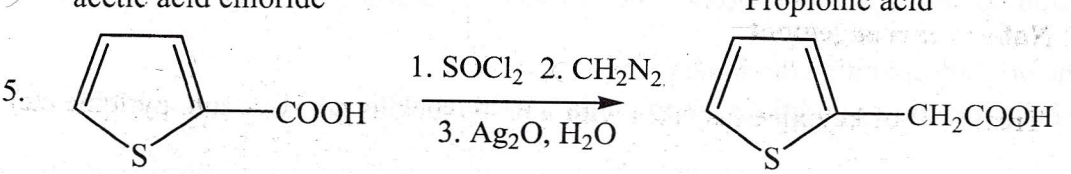
o-Nitrobenzoic acid 2-Nitrophenylacetic acid

4. Double bond in the substrate remains unaffected



2 - Methyl cyclohexenyl acetic acid chloride

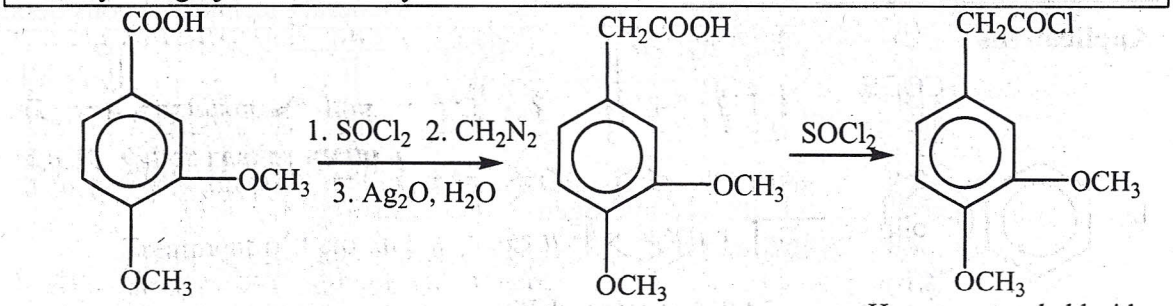
2 - Methyl cyclohexenyl Propionic acid

5. 

2 - Thienylacetic Acid

6. **Synthesis of homoveratroyl chloride, an intermediate for papaverine synthesis**

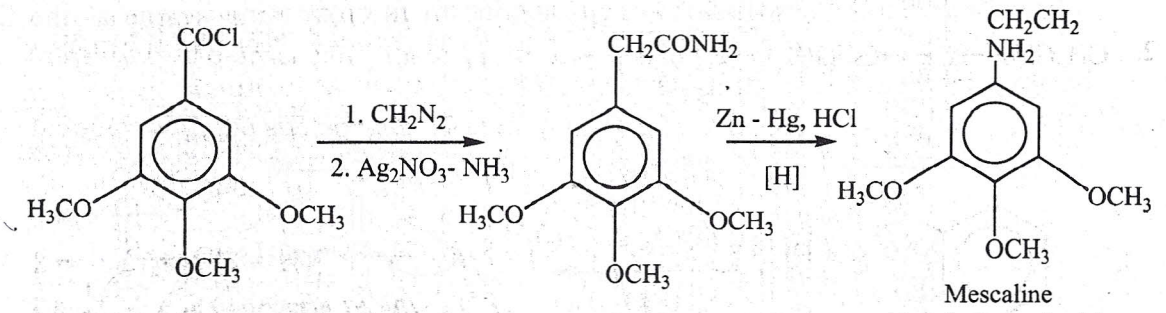
migration of phenyl, methyl and hydrogen.



3,4-Dimethoxy benzoic acid

Homoveratroyl chloride

7. Synthesis of mescaline.

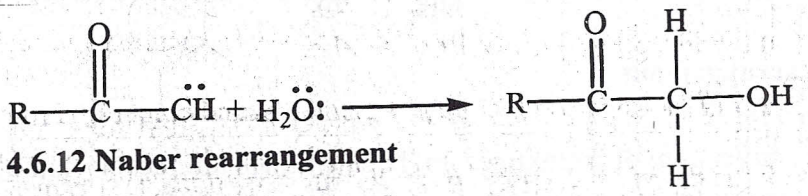


Mescaline
(produces euphoris)

8. Diazoketones on treatment with aqueous formic acid give hydroxyl ketones

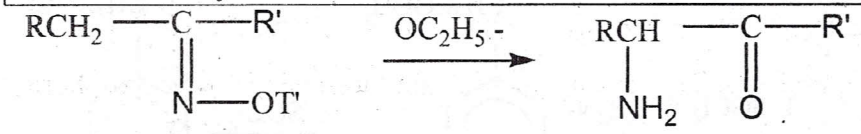
$$RCOCHN_2 \xrightarrow{HCOOH + H_2O} RCOCH_2OH$$

Probably in the absence of the catalyst, the species (iii) behaves as a carbocation and combines with the nucleophile, H_2O to form hydroxyl ketone



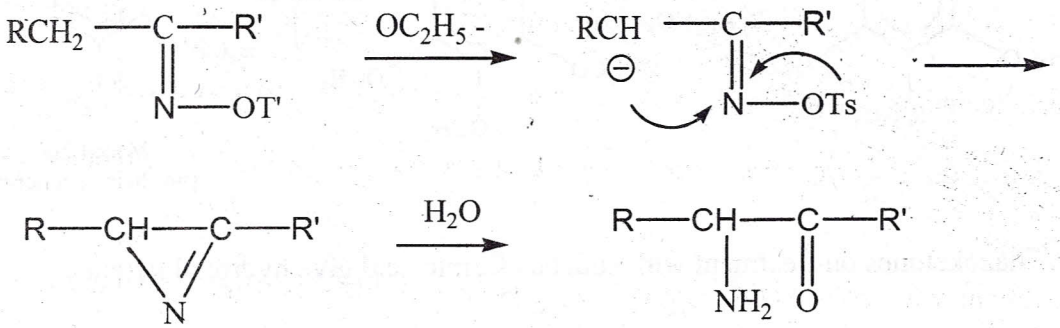
4.6.12 Naber rearrangement

Treatment of ketoxine tasylates with a base (such as ethoxide ion, pyridine etc) to form α-amino ketones is known as Neber rearrangement.



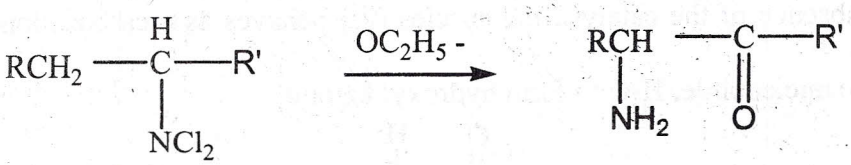
Where R = Aryl, alkyl or hydrogen
R' = Alkyl or aryl

Mechanism : The complete mechanism consists (or) three steps (1) the loss of more acidic proton to form carbonium (2) rearrangement of carbanion to form azirine intermediate and (3) Hydrolysis of the ozirine to form α-amino ketone as the final product.



Azirine intermediate

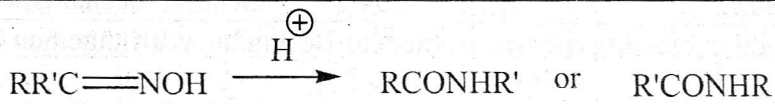
Neber rearrangement can also be applied to N, N-dichloro-amines.



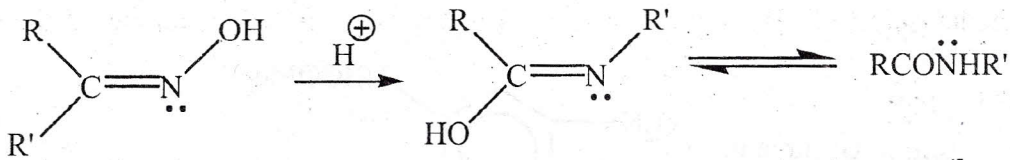
4.5.13 Beckmann rearrangement

The acid catalyzed conversion of ketoximes to N-substituted amides is known as Beckmann rearrangement. The [illegible]s catalysed by acidic reagents such as, H_2SO_4, $SOCl_2$, SO_3, P_2O_5, PCl_5, $C_6H_5SO_2Cl$, etc.

The reaction involves the migration of a group from carbon to electron-d[illegible]cient nitrogen.

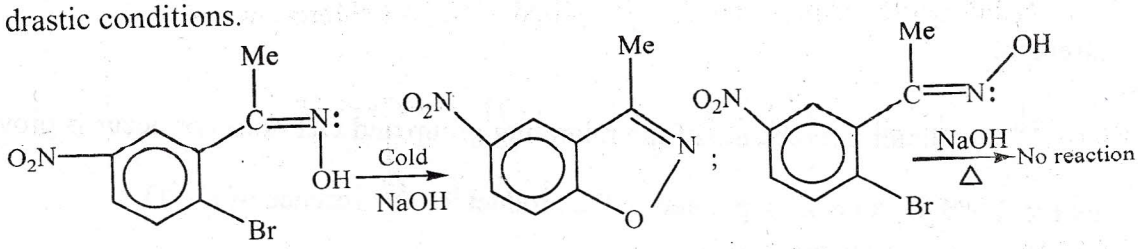


Some aldoximes undergo the rearrangement in the presence of polyphosphoric acid (PPA) but the reaction is not a general one. The migration of the group depends not on the migratinal aptitude but upon the orientation of the group in relation of the OH group. It is found that the migrating group is always anti (i.e., rrans) to the hydroxyl group. Thus, the reaction is stereospecific.



That it is always the antigroup which migrates has been has been confirmed by the rearrangements of the two isomeric oximes of 2-bromo-5-nitroacetophenone. The structures of the two isomeric oximes were first determined by an elegant method as given below.

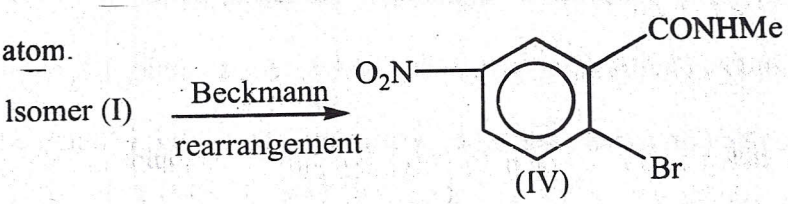
On treatment with cold NaOH solution, one isomer (I) was cyclized to 3-methyl-5-nitrophenyl isooxazoine (III) while the other isomer(II) remained unaffected even under drastic conditions.



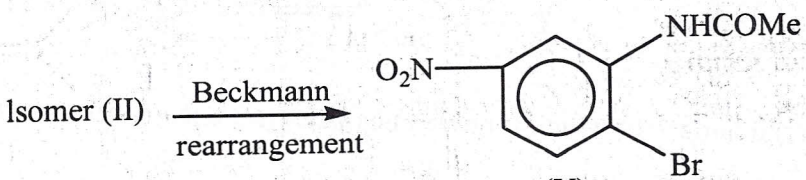
(I) (III) (II)

Obviously, the OH and Br groups in isomer (i) are close enough for reaction and cyclization. Hence, the Me and OH groups are anti i.e., trans) to each other. In isomer (ii), the OH and Br groups are far apart for reaction, i.e., the Me and Oh groups are syn Ii.e., cis) to each other. Thus, the structures of isomers(i) and (ii) are confirmed.

Now, on subjecting the two isomers to Beckmann rearrangement it is found that (a) isomer (i) gives N-methyl-2-bromo-5-nitrobenzamide (iv) indicating the migration of the antigroup Me to the nitrogen atom and (b) isomer(ii) gives N-(2-bromo-5-nitrophenyl)-acetamide (v) dueto the migration of the anti-aryl group to the nitrogen atom.



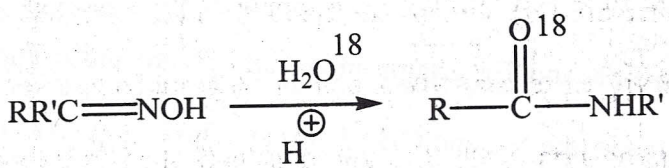
(IV)



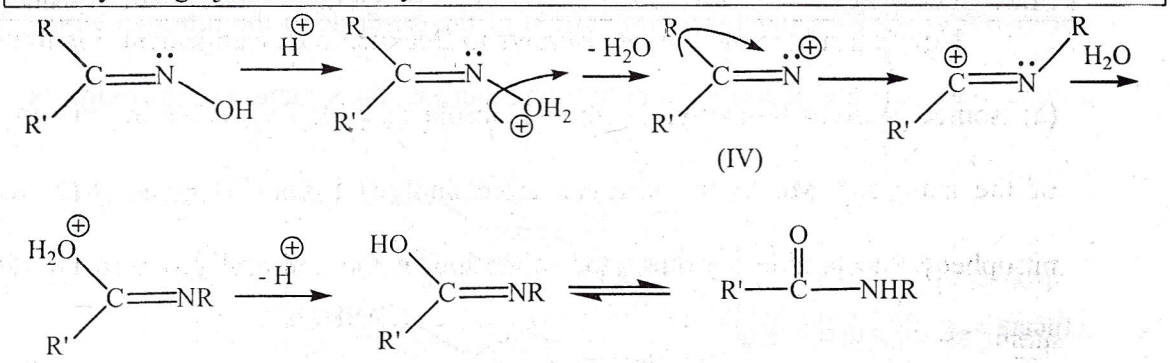
(V)

Oxime esters and ethers also undergo Beckmann rearrangement. The acidic reagents convert the OH group to a better leaving group-acids convert OH to H_2O, other reagents convert OH to an ester-leaving group, e.g., $OPCl_4$ from PCl_5, $OSO_2C_6H_5$ etc. The reaction is facilitated by heat, polar solvents or an increase in the acid strength.

The direct interchange of the migrating group and OH does not occur is proved by the fact that ^{18}O is incorporated in the product in the presence of $H_2{}^{18}O$.

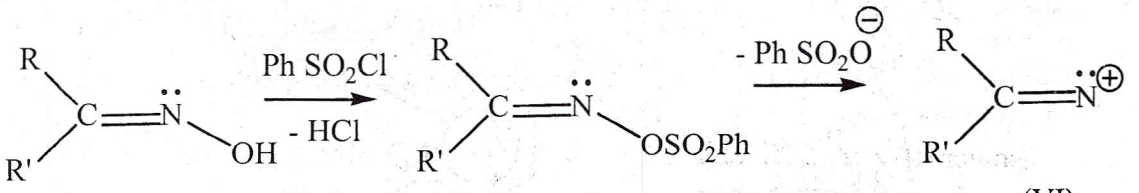


Mechanism : The mechanism of the reaction has been suggested as given below.



(IV)

With other acidic reagents, e.g., $PhSO_2Cl$. the same intermediate (VI) is obtained.



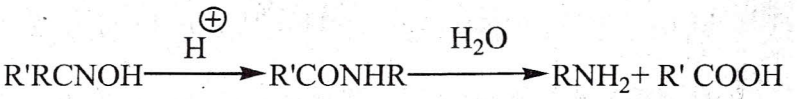
(VI)

In strong acids,the reaction proceeds with the protonation of the OH group of the oxime with subsequent loss of water to yield the species (VI) with electron-deficient nitrogen which is also obtained with other acidic reagents by the loss of ester group. The migration of R then gives a carbocation. The attack of water molecule on the carbon followed by the loss of proton given the amide.

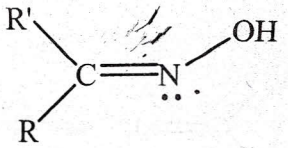
The migrating group retains its configuration and hence the migrating group does not become completely free during the migration, otherwise the reaction can not be stereospecific. Thus, the migfation and the breaking of N-O bond may be concerted or at least very rapid. This has been supported by crossover experimens.

Applications

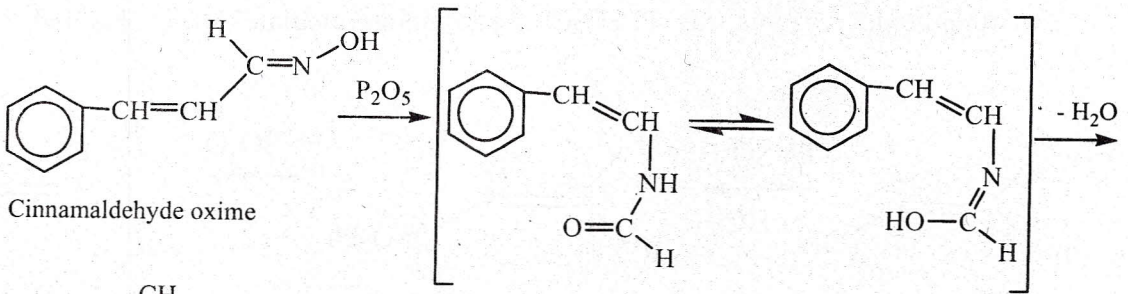
1. configuration of ketoximes can be assigned : A ketoxime gives an amide on Beckmann rearrangement. From the products of hydrolysis of the amide, the structure of the amide is known and for that matter, the configuration of the oxime is known.



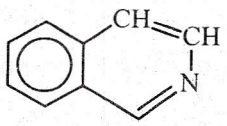
Formation of RNH_2 indicates the migration of the group R to the nitrogen atom. The groups R and OH are, therefore, anti to each other i.e., the structure of the oxime is



2. synthesis of isoquinoline



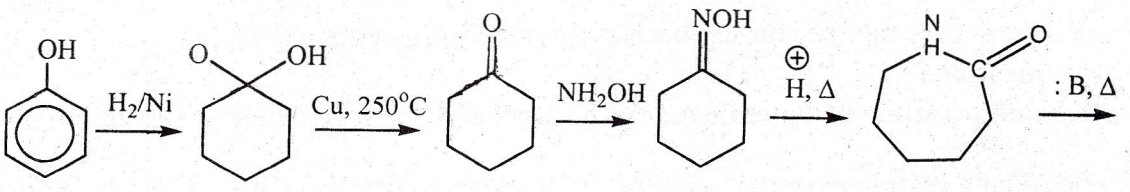
Cinnamaldehyde oxime



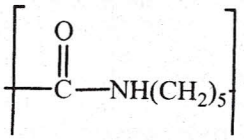
Isoquinoline

3. Synthesis of lactams : Alicyclic ketones of all ring sizes undergo the Beckmann rearrangement of their oximes to yield lactams.

A product of considerable industrial importance is perlon (valuable textile polymer) which is prepared from ω-carprolactam. This is obtained by the Beckmann rearrangement of cyclohexanone oxime it is synthesized from phenol as below.

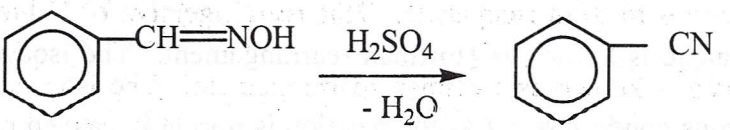


Cyclohexanol Cyclohexanone Cyclohexanone oxime ε- Caprolactam



Similarly, cyclopentanone oxime gives 2-piperidone under Beckmann condition.

Aldoximes under the Beckmann reaction conditions undergo dehydration to nitriles.



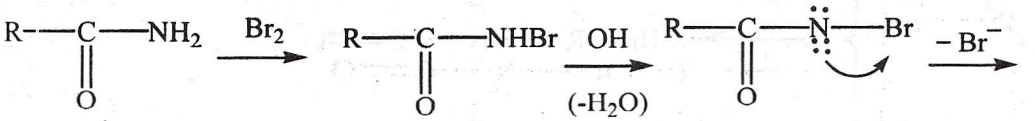
Benzaldoxime Benzonitrile (Phenyl Cyanide)

4.6.14 Hofmann reaction, Hofmann degradation of amides or Hoffman rearrangement

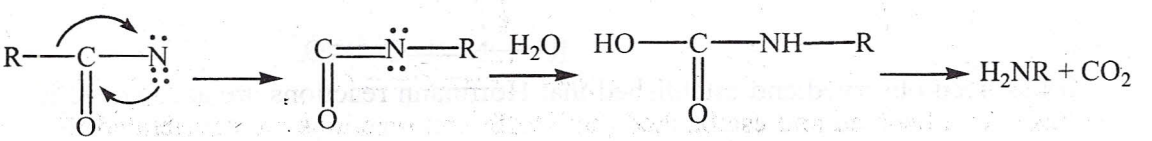
The conversion of an amide to an amine with one carbon atom less by the action of alkaline hypohalite (or) bromine in alkali is known as the Hofmann reaction. The overall reaction for this conversion may be represented as below.

$RCONH_2 + Br_2 + 4\ KOH \rightarrow RNH_2 + 2KBr + K_2CO_3 + 2\ H_2O$

Mechanism : This reaction is found to follow the following path.



Amide N-Bromamide, 1 Anion of N-bromamide, II



III+ Isocyanate + IV, Carbamic acid amine

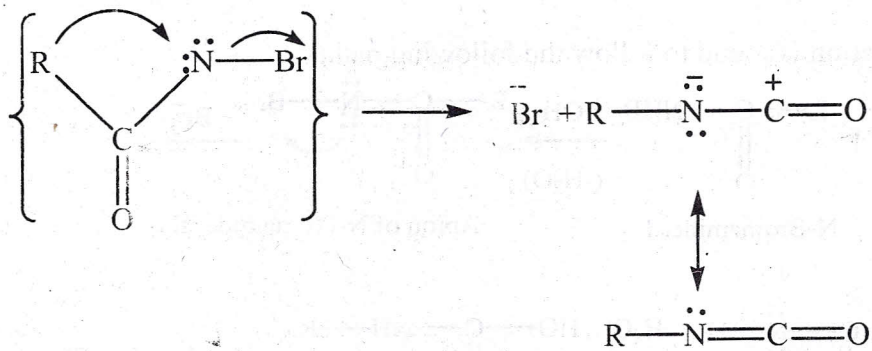
The formation of N-bromamide I, its anion II and isocyanate IV as the intermediate products and hence the above mechanism for Hofmann reaction is proved further reaction with the reagents to yield amine as the final product.

Note that the elimination of bromide ion form the anion of N-bromamide II forms a highly unstable neutral species RCON, which has only a sextet of valency by their isolation under suitable conditions. These intermediate species can undergo

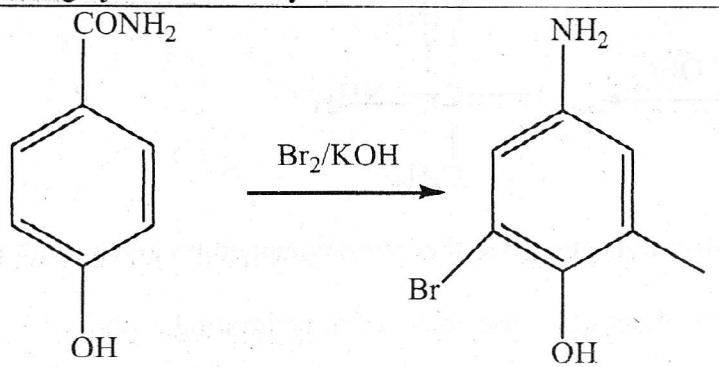
electrons around the nitrogen atom. This species is therefore highly electron deficient on nitrogen and it gains some stability by the migration of the methyl group with its pair of bonding electrons to form isocyanate. This rearrangement of N bromamide or its anion to isocyanate is known as Hoffman rearrangement. The isocyanate may be isolated in anhydrous conditions but as the reaction is normally carried out in aqueous or alcohololic solution the isocyanate is converted into amine or urethane, respectively.

$$\underset{\text{Urethane}}{RNHCOOR^1} \xleftarrow{R^1OH} \underset{\text{Isocyanate}}{R-N=C=O} \xrightarrow{H_2O} \underset{\text{Amine}}{RNH_2 + CO_2}$$

However, Wright (1968) by using ^{14}C – and N^{15} – labelled compounds observed that the intermediate III (acyl nitrene) may not involve during the Hoffman, Curtius and Lossen rearrangements, and the compound II is directly converted into isocyanate i elimination of halide ion and migration of alkyl group take place simultaneously.



It has been observed and established that Hoffmann reactions are accelerated if the migrating group R has an increased electron releasing capacity. A strongly electron donating migrating group not only eases the departure of Br from the bromamide anion, but also enables to satisfy the electron deficiency of the residual nitrogen atom more effectively. Thus the rate of amine formation from p-hydroxy benzamide is more rapid than that for benzamide itself due to the activating effect of the phenolic – OH group.

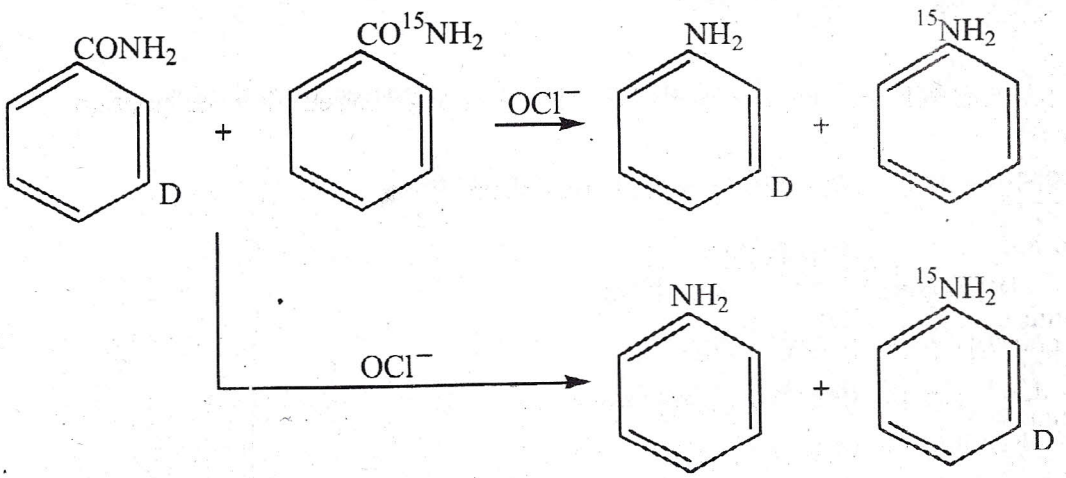


In general, the p-substituted benzamides show the following order of reactivity.

$-OCH_3 > -CH_3 > -H > -Cl > -NO_2$

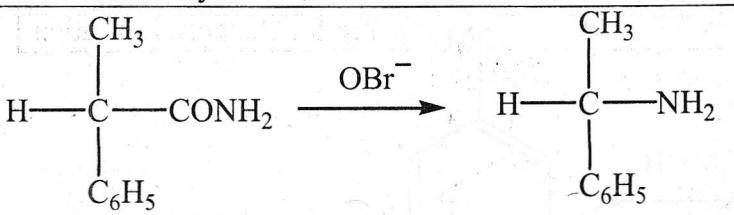
Intramolecular nature of Hoffman rearrangement : The intramolecular nature of the rearrangement can be shown by the following two experiments.

i) When a mixture of m-deuteriobenzamide and benzamide - ^{15}N are treated with alkaline chlorine, only two products (m-deuterioaniline and aniline – ^{15}N) are found to be produced; no cross products is produced which would have been formed if the phenyl group from one molecule had become attached to nitrogen of another.



cross product
(not formed)

ii) When optically active α-phenyl propionamide undergoes the Hoffman degradation, α-phenylethyl amine of the same configuration is obtained.



This reaction also indicates that the rearrangement proceeds with complete retention of configuration about the chiral centre of the migrating group.

Applications : i) Primary aliphatic and aromatic amines : Hoffman reaction provides an efficient route for making both aliphatic and aromatic primary amines from amides containing upto seven carbon atoms, while the higher amides form cyanides which can be converted into amines by reduction.

$$RCONH_2 \xrightarrow{Br_2/KOH} RNH_2$$

Where, R = CH_3 – to C_6H_{13}-

$$RCH_2CONH_2 \xrightarrow{Br_2/KOH} RCN \rightarrow RCH_2NH_2$$

Where, R = > C_6H_{11}-

The following type of primary amines can be prepared from the reaction

a) Preparation of methylamine, alinine, benzylamine etc.

$$CH_3CONH_2 \xrightarrow{Br_2/KOH} CH_3NH_2$$

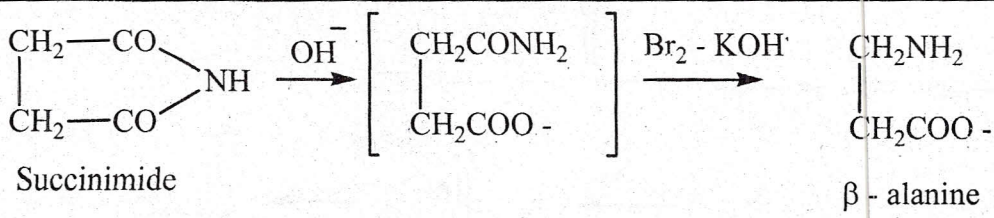
$C_6H_5CONH_2 \rightarrow C_6H_5NH_2$

$C_6H_5CH_2CONH_2 \rightarrow C_6H_5CH_2NH_2$

$H_2NCO.NH_2 \rightarrow H_2N.NH_2$

Urea Hydrazine

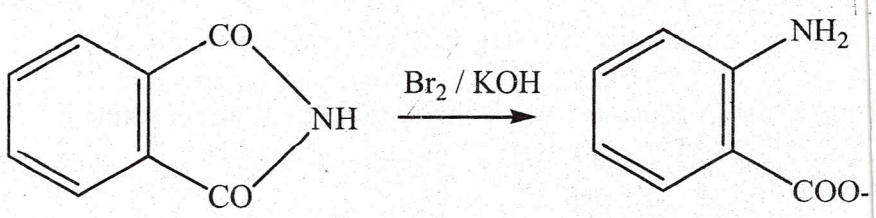
b) Preparation of amino acids : β Alanine e.g., can be obtained in about 45% yield by treating succinimide with bromine and aqueous caustic potash; reaction occurs through the half amide of succinic acid.



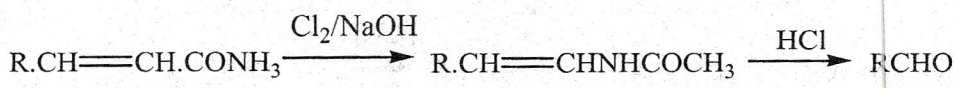
Succinimide

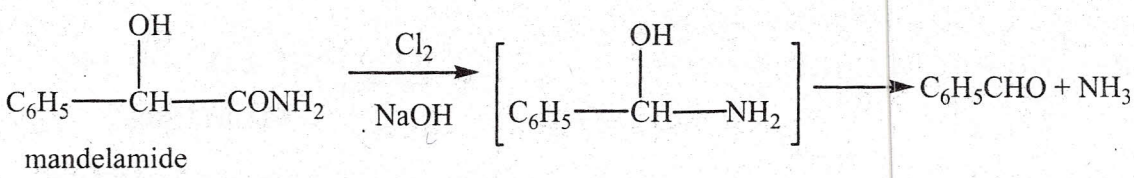
β - alanine

In a similar way anthranilic acid can be prepared from phthalimide



ii) Preparation of aldehyde : α, β-Unsaturated acids and α-hydroxy acid amides are converted into aldehydes by Hoffmann reaction according to the following steps

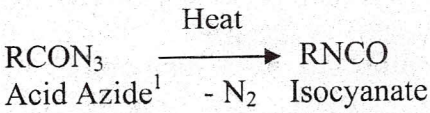




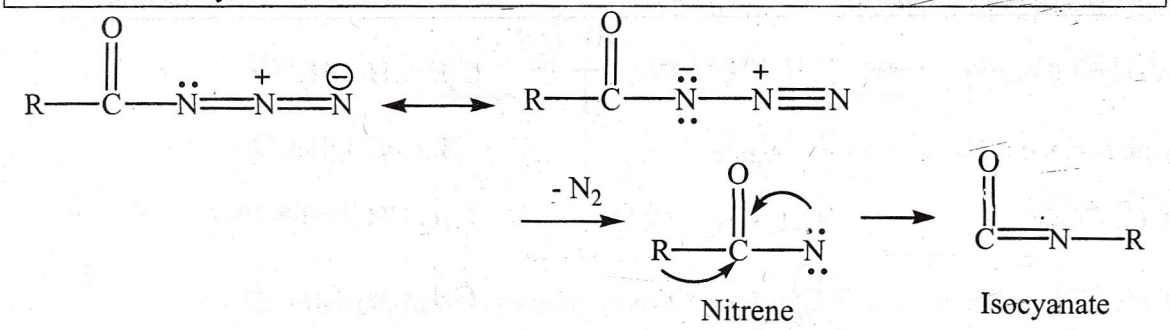
mandelamide

4.6.15 Curtius rearrangement

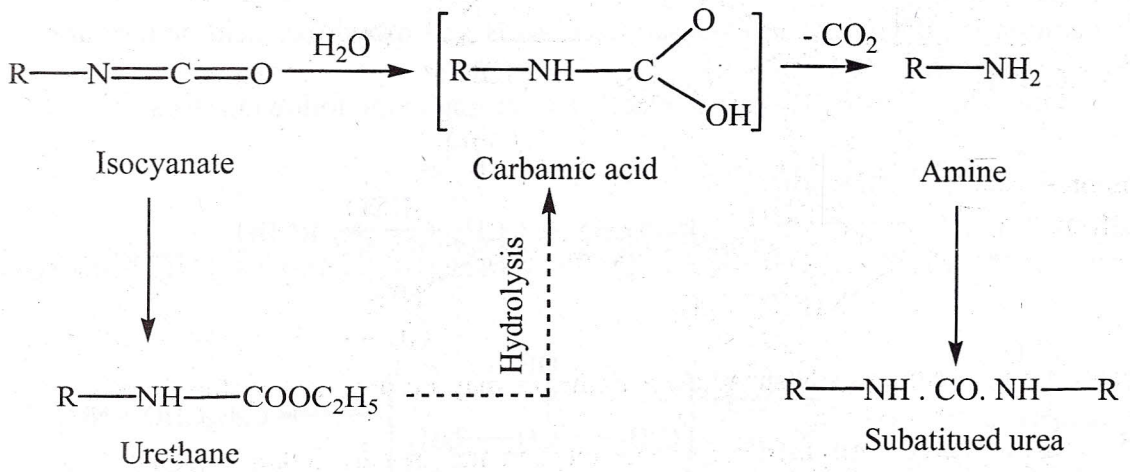
The decomposition of acids azides on heating to give isocyanates is known as Curtuis reaction, citius degradation of amid azides (or) cirtius rearrangement.



Mechanism : The mechanism of Cirtius reaction is quite similar to Hofmann reaction and can be represented as below



The isocyanate may be isolated by carrying out the reaction in an aprotic solvent such as chloroform, while in aqueous and alcoholic solvents it forms amine or urea and urethane respectively.

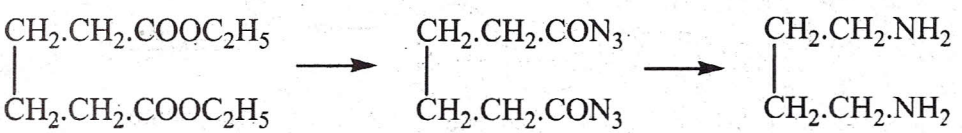


However, Wright (1968) observed that the acyl nitrene is not formed as an intermediate during the reaction

Application : i) Preparation of primary amines. Although Curtius rearrangement involves the mildest conditions for the preparation of primary amines (having carbon atom less) free from secondary and tertiary amines. If requires the preparation of the azides

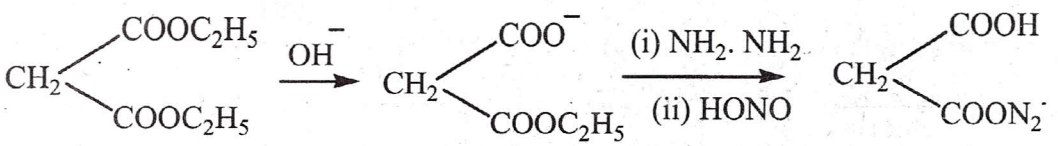
$C_6H_5CH_2COOC_2H_5 \longrightarrow C_6H_5CH_2CON_3 \xrightarrow[(ii)\ H_2O]{(i)\ Heat} C_6H_5CH_2NH_2$

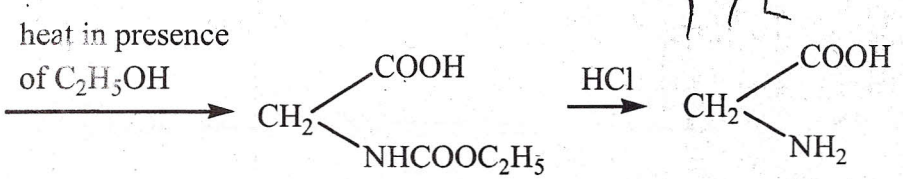
Ethylphenylacetate Azide Benzylamine



Ethyladipate Tetreamethylenediamine (Putrescine)

ii) Preparation of α-amide acids : The curtius rearrangement has been applied in the synthesis of α-amino acids, e.g.





Glycine

iii) Preparation of urethanes : N-substituted urethanes may be prepared by the Curtius reaction. The acid azide is refluxed in benzene solution and then an alcohol is added.

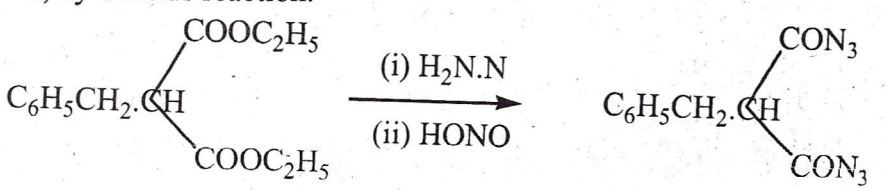
$R.CO.N_2 \xrightarrow{-N_2}$ or $R.NCO \xrightarrow{R.OH} R.NH.COOR^1$

Acid Azide Urethane

iv) Preparation of aldehydes . α,β-unsaturated acids and α-hydroxy acids as in Hoffmann reaction are converted into aidehydes by the Curtius reaction, e.g.

$CH_3.CH(OH).COOH \rightarrow CH_3.CH(OH).CON_3 \rightarrow [CH_3.CH(OH).NH_2] \rightarrow CH_3CHO + NH_3$

Certain aldehydes may be prepared from substituted malonic ester via acid azides, i.e., by Curtius reaction.



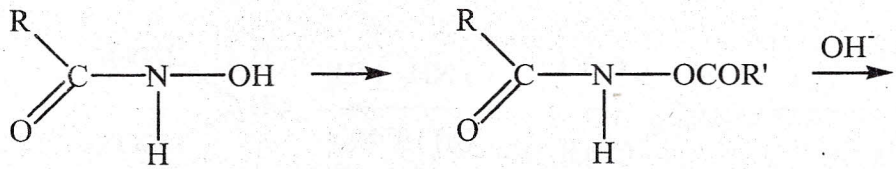
$\rightarrow C_6H_5CH_2CHO$

Diethylbenzylmalonate Phenyl acetaldehyde

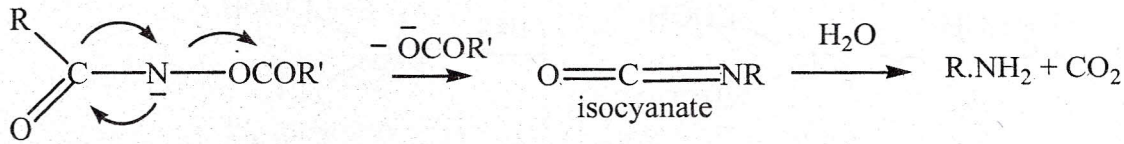
Lossen rearrangement

The conversion of hydroximic acid or its esters into primary amine is known as Lossen reaction.

Mechanism : The mechanism of the lossen rearrangement is closely related to that of Hofmann rearrangement. Except that in the former the leaving group is carboxylate anion while in the latter it is bromide anion.



hydroxamic acid ester of hydroxamic acid



isocyanate

Applications : As the hydroxamic acid is difficult to obtain, the reaction is of limited importance.

Schmidt reaction

Carboxylic acids react with hyddrazoic acid in the presence of concentrated sulphuric acid to give amine directly, reaction being known as Schmidt reaction.

$$RCHO + HN_3 \xrightarrow{H_2SO_4} R\text{-}NH_2 + CO_2 + N_2$$

The reaction also takes place between aldehydes or ketones and hydrozoic acid to form a mixture of cyanides and formyl derivatives of primary amines and amides respectively.

$$RCOOH + HN_3 \xrightarrow{H_2SO_4} R.CN + RNH.CHO$$

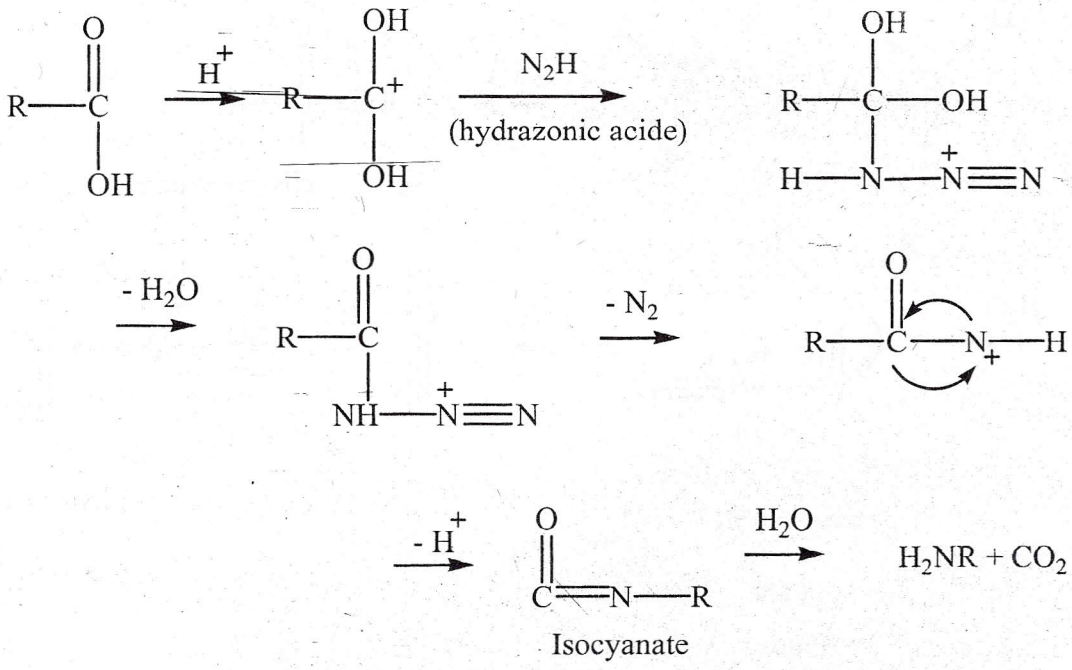
Aldehyde Cyanide Formyl derivative of amine

$$RCOR + NH_3 \xrightarrow{H_2SO_4} RCONHR + N_2$$

Mechanism : The reaction mechanism with acids is similar to that of the Hoffman and Curtius reactions, while with aldehydes and ketones it resembles with the Beckmann rearrangement.

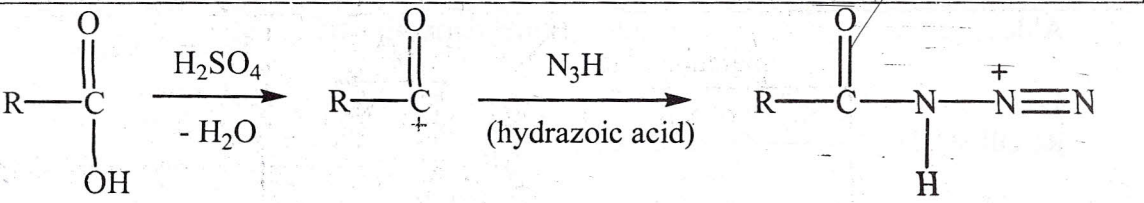
Reaction with acids : The reaction occurs through the acid azide which in presence of conc.sulphuric acid is present as its conjugate acid. The latter loses nitrogen on heating or without heating depending upon the nature of the acid used.

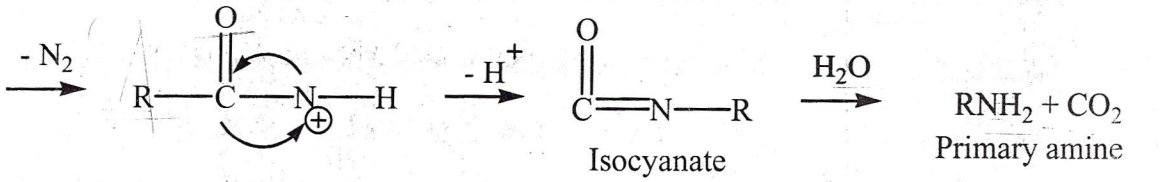
- The reaction with acid viz., benzoic acid, which require heating for the removal of nitrogen from acid azide proceeds as below.

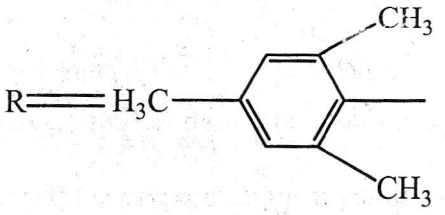


Isocyanate

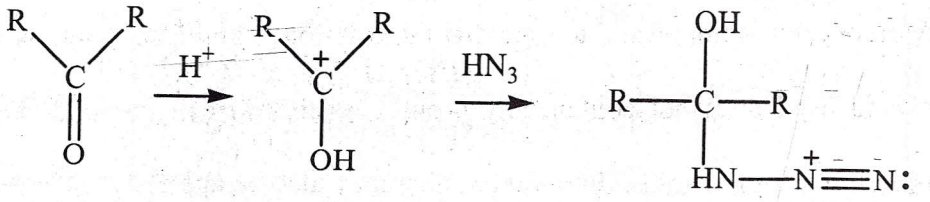
- The reaction with sterically hindered acids, viz mesitoic acid (2,4,6-trimethylbenzoic acid), which do not require heating for the removal of nitrogen proceeds as below.

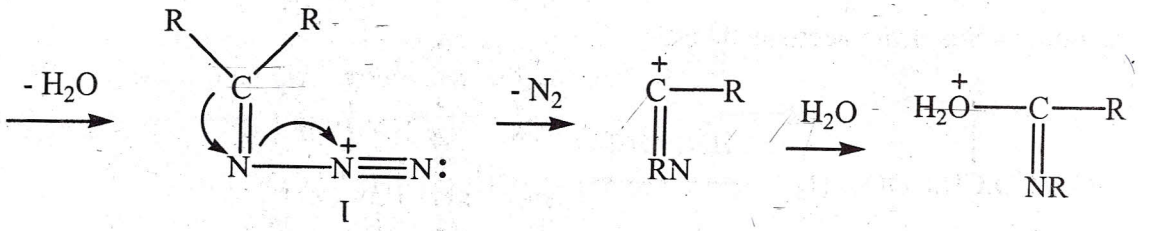


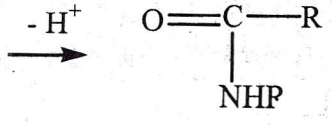




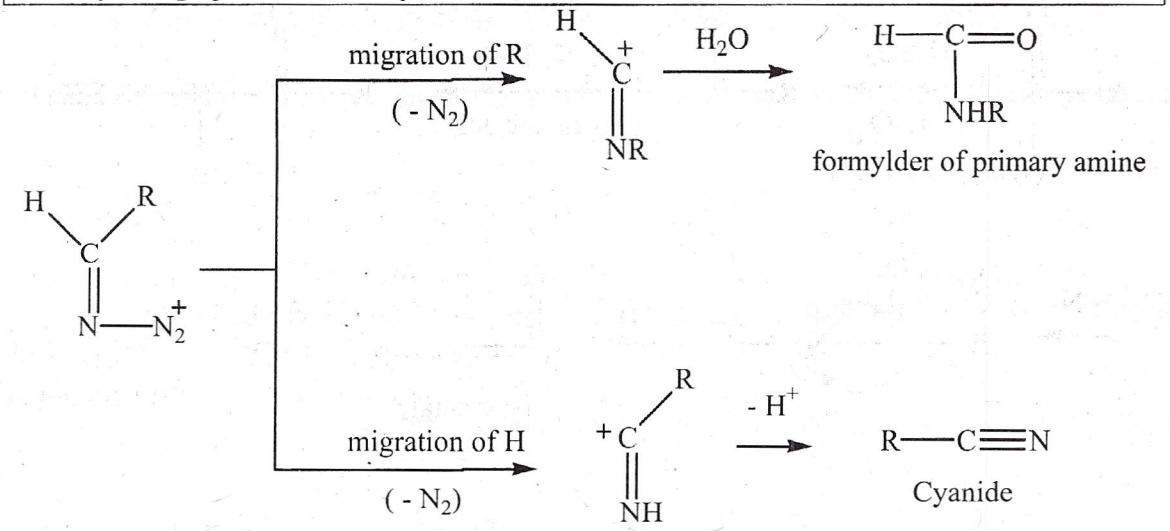
Reaction with ketones and aldehydes. The mechanism of the reaction is uncertain. Smith in 1941 proposed the following mechanism for ketones.





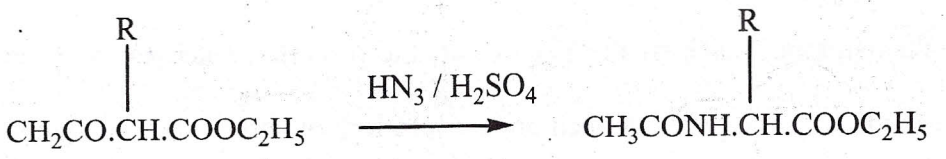


For aldehyde, the mechanism is the same, except that the ion I in the above case is now I_a and hence R or H can migrate to form a mixture of formyl derivative of primary amine and cyanide respectively.

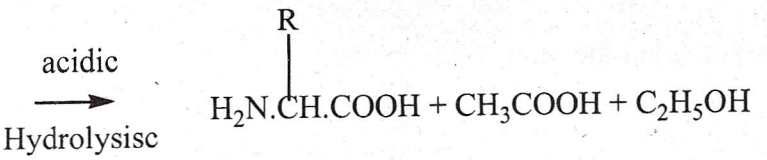


Application : i) Preparation of primary amines : although Schmidt reaction is a direct method for the preparation of primary amines from carboxylic acids and gives usually better yield than the Hofmann or Curtius reaction, it is somewhat dangerous owing to the explosive and poisonous nature of the hydrazoic acid and thus must be applied with caution. Moreover, it is important to note that the reaction is applicable only when the carboxylic acid used does not contain any group sensitive to concentrated sulphuric acid.

ii) Preparation of α-amino acids, Schmidt reaction may also be applied for the synthesis α-amino acids from acetoacetic ester.



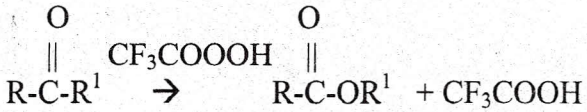
alkyl acetoacetic eater



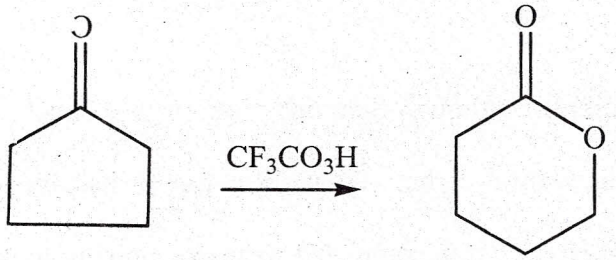
4.6.16 BAEYER VILLIGER REARRANGEMENT

Baeyer-Villiger rearrangement is an example of the migration of a group from carbon to electron deficient oxygen.

The reaction involves the oxidation of ketones to esters by the treatment with peracids such as peraacetic acid, perbenzoic acid, pertrifluoroacetic acid, permonosulphuric acid etc.



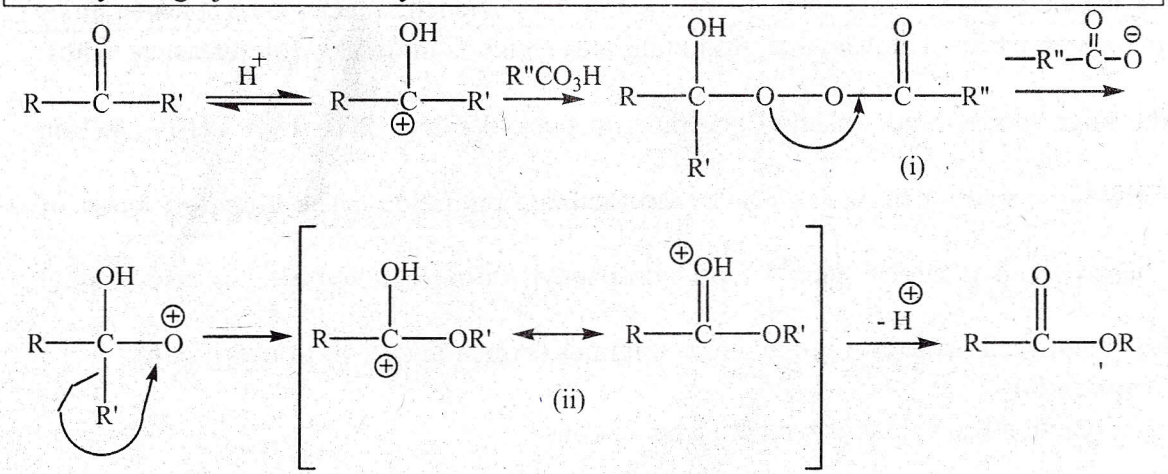
Cyclic ketones are converted to lactones with ring expansion



Cyclopentanone Lactone

The overall reaction is an insertion of oxygen atom between the carbonyl group and the adjacent carbon in ketone. Organic solvents which are inert under the conditions of reaction may be used. The choice of solvent depends upon the solubility of the reactants. Commonly used solvents are glacial acetic acid and chloroform.

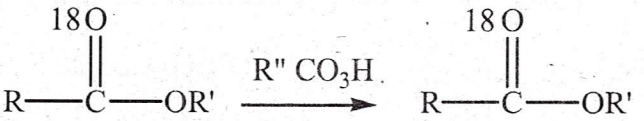
Mechanism : Nucleophilic attack of the peracid on the protonated ketone gives an intermediate peroxide (i). The peroxide then undergoesn loss of carboxylate anion and migration of a group from carbon to electron deficient oxygen to yield the protonated ester (ii). Finally the loss of proton gives the ester.



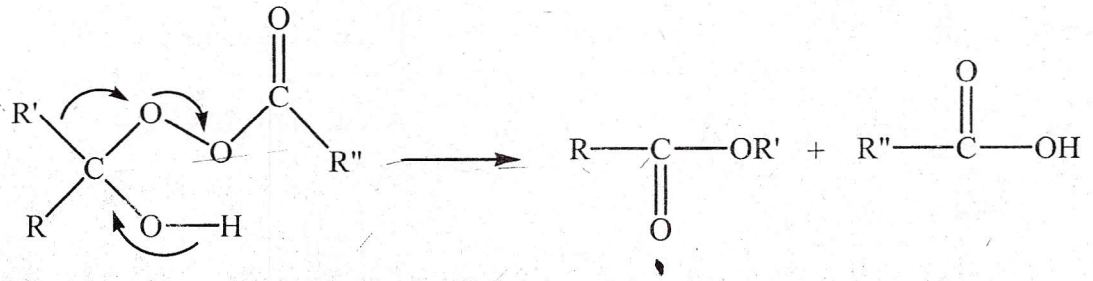
Where R' is equal to CH_3, C_6H_5,CF_3 , etc.

The reaction is catalysed by acids. Electron-releasing groups in the ketone and electron withdrawing groups in peracids promote the reaction rate. Pertrifluoroacetic acid is very effective because trifluoroacetate ion is a good leaving group.

The mechanism is supported by the fact that the labeled oxygen atom of the ketone is entirely present in the cathonyl oxygen of the ester.



The loss of carboxylate anion and the migration of the group may be concerted. Syrkin has suggested that the peroxide (i) transforms into products by a cyclic mechanism, which shows that the last three steps may be concerted.



The migrating group retains its configuration as in other concerted reactions. For acylic compounds the migrating group, R' must be 2°, 3° or vinylic. However, migration of 1° alkyl group may be brought about by using CF_3CO_3H or BF_3-H_2O_2 as reagent.

Baeyer-Villiger oxidation can be brought about with H_2O_2 and base also in some cases.

In unsymmetrical ketones, that group migrates which is more electron releasing. Thus, the migratory aptitude of alkyl groups is in the order $3° > 2° > 1° > CH_3$. Electron releasing substitutents in the aryl group facilitate migration. The migratory order of aryl groups is ρ-tolyl > phenyl > p-chlorophenyl > p-nitrophenyl etc. In case of alkyl aryl ketones, it is the aryl group which migrates (except in case of t-butyl group)

Applications

The reaction has valuable synthetic applications

1. Esters : Esters which are difficult to synthesize can be prepared by this method.

(a) $C_6H_5—CO—CH_3 \xrightarrow{CF_3CO_3H} CH_3—\overset{\overset{O}{\|}}{C}—OC_6H_5$

Acetophenone — Phenylaceltate

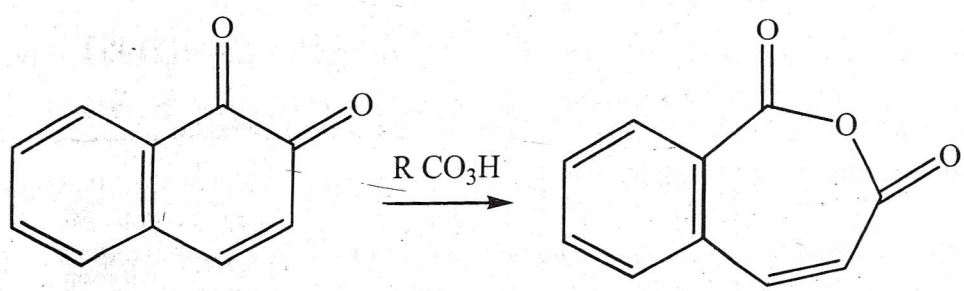
(b) $CH_3—CO—C(CH_3)_3 \xrightarrow{CF_3CO_3H} CH_3—\overset{\overset{O}{\|}}{C}—OC(CH_3)_3$

Pinacolone — *t* - Butylacetate

2. Anhydrides when 1,2 diketones or o-quinones are subjected to Baeyer-Villiger rearrangement, anhydrides are produced.

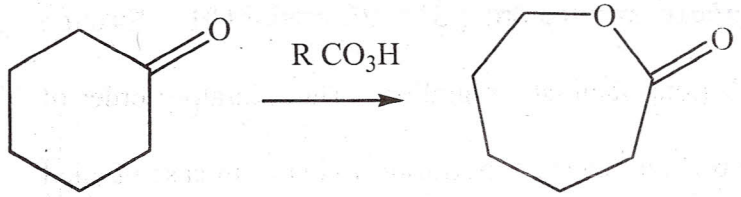
(a) $CH_3—\overset{\overset{O}{\|}}{C}—\overset{\overset{O}{\|}}{C}—CH_3 \xrightarrow{R\,CO_3H} CH_3—\overset{\overset{O}{\|}}{C}—O—\overset{\overset{O}{\|}}{C}—CH_3$

Diacetyl — Acetic anhydribe

(b) 

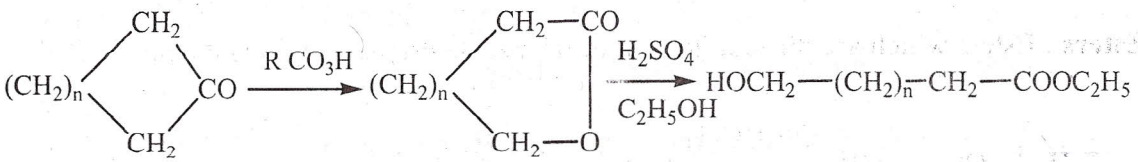
α - Naphthaquinone

3. Lactones Cyclic ketones are converted to lactones with ring expansion



Cyclohexanone ε - Caprolactone

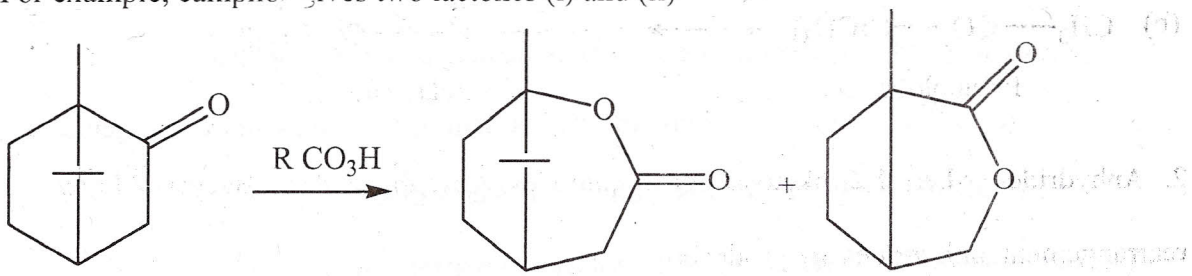
Long chain hydroxyesters can be prepared from large ring size ketones.



Lactone

With some condensed cyclic ketones, two lactones in varying proportions are formed.

For example, camphor gives two lactones (i) and (ii)

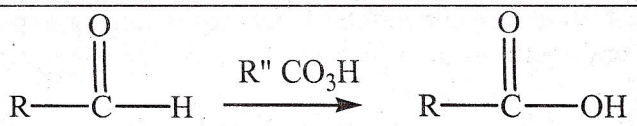


I (75%) II (25%)

Lactone (i) is the normal product formed by the migration of the tertiary bridge head carbon while lactone (ii) has been formed by the migration of the methylene group. The reason for the formation of two lactones in different proportions is steric factor.

4. Elucidation of structure. The ester obtained as a result of the rearrangementmay be hydrolysed to acid and alcohol from which structure of the substrate can be determined.

The reaction is not successful with aldehydes. Aliphatic aldehydes are oxidized to acids by the migration of the hydrogen.



4.6.17 Questions

Molecular rearrangements

1. Describe briefly general mechanistic consideration in molecular rearrangements?
2. Write short note on a) Nature of migration in molecular rearrangement; b) Migratory aptitude and c) Memory effects
3. Discuss of the following rearrangements on the basis of electronic theory.

   a) Beckmann rearrangement; b) The Pinacol-Pinacolone rearrangement and c) The Hofmann rearrangement
4. Write short note on the following rearrangements

   a) Wagner- Meerwein; b) Benzil-Benzlic acid and c) Favorskiik
5. Give modern views regarding the mechanism of the following rearrangement

   a) Demjanov; b) Armdt-Eistert and c) Beyer-Villiger
6. Describe the mechanism of the following rearrangement

   a) Neber; b) Curtius; c) Schmidt and d) Lossen
7. Give one example with mechanism for the molecular rearrangement involving electron deficient carbon?
8. Give one example with mechanism for the molecular rearrangement involving electron deficient nitrogen?
9. Give one example with mechanism for the molecular rearrangement involving electron deficient oxygen?
10. Give one example with mechanism for the molecular rearrangement involving electron rich atom?

Terpenoids

1. Explain general methods of structure determination of terpenoids?
2. Write short notes on the stereochemistry of the following

   a) Citral b) Geraniol c) Terpineol
3. Describe the structure determination and stereochemistry of menthol
4. Illustrate the structure determination and stereochemistry of faransol
5. Deduced the structure of geraniol and conform its structure by the synthesis
6. Deduced the structure of α-terpineol and conform its structure by the synthesis
7. Deduced the structure of citral and conform its structure by the synthesis
8. Write shot notes on a) isoprene rule b) special isoprene rule
9. Write the synthesis of the following : a) Citral b) Geraniol
10. Write the synthesis of the following : a) α-terpineol b) Menthol c) Faransol

Alkaloids

1. Explain general methods of structure determination of alkaloids
2. Write short note on stereochemistry of the following

   a) Atropine b) Quinine c) Nicotine
3. Describe the structure determination and stereochemistry of morphine
4. Illustrate the structure determination and stereochemistry of nicotine
5. Deduced the structure determination and structure of atropine by the synthesis
6. Deduced the structure determination and structure of quinine by the synthesis
7. Write the synthesis of the following

a) Nicotine b) Quinine

8. Write the synthesis of the following

a) Atropine b) Morphine