

6 Molecular Rearrangements

Introduction

Rearrangement is referred to the migration of an atom or a group of atoms from one atom to another within a molecule or from one molecule to another. The migrating group may leave the molecule during migration i.e., the migrating group first gets completely detached from the molecule, subsequently it gets reattached at some other reactive site of the molecule (intermolecular rearrangement). In some cases the migrating group never leaves the molecule during migration (intramolecular rearrangement).

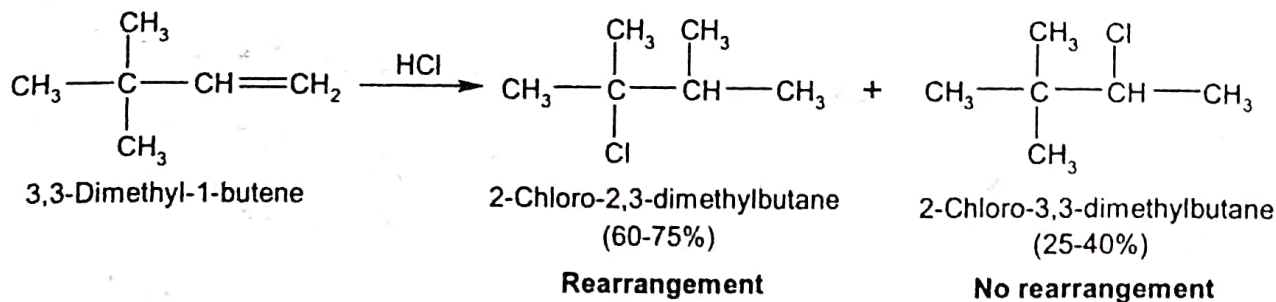
The most important rearrangement reactions involve migration of an atom or group from one atom to an adjacent atom i.e., 1, 2-shift. The most common migrating atoms are carbon or hydrogen, but migration of halogen, oxygen, sulfur and nitrogen is also well known. A group may migrate to an electron-deficient carbon, nitrogen, oxygen or to an electron rich carbon. The most important type of molecular rearrangements involve the 1,2-shift of alkyl or aryl group, with pair of electrons, from one atom to an adjacent electron-deficient atom.

6.1 Rearrangements involving migration to electron-deficient carbon

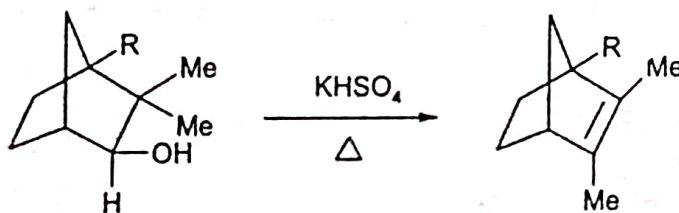
(A) Migration of carbon

6.1.1 Wagner-Meerwein and related rearrangements

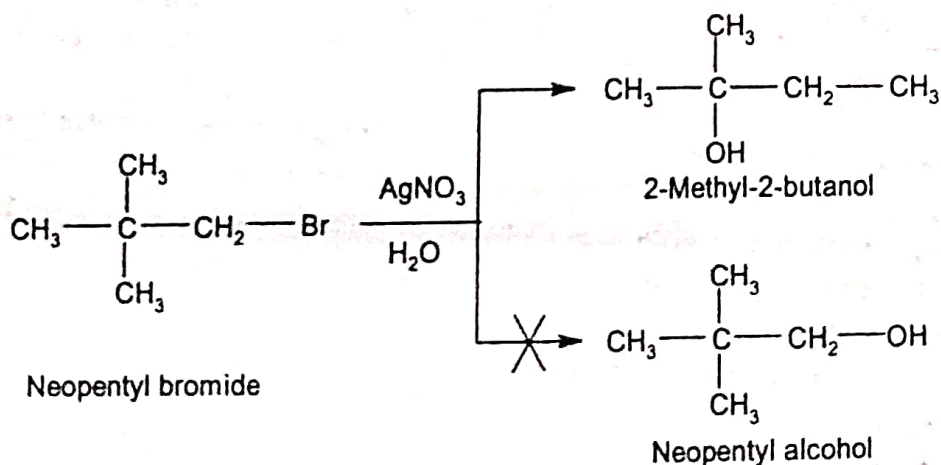
Wagner¹ was the first to recognize that the formation of camphene from borneol or bornyl chloride involved rearrangement. Meerwein² also found that molecular rearrangements occurred in the camphene hydrochloride-isobornyl chloride interconversion. He generalized these types of rearrangements indicating that they also occur in compounds other than bicyclic terpenoids and also in various substitution, elimination and addition reactions. Such rearrangements which occur during reactions involving the change in the carbon skeleton through the rearrangement of carbocations as intermediates, are collectively known as **Wagner-Meerwein rearrangements**. For example, 3,3,-dimethyl-1-butene adds HCl to give 2-chloro-2,3-dimethylbutane as major product (60-75%), along with the expected 2-chloro-3,3-dimethylbutane, in minor amount (25-40%).



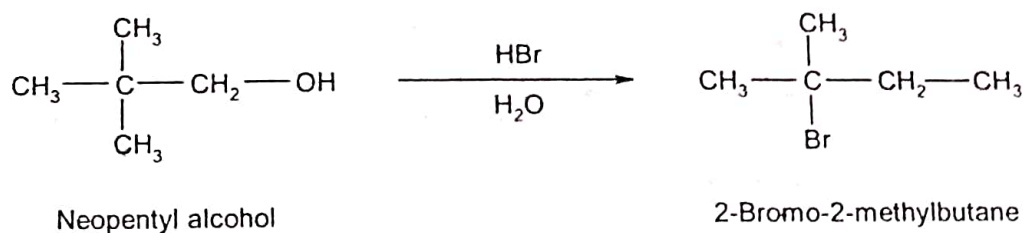
These rearrangements occur *via* an intermediate carbocation and involve the migration of alkyl group with its pair of electrons to an electron-deficient carbon atom. In terpenoids these rearrangements involve a change in ring structure or migration of methyl group. The rearrangement, which involves the migration of methyl group, is a special case of Wagner-Meerwein rearrangement, and is known as **Nametkin rearrangement**. Nametkin rearrangements often occur in monoterpenes when they are treated with acid. For example, Nametkin rearrangement is observed when 3,3-dimethyl[2.2.1] bicycloheptan-2-ols such as camphenilol or 4-methylcamphenilol are treated with acid.



Whitmore³ recognized that when neopentyl alcohol or neopentyl bromide reacts under conditions favoring the S_N1 mode, rearranged products are formed. For example, solvolysis of neopentyl bromide (1-bromo-2,2-dimethylpropane) in water leads to 2-methyl-2-butanol, instead of the expected neopentyl alcohol (2,2-dimethyl-1-propanol). Thus, solvolysis of neopentyl bromide does not take a normal course.

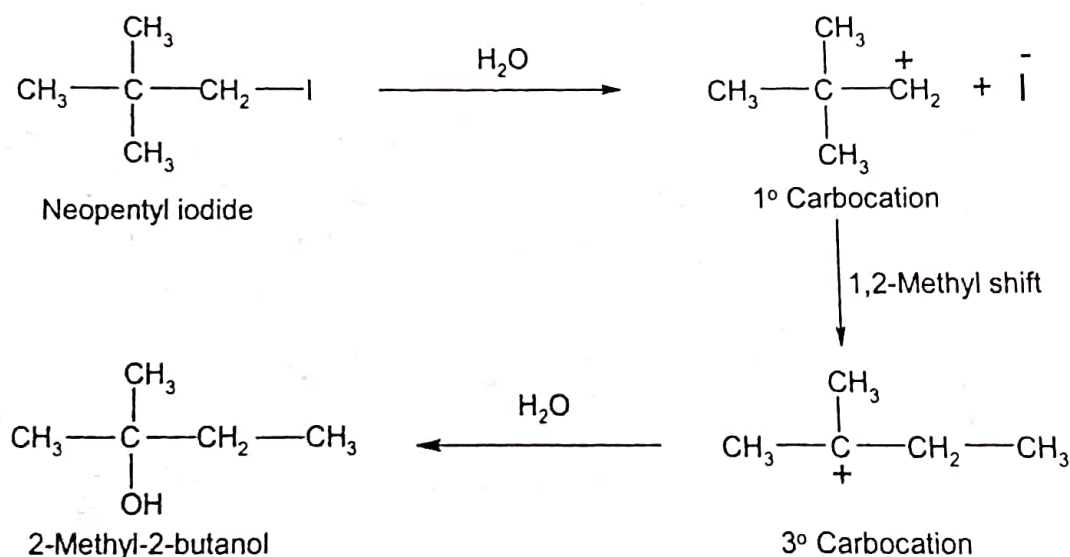


Similarly, action of HBr on neopentyl alcohol gives tert-pentyl bromide (2-bromo-2-methylbutane).

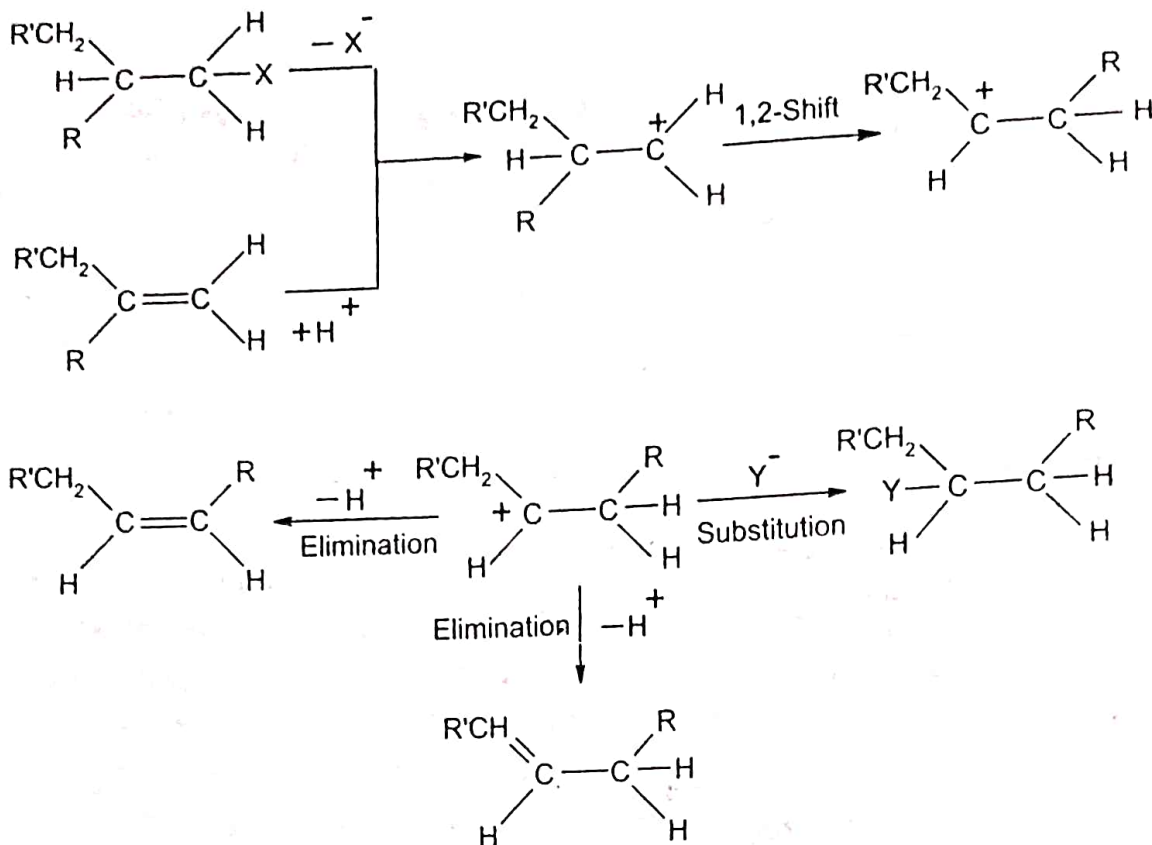


Mechanism

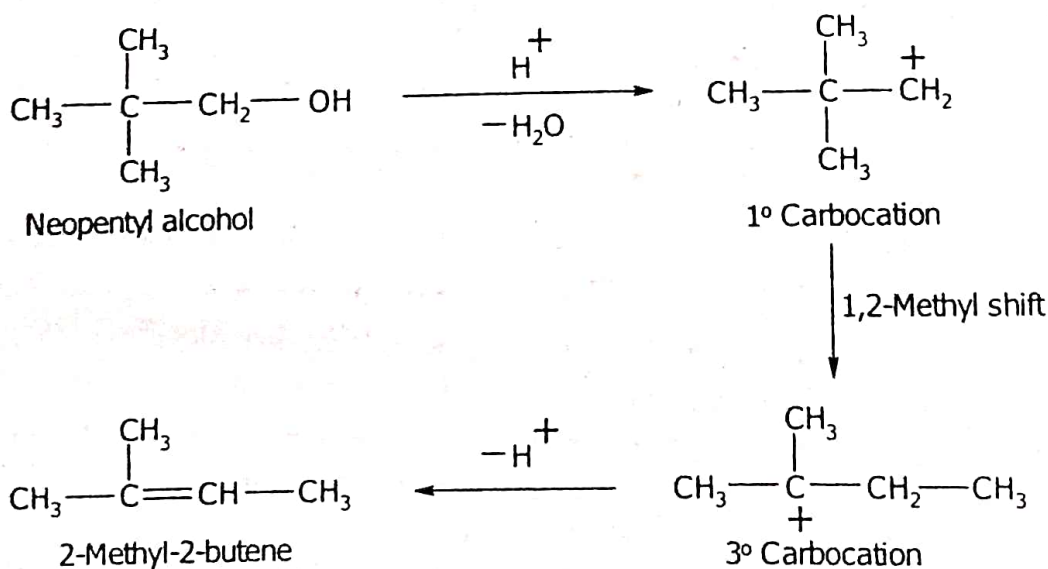
Wagner-Meerwein rearrangements are common in many reactions involving carbocation as intermediate. For example, nucleophilic displacements occur by an $\text{S}_{\text{N}}1$ mechanism and may be accompanied by the 1, 2-methyl shift (rearrangement). In the solvolysis reaction of neopentyl iodide in water, the rearranged alcohol, 2-methyl-2-butanol is formed. The expected neopentyl alcohol is not formed in this reaction. The unstable primary carbocation, formed by the dissociation of C-I bond, rearranges to a much more stable tertiary carbocation.



Thus, the first step in these rearrangement reactions is the generation of a carbocation, which can take place in a number of ways. Carbocation is formed in the reactions where loss of a leaving group occurs, for instance, loss of a water molecule from protonated alcohols, nitrogen (N_2) from aliphatic diazonium ions or halide ion from alkyl halides. The carbocation can also be formed by the addition of electrophile to a double bond. For example, protonation of alkene produces the carbocation. The addition of proton to alkenes takes place according to **Markownikoff's rule** (see sec. 1.4.1). In the second step, the shift of a group, along with the pair of electrons, occurs from one carbon atom to the adjacent cationic carbon atom. The resulting rearranged carbocation either combines with a nucleophile or loses proton to give alkene.

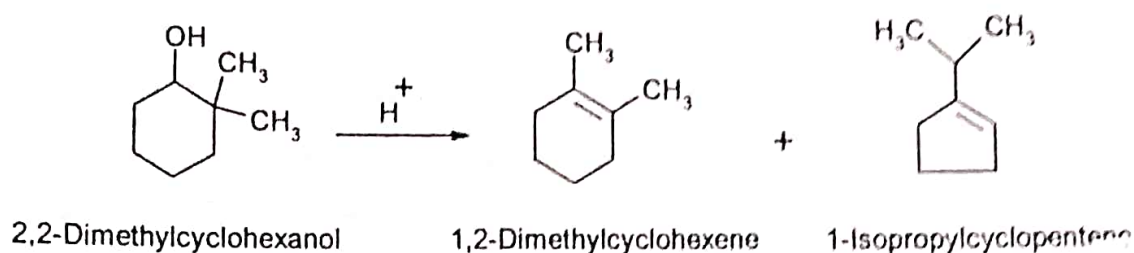


Acid-catalysed dehydration of neopentyl alcohol yields 2-methyl-2-butene, obviously a rearrangement has taken place here. When neopentyl alcohol is heated with sulfuric acid, water is eliminated and neopentyl carbocation (primary carbocation) is formed. Neopentyl carbocation undergoes 1,2-methyl shift to give tertiary carbocation. The greater stability of tertiary carbocation as compared to primary carbocation is the driving force for the shift of methyl group. Loss of proton from tertiary carbocation results in 2-methyl-2-butene.

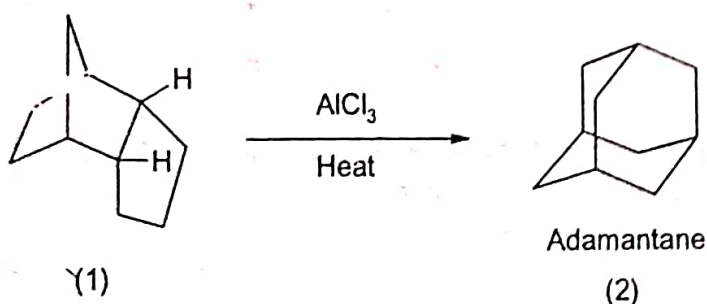


The Wagner-Meerwein type of rearrangements involving carbocation intermediate in alicyclic compounds lead to expansion or contraction of cycloalkane ring. For example,

dehydration of the cyclic secondary alcohol 2,2-dimethylcyclohexanol in presence of acid leads to a mixture of 1,2-dimethylcyclohexene and 1-isopropylcyclopentene. In the alicyclic systems, the relieve of strain is the driving force for this rearrangement.



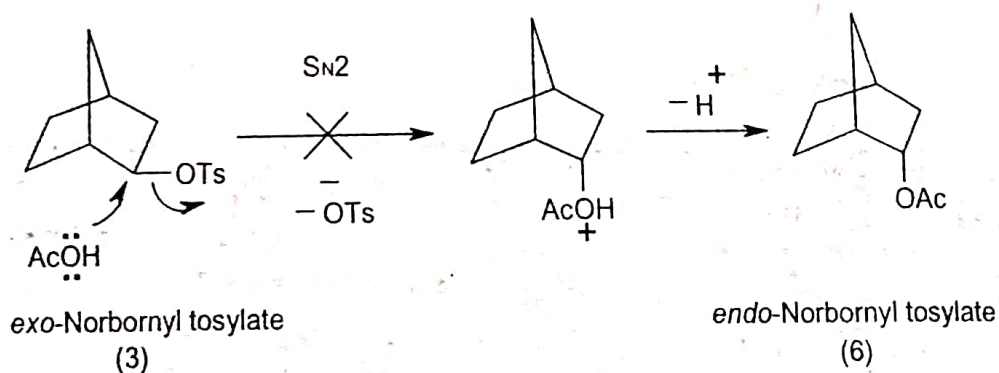
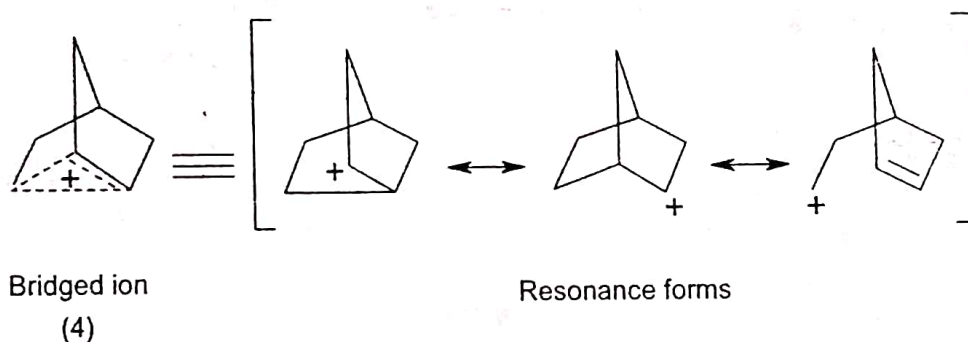
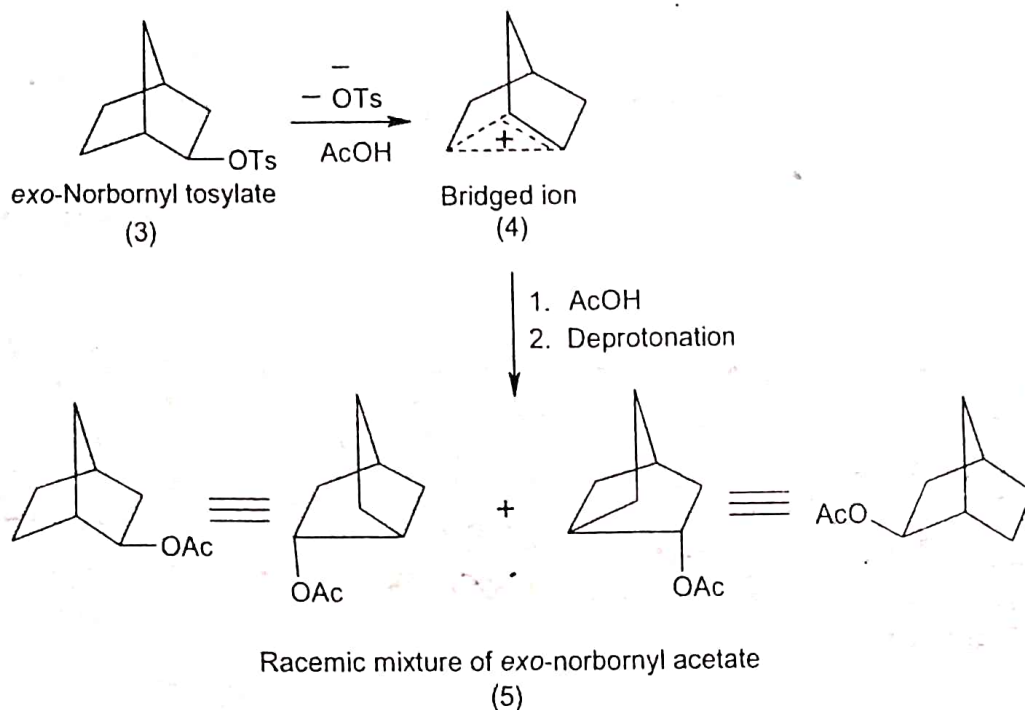
Alkanes on treatment with Lewis acids and a small amount of initiator undergo Wagner-Meerwein rearrangement. Tricyclic hydrocarbons give adamantane and its derivatives by treatment with a Lewis acid such as AlCl₃ and the reaction is known as **Schleyer adamantization**. For example, (1) is converted into adamantane (2).



Stereochemistry of rearrangement

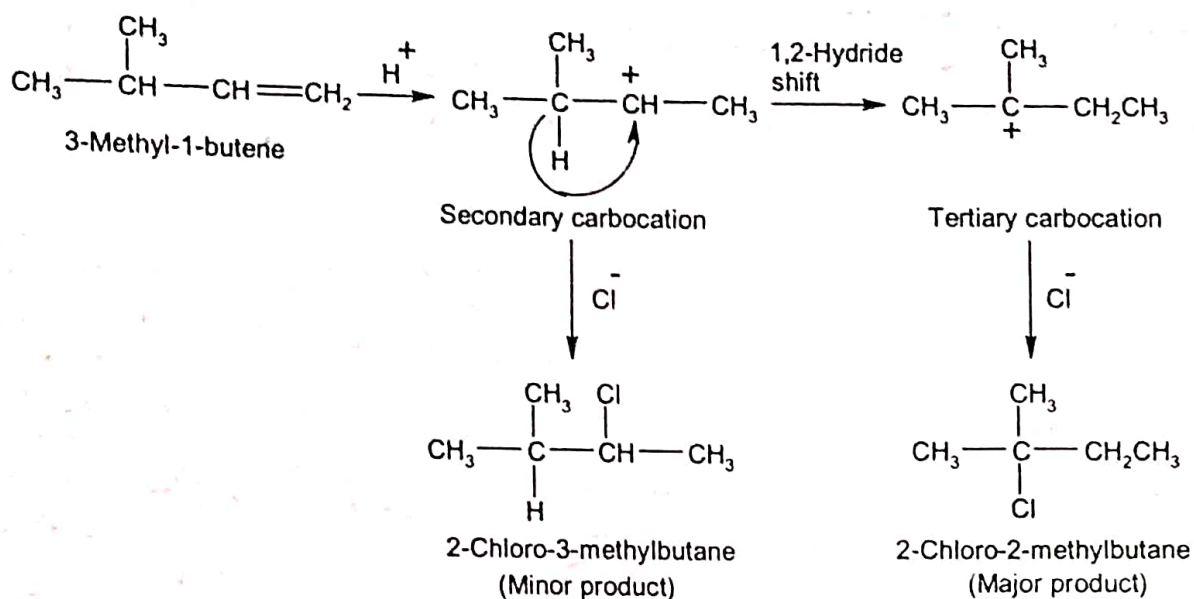
Most of Wagner-Meerwein and related rearrangements are stereospecific. The migrating group approaches the cationic carbon from the side opposite to the position that was occupied by the leaving group, as in S_N2 substitution. Thus, inversion of configuration takes place at the carbon linked to leaving group. However, when optically pure *exo*-norbornyl tosylate (3) undergoes solvolysis in acetic acid, the racemic mixture of *exo*-norbornyl acetate is formed (5). If the reaction is simple S_N2 displacement by acetic acid, the product would be the optically active *endo*-acetate (6). Instead, the *exo*-acetate obtained is the product of retention. Moreover, racemic mixture is formed. This can be explained by the involvement of neighboring carbon-carbon σ bond participation in ionization, and the cyclic, bridged ion (nonclassical carbocation, see sec. 2.2.5) is formed. The bridged carbocation is stabilized by resonance. Attack of acetic acid occurs with equal probability at the two equivalent carbons of the bridged ion (4). Therefore, racemic product is formed after deprotonation.

There is sufficient evidence to prove the existence of nonclassical carbocation. Martin Saunders in 1931 proved the existence of bridged 2-norbornyl cation (4) by spectroscopic technique.



Migratory Aptitude

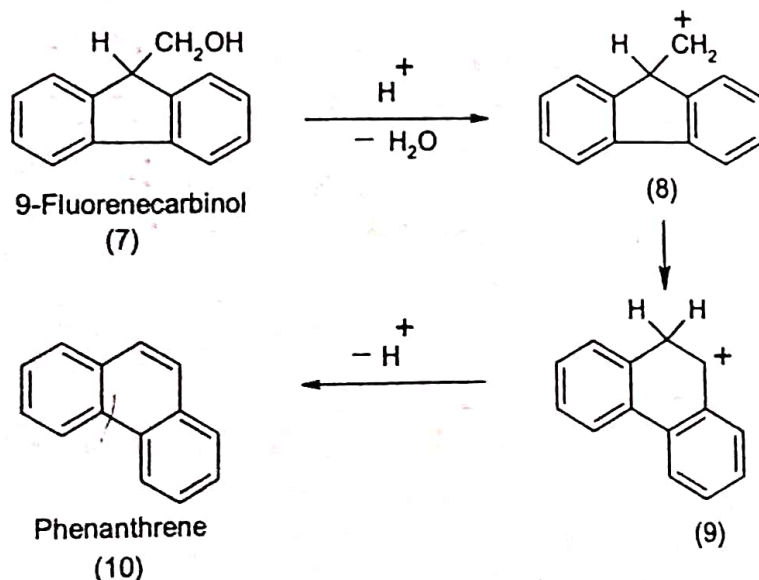
A number of experiments carried out to determine the relative migratory aptitude of various groups in Wagner-Meerwein rearrangements showed that the aryl groups have a far greater migratory aptitude than alkyl groups or hydrogen. Electron-releasing group in the aryl group increases the rate of migration while electron-withdrawing group decreases the rate of migration. The migration of hydride ion is also possible. The rearrangement of 3-methyl-1-butene to 2-chloro-2-methylbutane in the presence of HCl is one such example.



Such shift of hydrogen with its pair of electrons between adjacent carbon atoms is known as **1,2-hydride shift**. The 1,2-hydride shift does not change the carbon skeleton of the molecule.

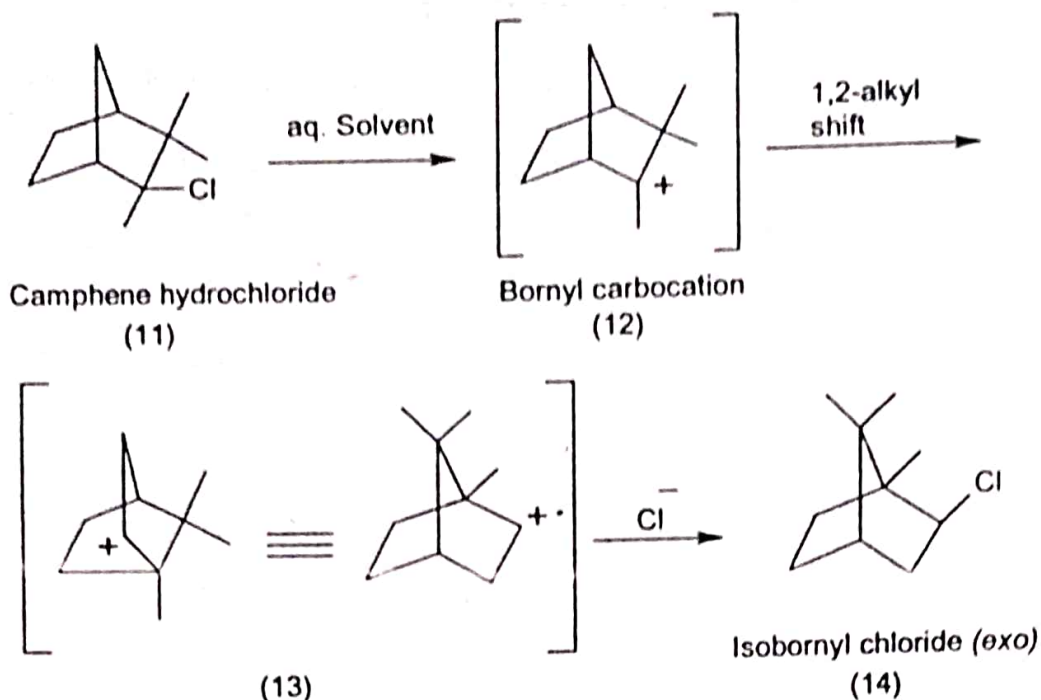
Applications

1. The conversion of 9-fluorencarbinol (7) into phenanthrene (10) involves the Wagner-Meerwein rearrangement. Protonation of the hydroxyl group followed by the loss of water molecule gives the primary carbocation (8). The (8) then rearranges to give much more stable benzyl carbocation (9) which loses a β -hydrogen to give the phenanthrene (10).

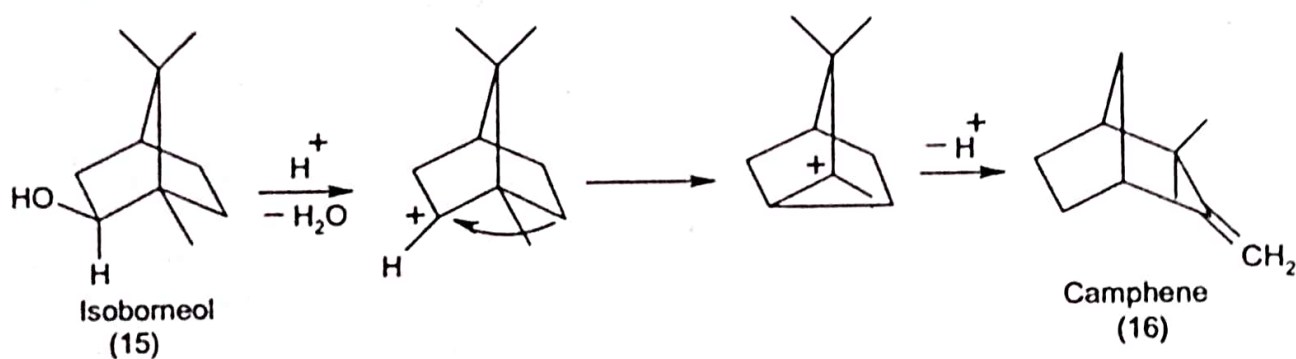


2. Wagner-Meerwein rearrangements are most common in terpenes. In the conversion of camphene hydrochloride (11) to isobornyl chloride (14), the camphene hydrochloride (11) loses chloride ion to form bornyl carbocation (12), which rearranges by a 1,2-alkyl shift to form another carbocation (13). In the final step, the carbocation combines with a chloride ion to yield isobornyl chloride (14). In this case only isobornyl

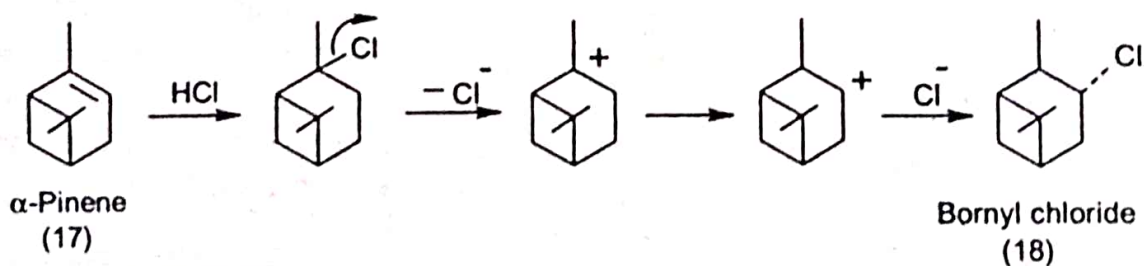
chloride is obtained in which chloride is *exo*. The bornyl chloride, in which chloride is *endo*, is not obtained.



3. Dehydration of isoborneol (15) to camphene (16) is another typical example of this rearrangement.



4. Bornyl chloride (18) can be obtained by the addition of HCl to α -pinene (17).

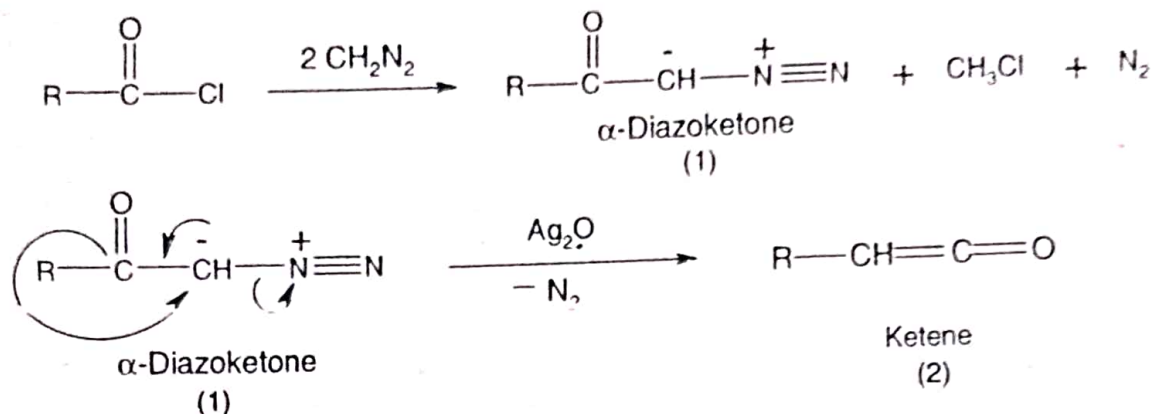


References

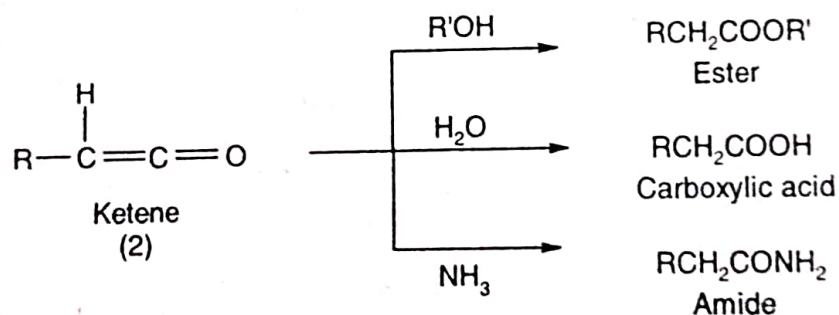
1. G. Wagner, J. Russ. Phys. Chem. Soc., 1899, 31, 680; Ber., 1899, 32, 2302.
2. H. Meerwein, Ann., 1914, 405, 129.
3. F. C. Whitmore, J. Chem. Soc., 1948, 1090; F. C. Whitmore and H. S. Rothrock, J. Am. Chem. Soc., 1933, 55, 1100; 1932, 54, 3431.

6.1.3 Wolff rearrangement

The α -diazoketones (1) undergo rearrangement with elimination of very stable nitrogen molecule in presence of silver oxide to form a ketene (2). The reaction is known as **Wolff rearrangement**.¹ The α -diazoketones can be prepared by the reaction of acid chlorides with diazo compounds in a normal addition-elimination process. The diazoketones must be treated with great caution as they are liable to explode.



The Wolff rearrangement generates ketene in the absence of any nucleophile, and therefore it can be isolated in this reaction. However, when this rearrangement is carried out in the presence of water, alcohol² or amine, the ketene is converted into carboxylic acid, ester or amide, respectively. The overall reaction is called **Arndt-Eistert Synthesis** (sec. 5.4). Arndt-Eistert reaction is useful for converting an acid, RCOOH into its next higher homologue, RCH₂COOH.

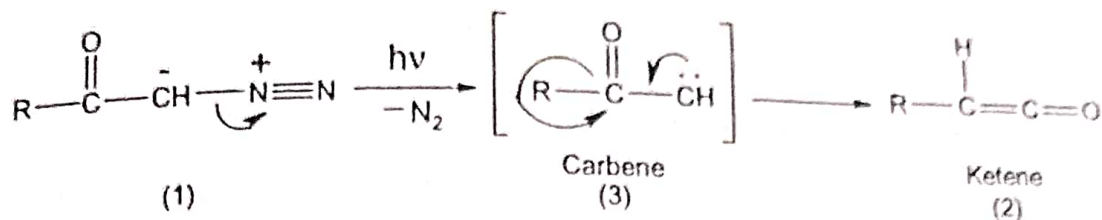


The Wolff rearrangement can be brought about either thermally or by photolysis. Generally, the thermal reaction is carried out in the presence of silver oxide (colloidal platinum or copper can also be used instead of Ag₂O).

Mechanism

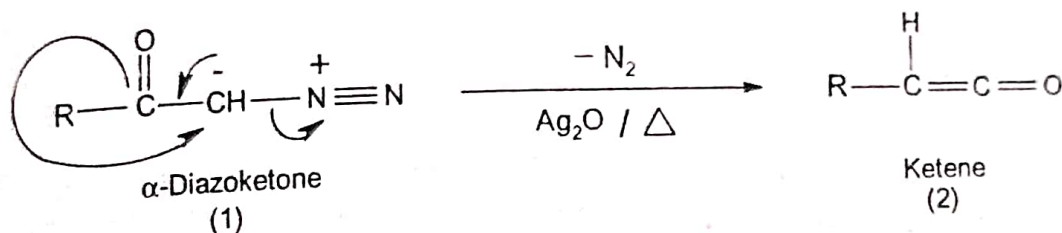
Loss of nitrogen from the α -diazoketone (1) is accompanied by 1,2-shift of the alkyl group with electron pair. The resulting ketene (2) readily combines with the solvent molecule, which may be water to give acid, alcohol to give an ester, or amine to give an amide. When reaction is brought about by photolysis³, the Wolff rearrangement is believed to involve formation of a carbene (3). The migration of a group (alkyl or aryl) with its pair of electrons to electron deficient carbon of carbene (3) gives the ketene (2). The ketene then reacts with solvent to give the final product. The mechanism is analogous to Hofmann and related rearrangements (sec.6.2.2) where migration of alkyl

group occurs from adjacent carbon to electron deficient nitrogen of nitrene, which is

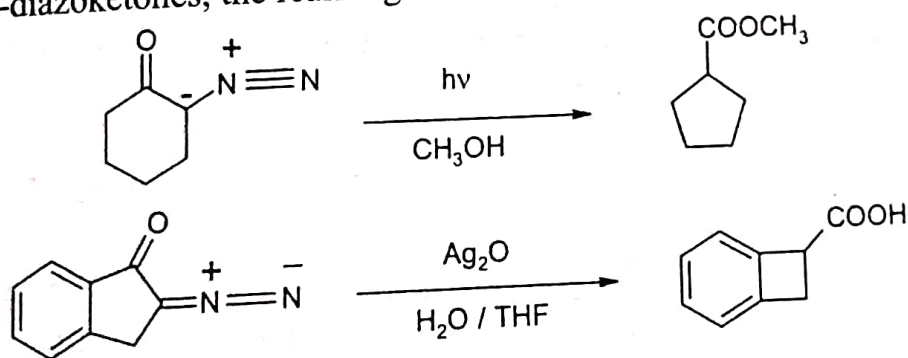


formed as an intermediate.

It is believed that when the rearrangement is carried out thermally in presence of silver oxide, a concerted migration of alkyl group and expulsion of nitrogen is involved and there is no clear evidence that carbene is formed as an intermediate.

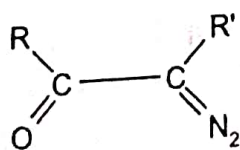


With cyclic α -diazoketones, the rearrangement leads to contraction of rings.



Stereochemistry

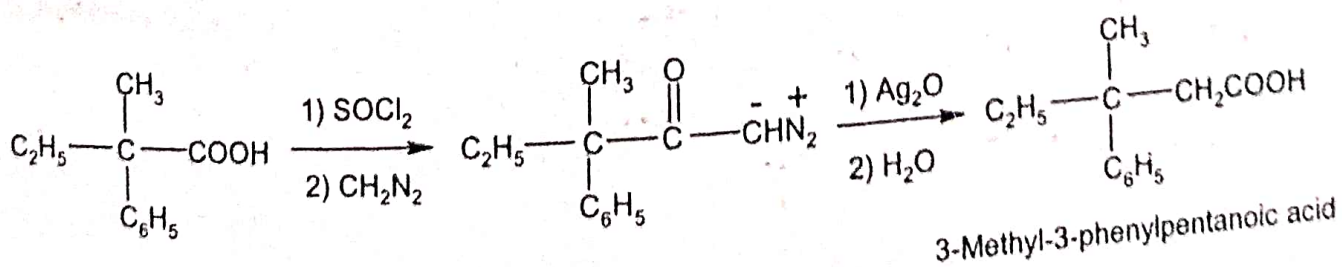
It is found that the Wolff rearrangement occurs preferentially from the S-Z conformation⁺ of α -diazoketone.



S-Z

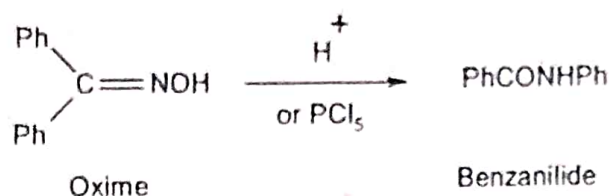
Applications

Wolff rearrangement is involved in an important reaction (Arndt-Eistert reaction) for converting an acid into its next higher homologue.



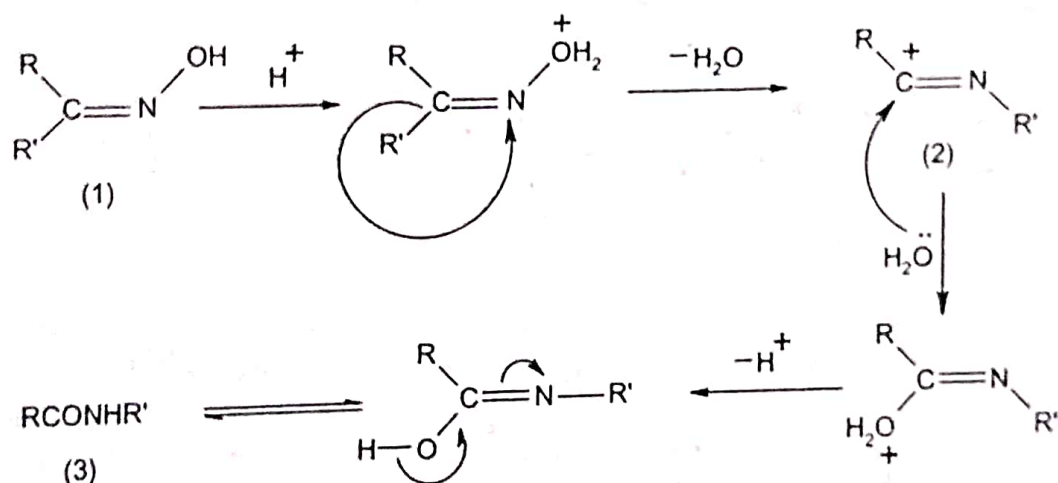
6.2.1 Beckmann rearrangement

The rearrangement of oximes under the influence of a variety of acidic reagents to *N*-substituted amides is known as **Beckmann rearrangement**¹. Phosphorous pentachloride is commonly used as a catalyst in Beckmann rearrangement, but conc. sulfuric acid, polyphosphoric acid, formic acid, thionyl chloride, silica, etc., have been used successfully. A typical example is rearrangement of benzophenone oxime to benzanilide in the presence of phosphorous pentachloride.



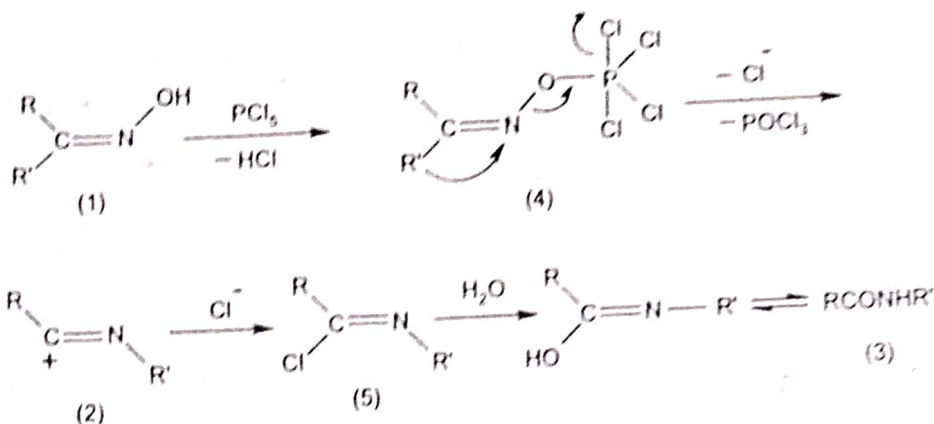
Mechanism

The proposed mechanism is shown below:

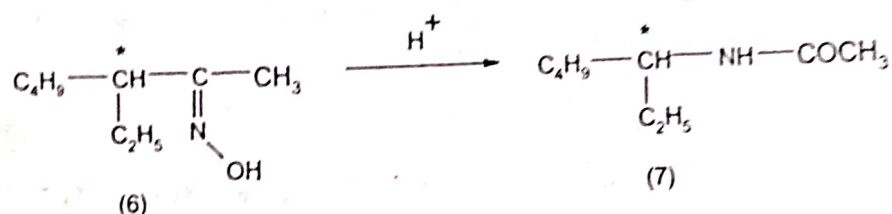


Treatment of oxime (1) with acid generates a good leaving group (-OH group is converted to H₂O⁺ with H₂SO₄, -OPCl₄ with PCl₅, and -OSOC₆H₅ with C₆H₅SO₂Cl) on the nitrogen atom. Loss of the leaving group generates an electron-deficient species, which is accompanied by migration of a group from adjacent carbon to the electron-deficient nitrogen. The resulting iminocarbenium ion (2) traps water to give an amide (3) as the final product. The driving force for the 1,2-alkyl shift is the formation of more stable carbocation. It is established that when migrating group is aryl, the electron-withdrawing groups (e.g., *p*-nitro and *p*-chloro) on the migrating group strongly retard rearrangement and electron-donating groups (e.g., *p*-methyl and *p*-methoxy) strongly accelerate it.

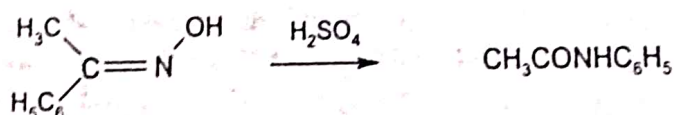
The role of most acylating agents in bringing about rearrangement is clearly one of esterification. For most acylating agents the oxime esters can be isolated at low temperature but rearrange explosively when brought to room temperature. When phosphorus pentachloride is used to effect rearrangement, a tetrachlorophosphonyl derivative² (4) is first produced. This undergoes rearrangement with cleavage of phosphoryl chloride and chloride ion. The chloride ion unites with iminocarbenium cation (2) to form the imidoyl chloride (5), which reacts with water to yield (3).



Since chiral groups migrate intramolecularly with retention of configuration, it is most likely that the migrating group is never completely separated from the remainder of the molecule. For example, (+)-methyl-3-heptyl ketoxime (6) is converted by rearrangement to 3-acetamidoheptane (7) with retention of configuration³.

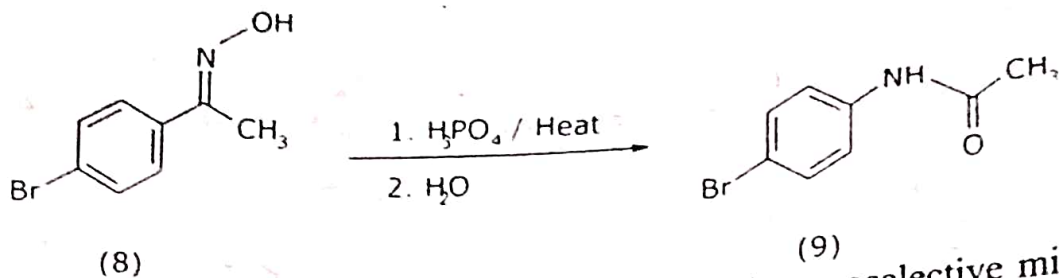


The rearrangement is highly stereospecific, that is, the group *anti*- to the oxime hydroxyl group always migrates regardless of relative migratory aptitude of the two groups. Thus, different geometrical isomers of oximes* sometimes give isomeric amides by the Beckmann rearrangement. For example, in acetophenone oxime with the stereochemistry shown below, it is the phenyl group which migrates and thus the product formed is acetanilide (for its mechanism, see sec. 5.11).



Similarly, *anti* 4-bromophenyl methyl ketoxime (8) when treated with H_3PO_4 gives *p*-bromoacetanilide (9).

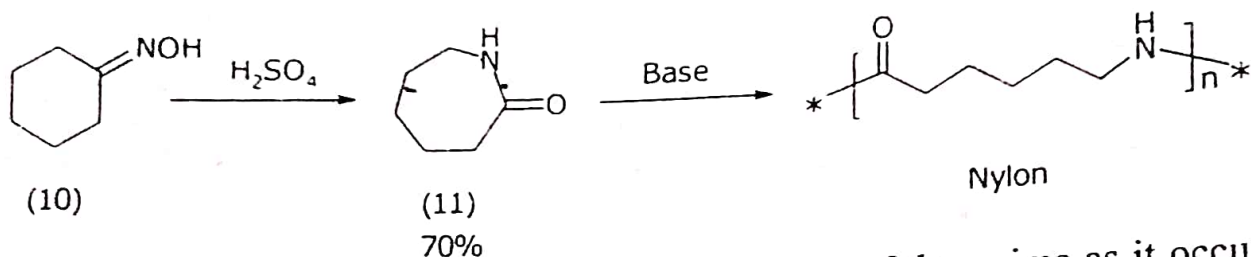
* Oximes can exhibit geometrical isomerism. The customary nomenclature for geometrical isomers of oximes is the *syn* and *anti* in place of *cis* and *trans*. The usual convention is to refer the position of the hydroxyl group to the first named portion of the ketone skeleton, or to the hydrogen of aldehydes.



Thus, Beckmann rearrangement involves the concerted stereoselective migration of the alkyl group or aryl group *anti* to the OH group in the starting material. However, sometimes *syn-anti* isomerisation under the acidic conditions of rearrangement leads to mixture of isomeric amides. Aldoximes are not usually good substrates for Beckmann rearrangement and the yields of amides obtained from aldoximes are generally poor.

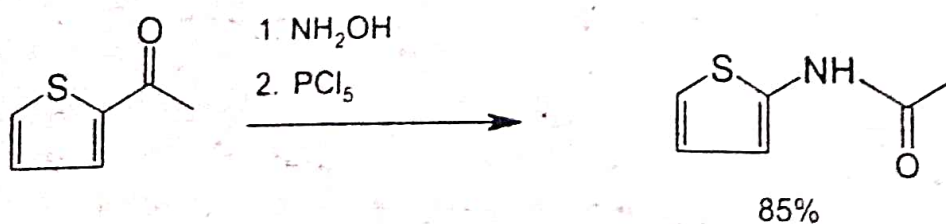
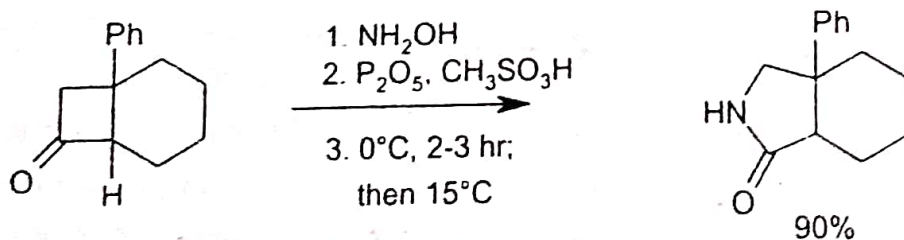
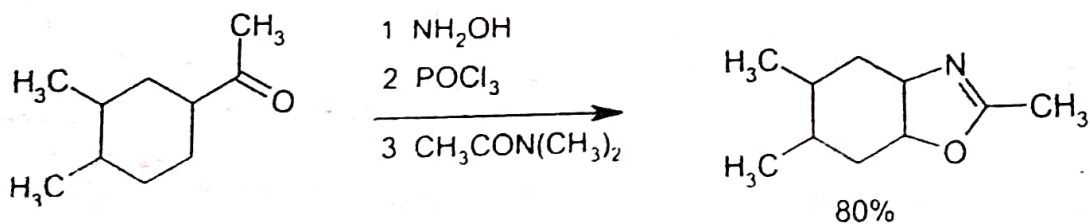
Applications

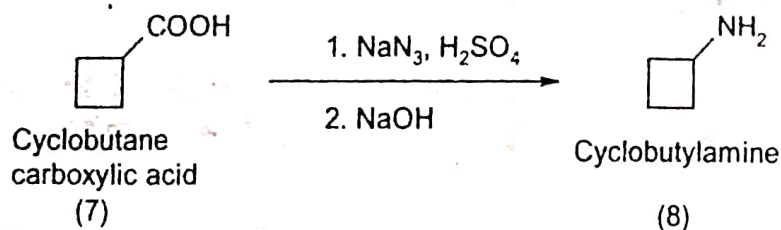
1. A synthetically useful example of Beckmann rearrangement is the synthesis of caprolactam⁴ from cyclohexanone oxime (10) in presence of concentrated sulfuric acid. Caprolactam (11) upon alkaline polymerization gives nylon.



2. Beckmann rearrangement establishes the stereochemistry of the oxime as it occurs by migration of a group *anti* to the oxime hydroxyl.

3. Some other applications⁵⁻⁷ are given below.





References

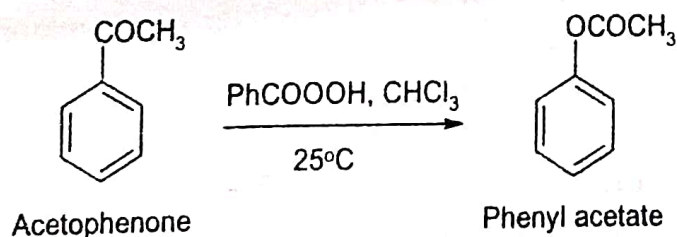
1. L. H. Briggs, G. C. DeAth and S. R. Ellis, *J. Chem. Soc.*, 1942, 61; H. Wolff, *Org. React.*, 1946, 3, 307.
2. K. F. Schmidt, *Z. Angew. Chem.*, 1923, 36, 511; *Ber.*, 1924, 57, 704
3. N. W. Werner, J. Casanova, Jr., *OS*, 1967, 47, 28.

6.3 Rearrangements involving migration to electron-deficient oxygen

This section treats the rearrangements involving migration of an alkyl, aryl, and acyl group, with the pair of electrons, to electron deficient oxygen. The rearrangements in which the migration terminus is an electron-deficient oxygen atom, are parallel to rearrangements in which the migration terminus is an electron-deficient nitrogen. The only difference is that, the leaving group in the former cases is an oxy anion (or the conjugate acid) formed by heterocyclic cleavage of the O-O bond in peroxides.

6.3.1 Baeyer-Villiger oxidation

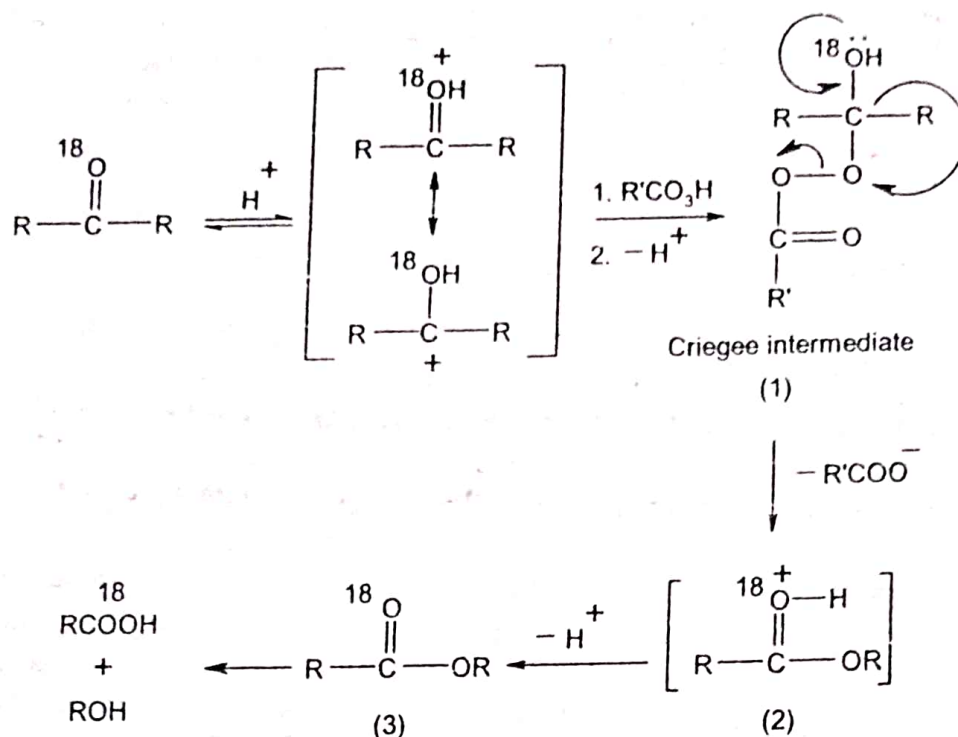
Oxidation of ketones to esters with hydrogen peroxide or with peracids (RCO_3H) is known as **Baeyer-Villiger oxidation**¹. Baeyer-Villiger used Caro's acid (peroxy sulfuric acid) in their experiments. The reaction can be brought about conveniently by hydrogen peroxide in weakly basic solutions. Typical peracids used are peracetic acid, trifluoroperacetic acid, perbenzoic acid, performic acid and *m*-chloroperbenzoic acid (*m*-CPBA). A typical example of Baeyer-Villiger oxidation is reaction of acetophenone with perbenzoic acid at room temperature to furnish phenyl acetate in 63% yield.



With Caro's acid the rearrangement step is much faster than with peracetic acid because sulfate is a better leaving group than acetate. Trifluoroperacetic acid is the most efficient reagent for this rearrangement². For instance, cyclohexanone reacts 200 times faster with trifluoroperacetic acid than peracetic acid. However, *m*-CPBA is the most common reagent because it is commercially available. An important modification of the Baeyer-Villiger oxidation is **Dakin reaction** (sec.6.3.3).

Mechanism

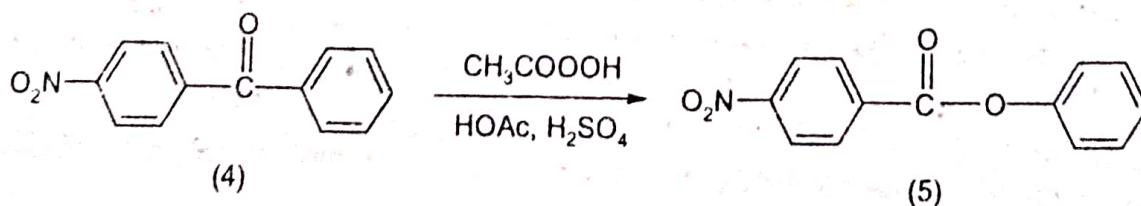
The mechanism of Baeyer-Villiger rearrangement is not clear, however it is believed that the reaction proceeds as follows.



The first step involves the protonation of carbonyl oxygen. The addition of peracid to the initially protonated ketone gives a tetrahedral intermediate (1). Elimination of carboxylate anion and migration of R to the electron deficient oxygen atom occur simultaneously. The resulting protonated form of ester (2) loses a proton to yield ester (3). Thus, the reaction involves a migration of alkyl or aryl group from adjacent carbon to electrophilic oxygen. As the leaving group, carboxylate anion departs, partial positive charge develops at the oxygen atom and 1,2-alkyl shift from adjacent carbon to oxygen takes place. It is believed that the loss of carboxylate anion and migration of R are concerted. A mechanistic study using ^{18}O labelled ketone has demonstrated that the carbonyl oxygen of the ketone becomes the carbonyl oxygen of the ester and the ester has the same ^{18}O content as the ketone. These observations support the above mechanism suggested for Baeyer-Villiger oxidation.

Migrating aptitude

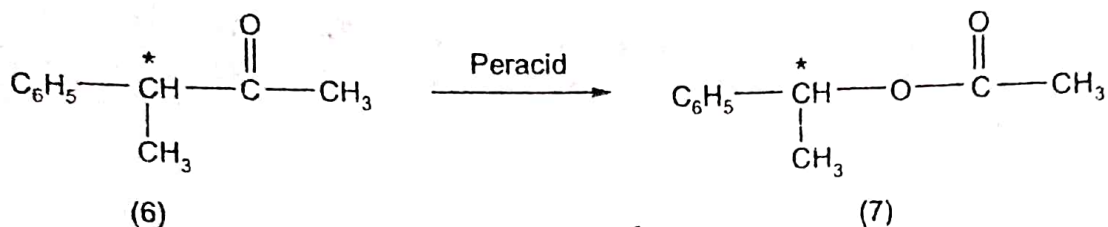
The order of preference for migration among alkyl groups is tertiary > secondary > primary > methyl. Aryl group migrates in preference to methyl and primary alkyl groups. In the aryl series, migration is facilitated by electron-releasing *para* substituents. Thus migratory aptitude among aryl groups is $p\text{-CH}_3\text{OC}_6\text{H}_4 > \text{C}_6\text{H}_5 > p\text{-O}_2\text{NC}_6\text{H}_4$. For example, phenyl *p*-nitrophenyl ketone (4) yields only phenyl *p*-nitrobenzoate (5) by migration of phenyl group.



The reaction is faster for peracids substituted by electronegative group and for ketones bearing electropositive substituents. Phenyl groups which are *ortho*-substituted migrate less readily than their *para*-substituted counterparts.

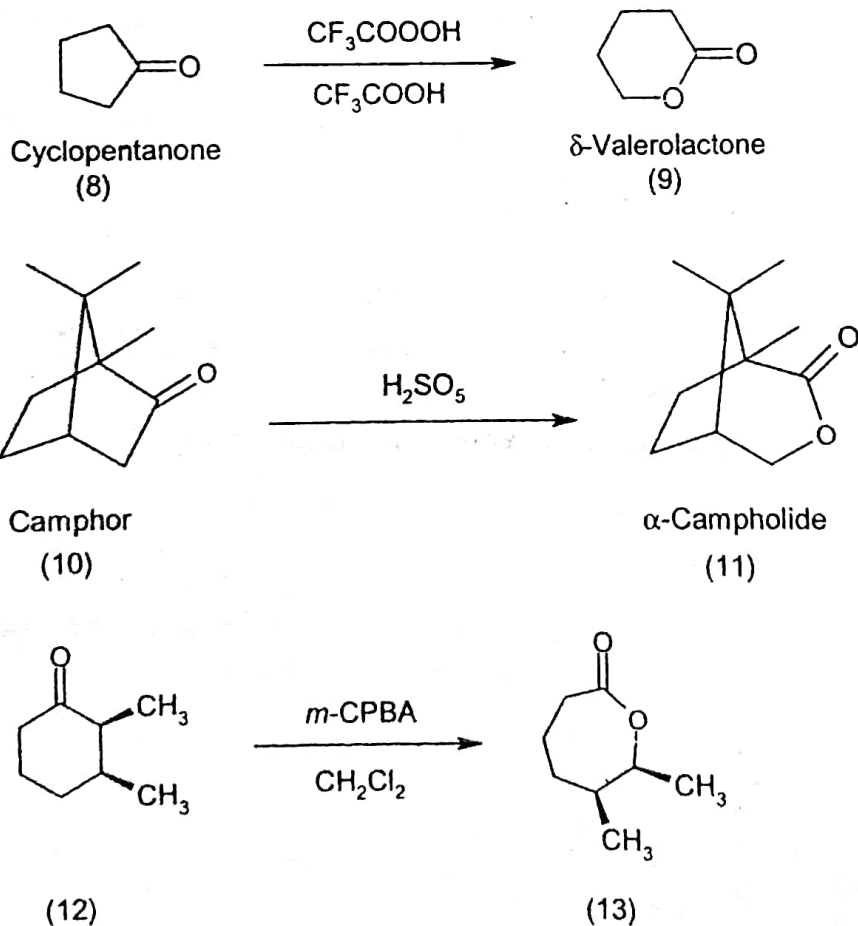
Stereochemistry

The stereochemistry of the Baeyer-Villiger oxidation is same as that of carbon to nitrogen rearrangements. The ketone (6) in which the migrating group has an asymmetric center gives product, (7), with complete retention in configuration.

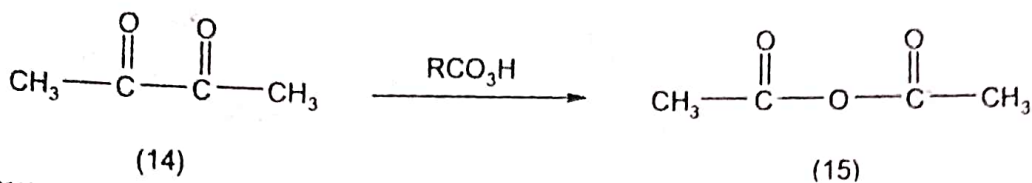


Applications

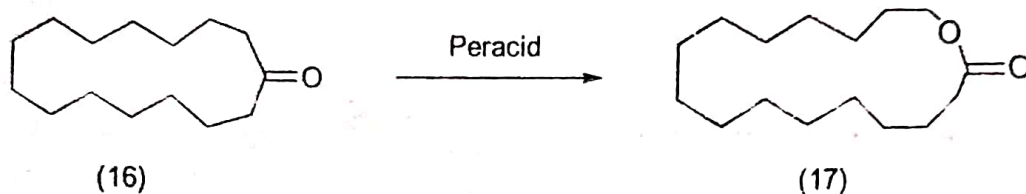
Baeyer-Villiger oxidation has great synthetic utility as it permits the transformation of ketones into esters. An oxygen atom is inserted next to the carbonyl group. This reaction is applicable to both acyclic ketones and cyclic ketones. Oxidation of cyclic ketones occurs with ring expansion and form lactones as illustrated in the conversion of cyclopentanone (8) to the δ -valerolactone (9). Similarly, camphor (10) on Baeyer-Villiger oxidation gives α -campholide (11) in 30% yield by use of Caro's acid and 2,3-dimethyl cyclohexanone (12) can be converted into the lactone (13) by this method.



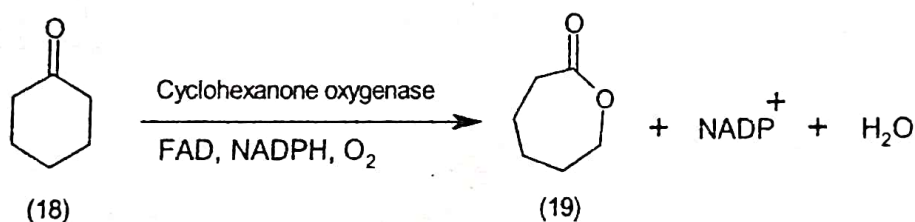
Other carbonyl compounds that undergo oxidation with peracids are 1,2-diketones and α -ketoesters. For example, oxidation of α -diketone (14) gives an anhydride, (15).



Baeyer-Villiger oxidation is a very useful method for the synthesis of large ring lactones, which are otherwise difficult to prepare by intramolecular esterification of long-chain hydroxyacids. For instance, the lactone (17) (from angelica oil) can be prepared by the Baeyer-Villiger oxidation of cyclopentadecanone (16).

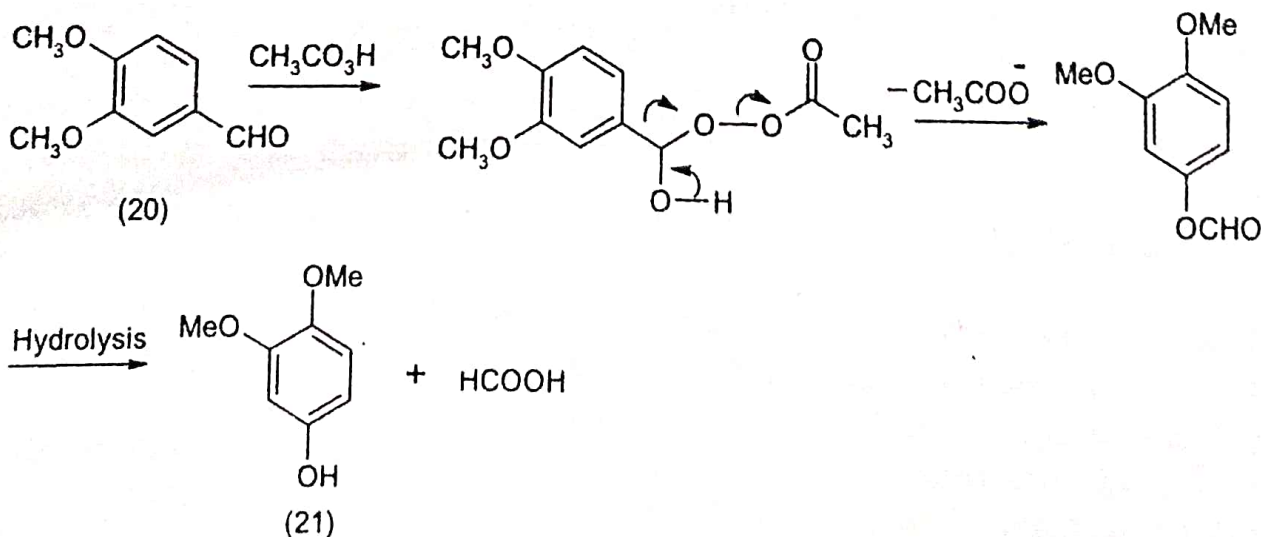


Baeyer-Villiger oxidation is also possible by the action of enzymes³. For example, cyclohexanone (18) is converted into (19) by using a purified cyclohexanone oxygenase enzyme.



Aldehydes also undergo the Baeyer-Villiger oxidation to usually give carboxylic acids⁴. The reaction involves either migration of hydrogen or fragmentation of the intermediate.

The ester formed in Baeyer-Villiger oxidation can be hydrolyzed to corresponding phenol, thus it provides a route to transfer aldehydes or ketones to phenol. Veratraldehyde (20), for example, is converted into 3,4-dimethoxyphenol (21) by oxidation with peracid followed by hydrolysis (also see Dakin reaction, sec. 6.3.3).

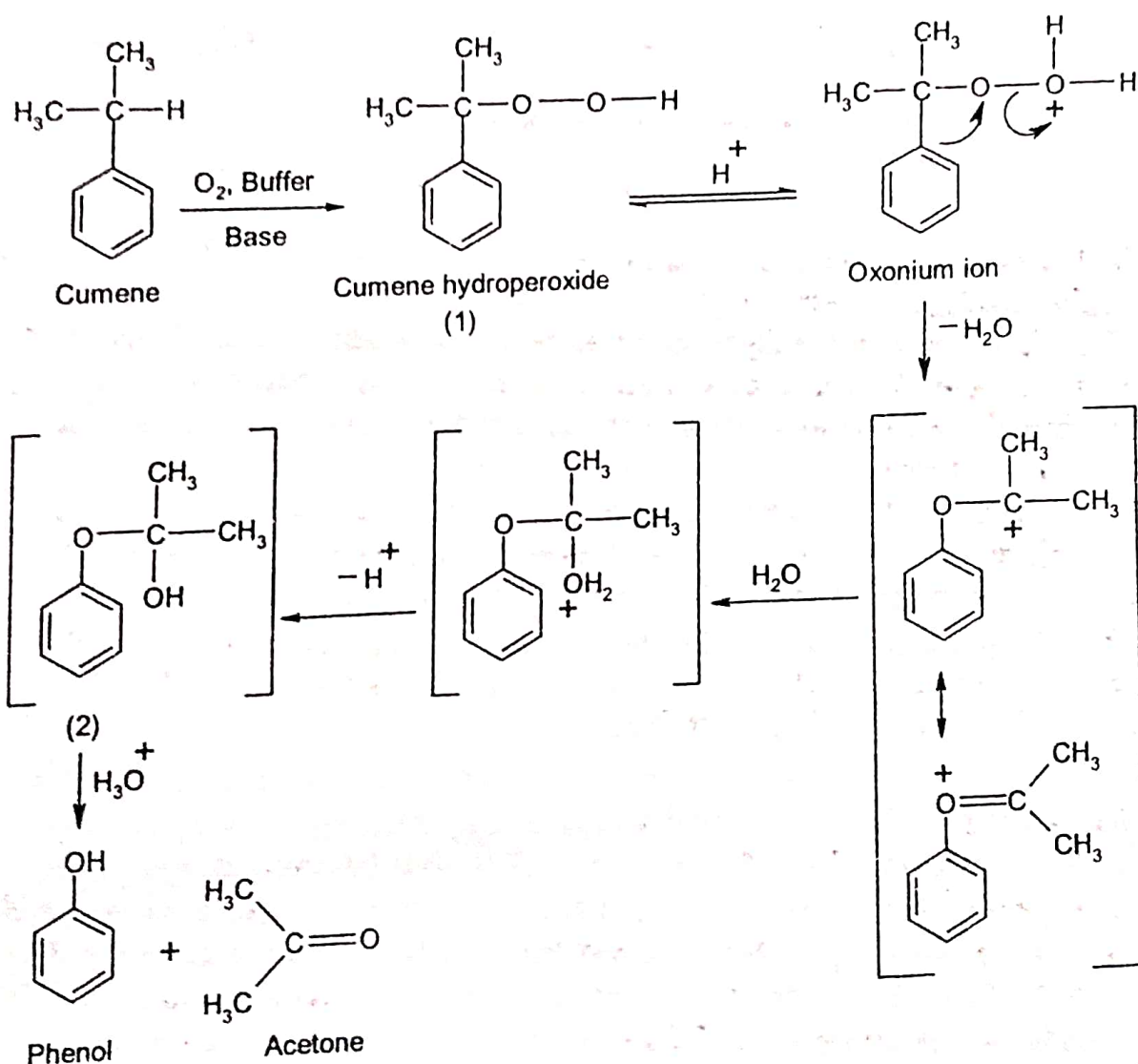


References

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2. H. O. House, *Modern Synthetic Reactions*, 2nd edn., Benjamin: Menlo Park, New York, 1972, pp. 321; W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, 1955, 77, 2287.
3. C. C. Ryerson, D. P. Ballou, C. Walsh, *Biochemistry*, 1982, 21, 2644; N. A. Donoghue, D. B. Norris, P. W. Trudgill, *Eur. J. Biochem.*, 1976, 63, 175.
4. H. Kwart and N. J. Wegemer, *J. Am. Chem. Soc.*, 1961, 83, 2746.

6.3.2 Hydroperoxide rearrangement

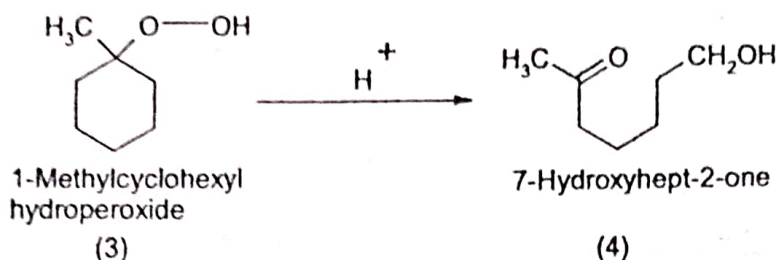
The acid-catalysed rearrangement of hydroperoxides proceeds by a mechanism similar to that of **Baeyer-Villiger oxidation** (sec. 6.3.1). For example, cumene hydroperoxide (1) when treated with sulfuric acid gives hemiacetal (2). Hydrolysis of unstable hemiacetal gives phenol and acetone. The cumene hydroperoxide can be obtained by autooxidation of cumene. This is the commercial method for the preparation of phenol.



The first step in the mechanism involves the protonation by acid at the oxygen atom of alkyl hydroperoxide. This is followed by the cleavage of the peroxide bond and migration of alkyl or aryl group from adjacent carbon to oxygen. The migration of phenyl group to the resulting electron-deficient oxygen atom is synchronous with the loss of water. The resulting carbocation intermediate is hydrated to give a hemiacetal.

Subsequently, hemiacetal under acidic conditions readily undergo hydrolysis to an alcohol and a carbonyl compound.

1-Methylcyclohexyl hydroperoxide (3) rearranges to give 7-hydroxyhept-2-one (4).



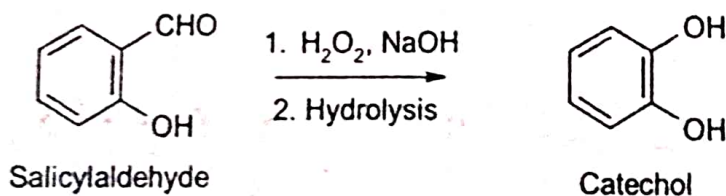
Rearrangements in hydroperoxide can be catalysed by strong acids such as sulfuric acid, perchloric acid and also by Lewis acids.

Migratory aptitude

When both aryl and alkyl groups are present in hydroperoxide, phenyl group migrates in preference to methyl group. The order of preference for migration among alkyl groups is $R_3C > R_2CH > RCH_2 > CH_3$.

6.3.3 Dakin reaction

The replacement of the aldehyde or acetyl group in phenolic aldehydes or ketones by a hydroxyl group on reaction with alkaline hydrogen peroxide is known as **Dakin reaction**^{1,2}. For example, salicylaldehyde is converted into catechol in 70% yield.



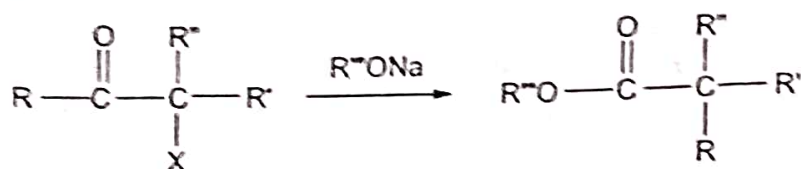
Mechanism

The mechanism of Dakin reaction is not certain. However, a mechanism analogous to **Baeyer-Villiger oxidation** (sec. 6.3.1) is suggested. The carbonyl carbon is attacked by the hydroperoxide anion. The resulting tetrahedral intermediate (1) undergoes migration of aryl group with subsequent elimination of hydroxide ion to give formate ester (2). An electron-releasing group (such as hydroxyl or amino) is necessary for efficient migration of aryl group. The intermediate formate ester (2) has been isolated and converted into catechol on hydrolysis under aqueous alkaline conditions of the reaction.

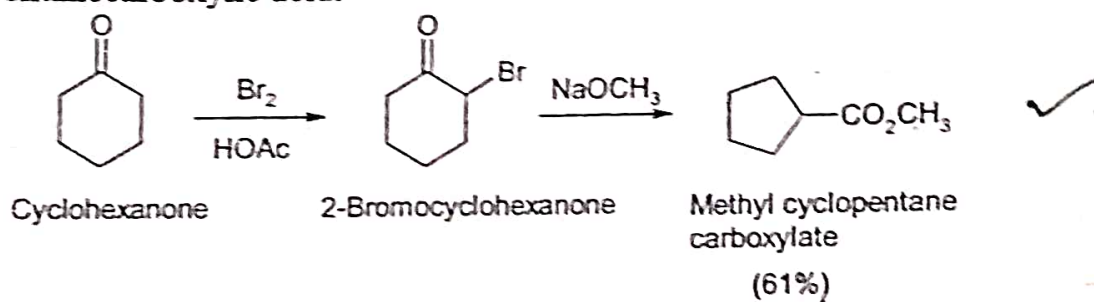
migration of carbon occurs from C, N, S and O to an adjacent atom bearing an unshared electron pair and negative charge. For example, **Wittig rearrangement** involves oxygen to carbon migration, **Stevens rearrangement** involves nitrogen to carbon migration. Carbon to carbon migration is also possible.

6.4.1 Favorskii rearrangement ¹⁻⁵

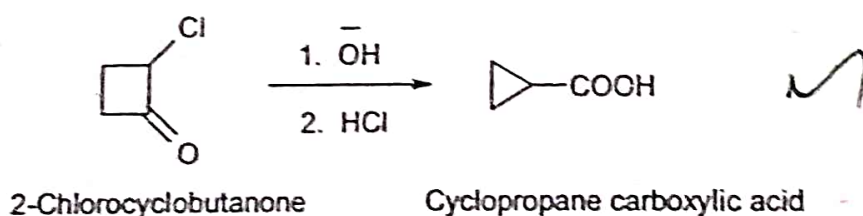
The base-catalysed rearrangement of α -haloketones (chloro and bromo) to carboxylic acid derivatives is called **Favorskii rearrangement** (reaction).



The rearrangement of cyclic ketones involves ring contraction, for example, 2-bromocyclohexanone when treated with sodium methoxide is converted into methyl ester of cyclopentanecarboxylic acid.

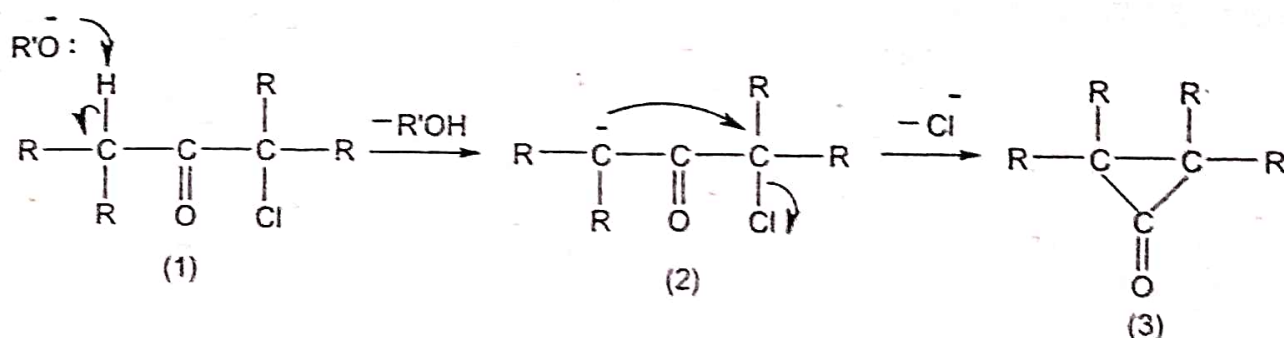


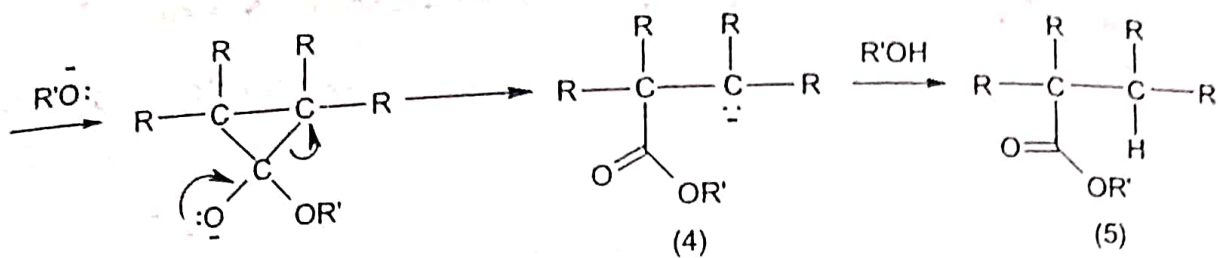
2-Chlorocyclobutanone on treatment with sodium methoxide, followed by hydrolysis is converted into cyclopropanecarboxylic acid.



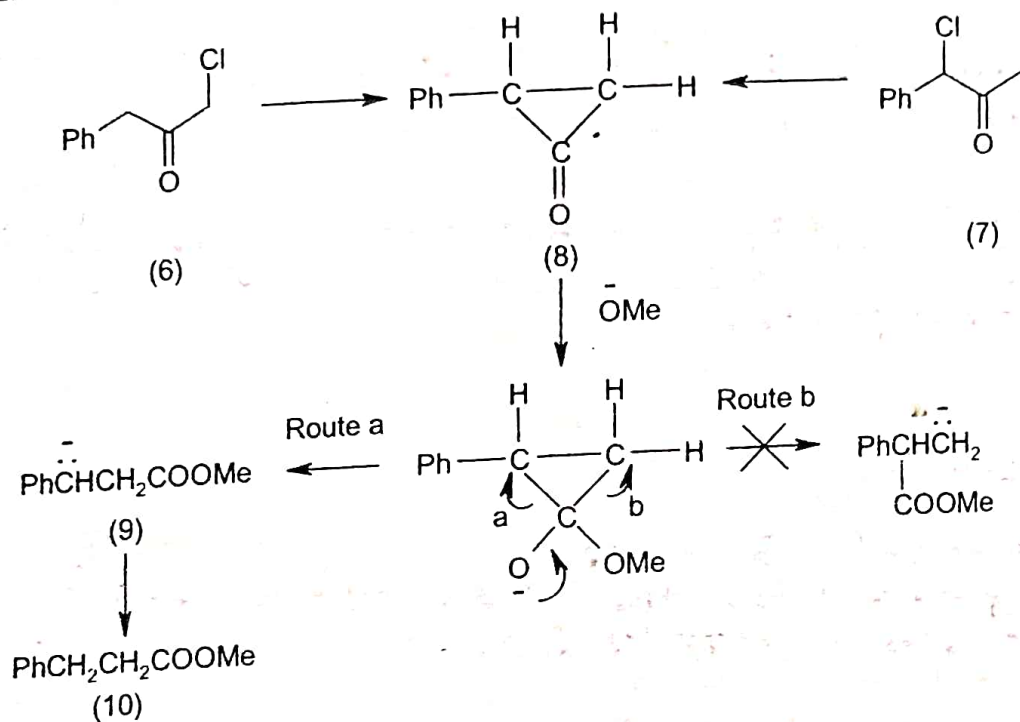
Mechanism

The generally accepted mechanism involves the reactive cyclopropanone intermediate. Base abstracts the α -hydrogen from (1) to give the carbanion (2), which undergoes intramolecular $\text{S}_{\text{N}}2$ displacement of the halide ion. The resulting cyclopropanone intermediate (3) is opened under the reaction conditions to give the more stable carbanion (4), which takes proton from solvent to furnish final product, ester (5).



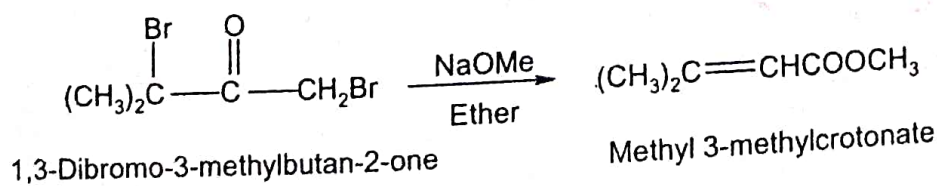


The above mechanism is supported by the fact that same ester (10) is formed from the isomeric haloketones (6) and (7).



In the symmetrical cyclopropanone intermediate, the two α -carbons are equivalent, and ring opening *via* route a or route b gives the same carbanion. However, unsymmetrical cyclopropanone ring opens in such a way so that the more stable carbanion of the two possible carbanions is formed. For instance, the cyclopropanone ring (8) opens *via* route-a to give the more stable of two possible carbanions that can be formed. The carbanion (9) is stabilized by resonance, therefore it is preferred and the product is $\text{PhCH}_2\text{CH}_2\text{COOCH}_3$ (10).

Favorskii rearrangement of α,α and α,α' -dihaloketones leads to the formation of α,β -unsaturated esters. In this case ring opening involves elimination of halide ion.

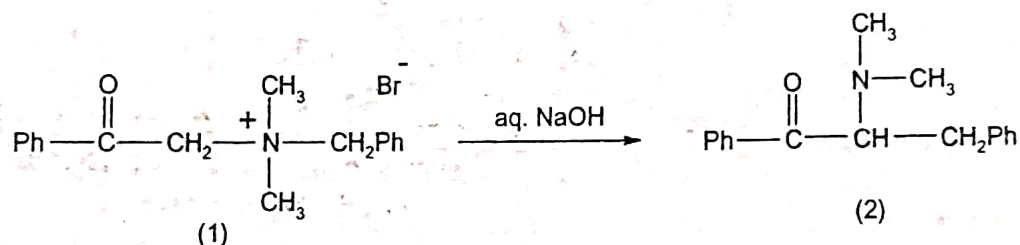


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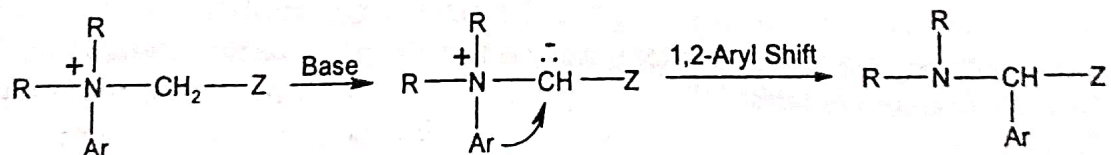
6.4.2 Stevens rearrangement

A quaternary ammonium salt, in which none of the alkyl group is having a β -hydrogen atom but one of the alkyl group has an electron-withdrawing group β - to the nitrogen atom, undergoes base-catalysed rearrangement¹ to yield a tertiary amine. The rearrangement involves migration of a group, without pair of electrons, from nitrogen to carbon having negative charge. For example, phenacylbenzyltrimethylammonium bromide (1) gives α -dimethylamino- β -phenylpropiophenone (2) on treatment with aqueous hydroxide.

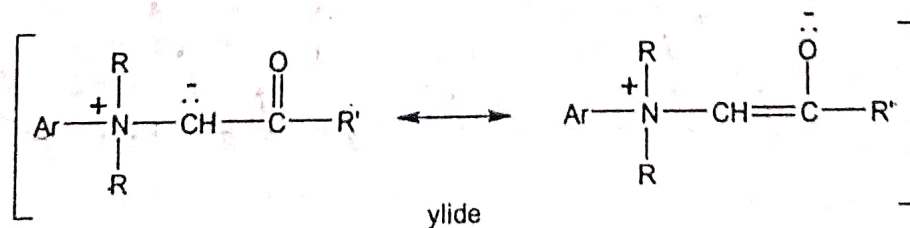


Mechanism

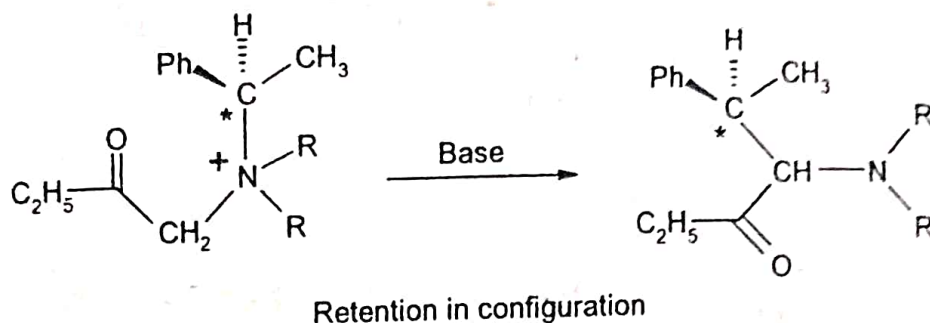
Crossover experiments showed the mechanism of Stevens rearrangement to be intramolecular. It was thought earlier that this rearrangement occurred in a concerted manner. The base abstracts the hydrogen from the ammonium salt to give the ylide, which rearranges to give the tertiary amine.



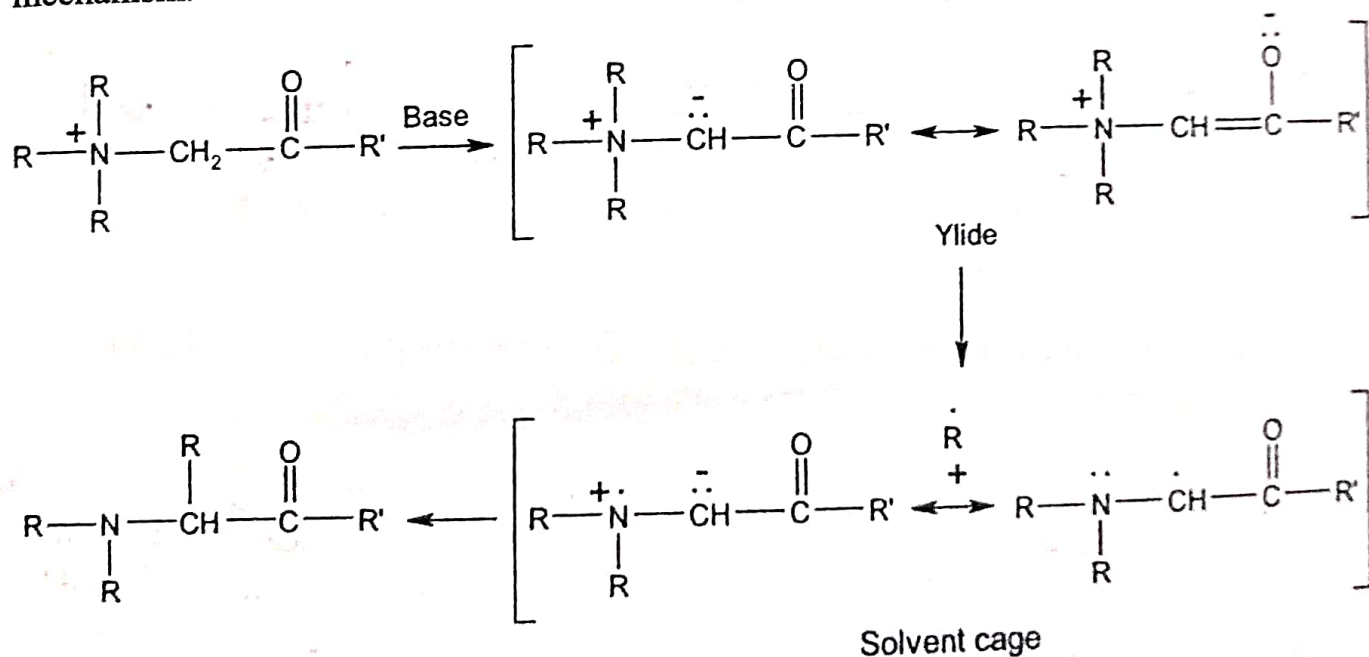
The role of electron-withdrawing group, such as a carbonyl group, is to stabilize the ylide.



However, it was further observed that the rearrangement occurs with retention of absolute stereochemistry at the migrating center.



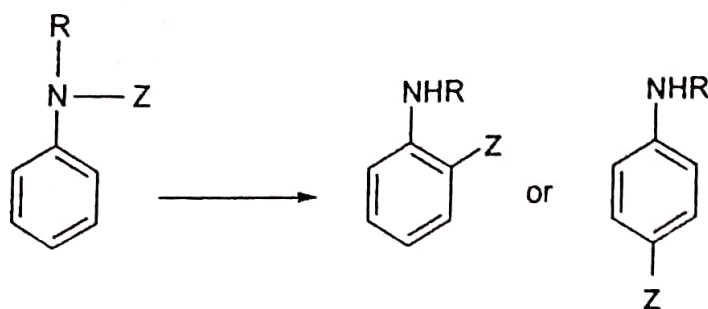
Concerted rearrangement shown above would not be an allowed reaction according to orbital symmetry rules. Such observations, therefore, rule out a concerted mechanism and a radical pair mechanism is proposed. The radical pair mechanism involves deprotonation followed by homolytic fragmentation of ylide to produce a pair of radicals. The rapid recombination of pair of radicals, which remain together in a tight solvent cage, gives the final product. Formation of small amount of coupling product R-R supports this mechanism.



A third mechanism is also proposed, in which ion pairs are formed instead of radical pairs. Benzyl group migrates in preference to alkyl group.

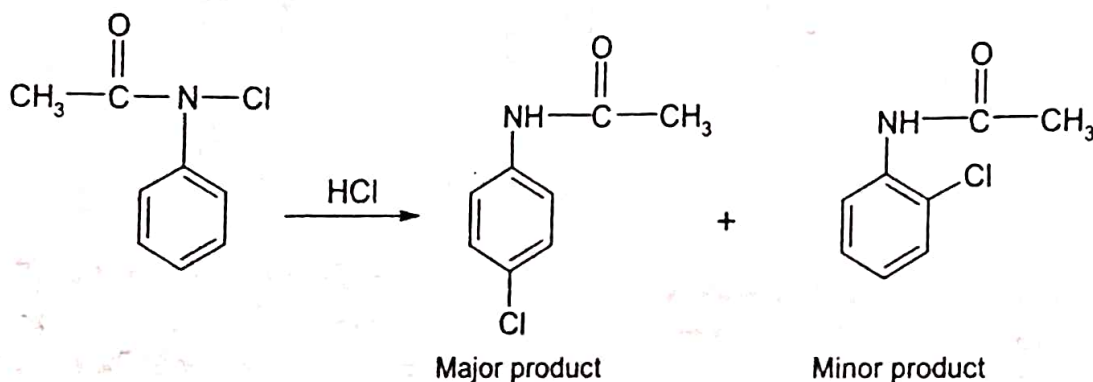
A variant of the Stevens rearrangement is the rearrangement of sulfur ylides². For example, sulfonium salt (3) on deprotonation gives a sulfur ylide (4), which subsequently rearranges to (5). Quaternary salts having β -hydrogen atom undergo elimination with base to give alkene and tertiary amine. The reaction is known as **Hofmann elimination** (see chapter 1.5; 5.43).

intermolecular or intramolecular mechanism. The aniline derivatives of the type PhN(R)Z , where Z is R, X, NH_2 , NO, or NO_2 , etc., undergo this type of rearrangement.

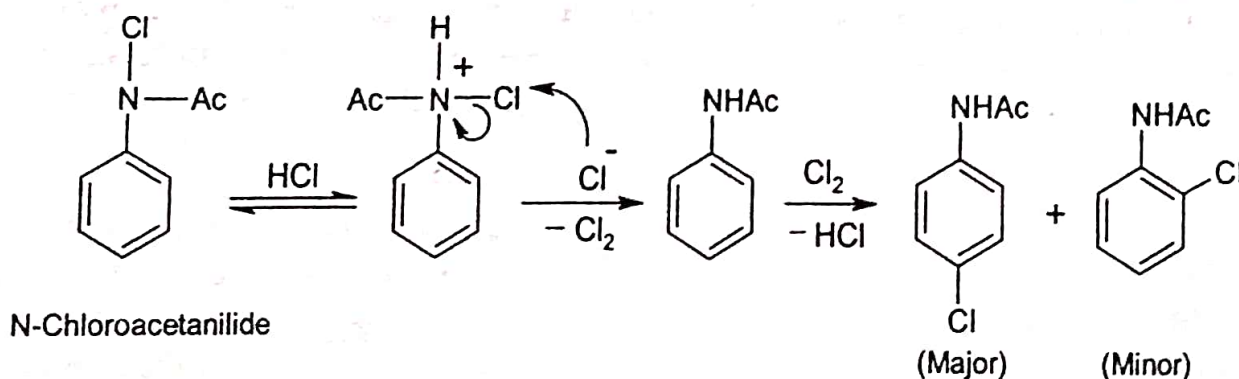


6.5.4 Rearrangement of N-haloacetanilides

Rearrangement of N-halogenated-N-arylamides in presence of corresponding aqueous HX to *p*-haloarylamides together with small amount of *o*-haloarylamides is known as **Orton rearrangement**. The rearrangement is also called **chloramine rearrangement** and is most commonly carried out with N-chloro and N-bromoamides.



The rearrangement of N-halogenated-N-arylamides in aqueous mineral acid takes place by an intermolecular mechanism as shown below.

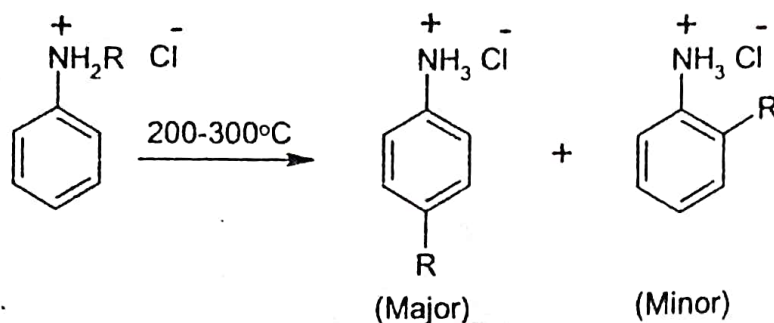


The reaction proceeds by the generation of Cl_2 which becomes attached to *p*- or *o*-positions of the aromatic nucleus in an ordinary electrophilic substitution reaction. When reaction is carried out in the presence of HCl having radioactive chlorine, the product contains some radioactive chlorine. Thus, mechanism of this reaction is intermolecular.

6.5.5 Hofmann-Martius rearrangement

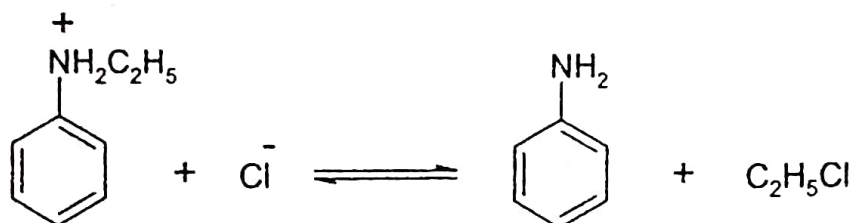
The rearrangement¹ of N-alkylarylamine hydrochloride salts on strong heating at about $200\text{--}300^\circ\text{C}$ is known as **Hofmann-Martius rearrangement**. In this reaction, an alkyl

group migrates from the nitrogen atom to *para*-position. If *para*- position is occupied, the *ortho* isomer is formed.



Mechanism

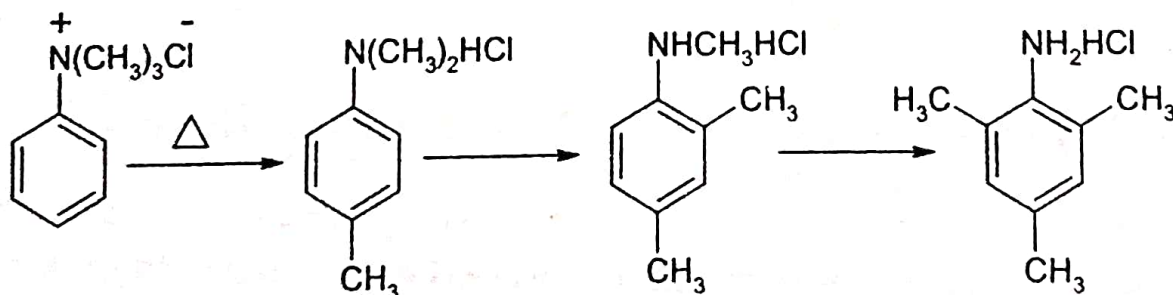
The mechanism of this rearrangement is intermolecular, and involves the formation of alkyl halide by the S_N2 reaction of mono N-alkylanilinium salt with Cl^- . Alkyl halide and aniline then undergo normal Friedel-Crafts alkylation process. However, with secondary or tertiary alkyl group, the reaction proceeds through the carbocations. While alkyl groups which are known to rearrange when set free in the form of carbocations do in fact give rearranged products, for example, n-butyraniline rearranges to tert-butyraniline.



Polyalkylated products may be isolated from the reaction mixture and primary alkyl side chains are isomerised. These observations support the above mechanism.

Applications

Phenyltrimethyl ammonium chloride when heated under pressure is converted to 2,4,6-trimethylaniline as its hydrochloride.



References

1. A. W. Hofmann and C. A. Martius, Ber., 1871, 4, 742; A. W. Hofmann, Ber., 1872, 5, 720.

6.5.6 Rearrangement of phenylhydroxylamine

N-Phenylhydroxylamine under strong acidic conditions rearranges to *p*-aminophenol and the reaction is known as **Bamberger rearrangement**¹.