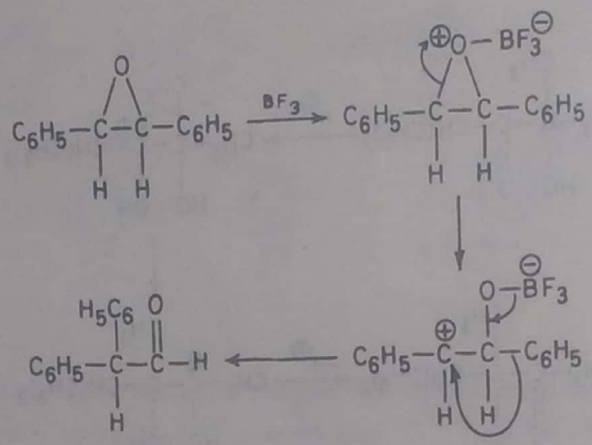
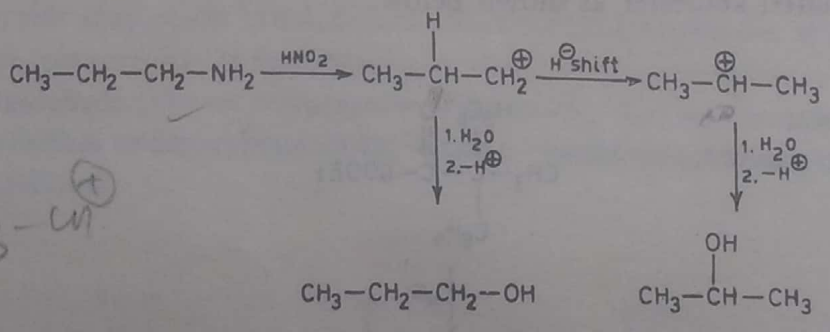
10.1.3 Rearrangement of Epoxides

Epoxides rearrange to carbonyl compounds under the influence of acids. Rearranged products are usually similar to those obtained from the acid-catalyzed rearrangement of the corresponding 1, 2-glycols.

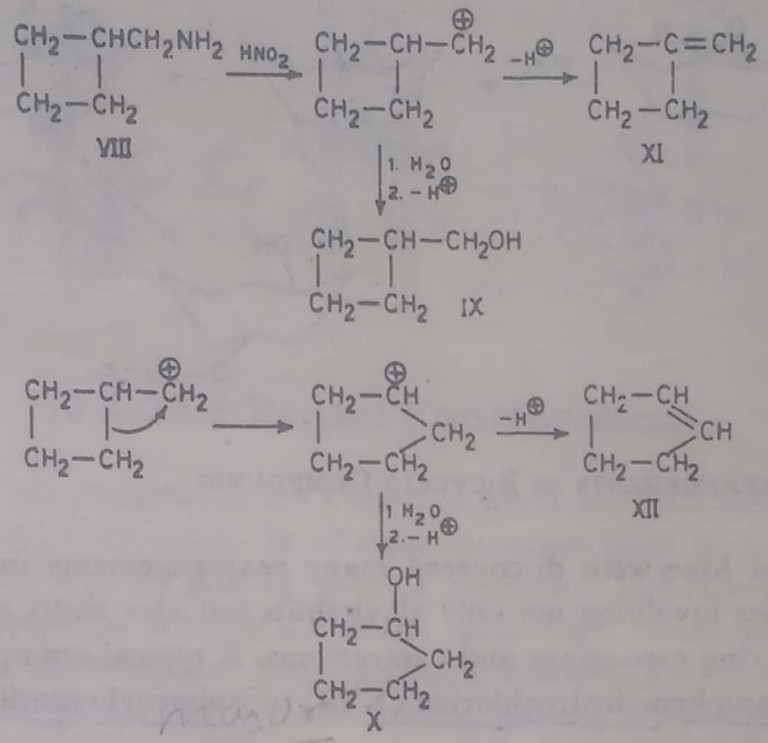


10.1.4 Demjanov Rearrangement

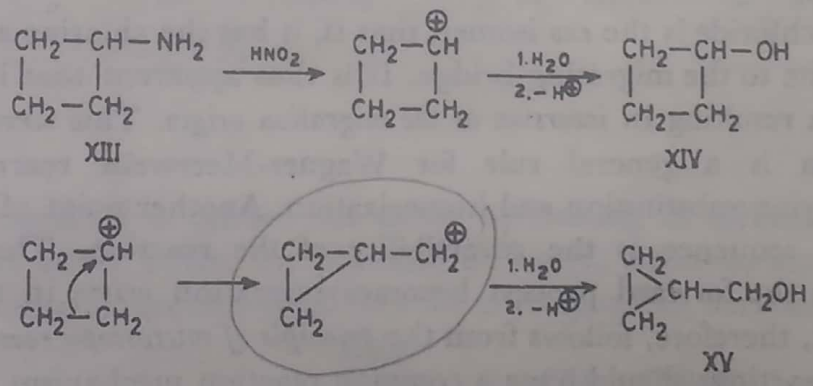
One of the most familiar methods for the generation of carbonium ions is the deamination of primary amines by means of nitrous acid. In many cases the initially formed carbonium ions undergo rearrangements to yield the rearranged products. Thus *n*-propylamine on treatment with nitrous acid yields some *n*-propyl alcohol together with a major proportion of *iso*propyl alcohol.



This reaction forms the basis of Demjanov's method of expanding and contracting alicyclic ring systems. For example, when cyclobutylmethylamine (VIII) is treated with nitrous acid it gives both cyclobutylcarbinol (IX) and cyclopentanol (X) besides methylenecyclobutane (XI) and cyclopentene (XII). The formation of these products can be readily rationalized by considering all the three typical properties of carbonium ions, viz., addition of nucleophiles, elimination of a proton and rearrangement to a more stable ion.



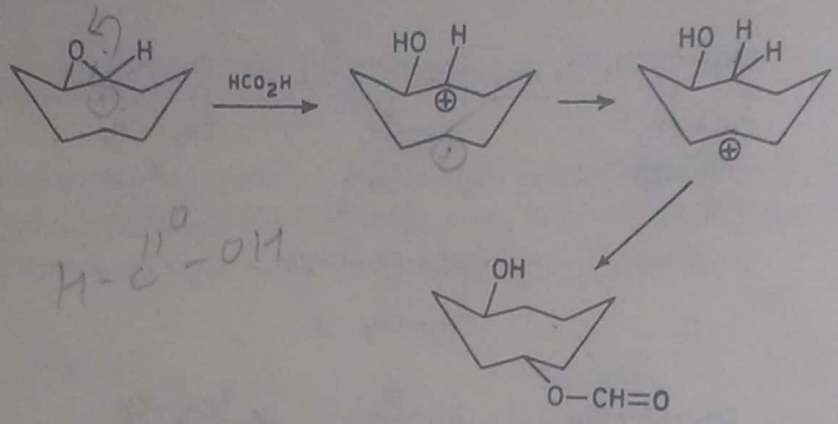
Cyclobutylamine (XIII) yields both cyclobutanol (XIV) and cyclopropylcarbinol (XV). The mechanism of ring contraction in this case can also be written in a similar fashion.



The formation of cyclopropylmethyl cation may be due to its relative stability by significant charge delocalization involving the ring bonds and the positive charge since the C—C bonds in cyclopropane have appreciable *p* character.

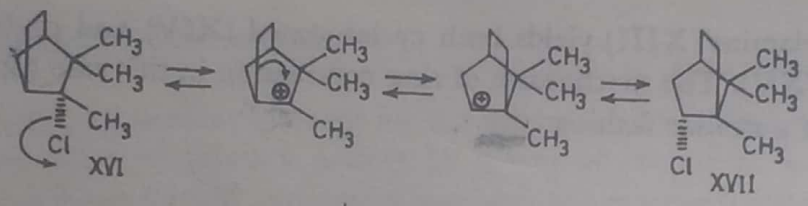
10.1.5 Transannular Rearrangements

Many cases are known where the migration origin and migration terminus are separated by more than two or three bonds. An illustrative example is the formolysis of cyclooctene oxide in which a transannular shift of the hydride ion follows the initial formation of a carbonium ion.

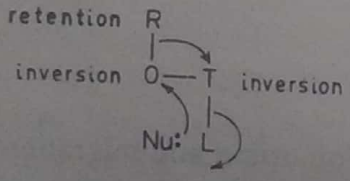


10.1.6 Rearrangements in Bicyclic Compounds

Wagner and Meerwein discovered many rearrangements in the bicyclic terpene series involving not only alkyl shifts but also shifts of ring bonds resulting in ring expansions and contractions. A typical example is the conversion of camphene hydrochloride (XVI) to isobornyl chloride (XVII).

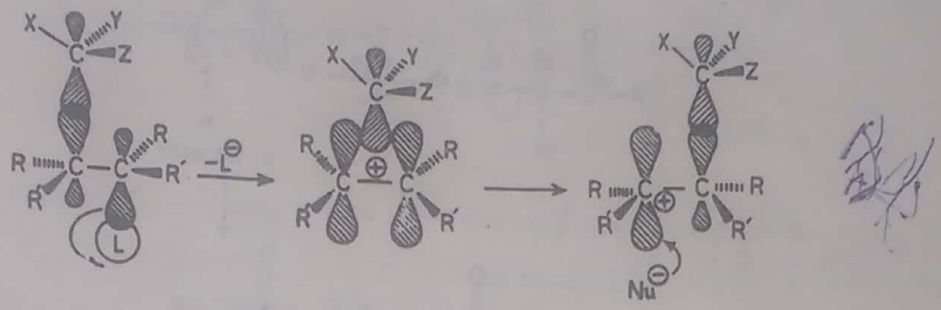


Isobornyl chloride is the *exo* isomer, that is, it has the chlorine atom on the side opposite to the migrating bridge. It is thus apparent that it is a rear-side attack resulting in *inversion at the migration origin*. This stereochemical implication is a general rule for Wagner-Meerwein rearrangements accompanying substitution and isomerization. Another point of interest in the above sequence is the reversibility of the reaction. The migration *terminus* in the forward process becomes migration *origin* in the reverse process. It, therefore, follows from the *principle of microscopic reversibility* that both the reactions should have a common reaction mechanism and identical stereochemical rules. There is inversion of configuration at both the migration origin and the migration terminus. Subsequently, we shall examine the evidence that proves the retention of configuration in the migrating group. We may summarize these rules in the following way.



R = Migrating group
O = Migration origin
T = Migration terminus
L = Leaving group
Nu = Nucleophile

These stereochemical rules have a general applicability for all 1, 2-shifts, and can be depicted in terms of the following orbital diagram.



10.2 Other Related Rearrangements

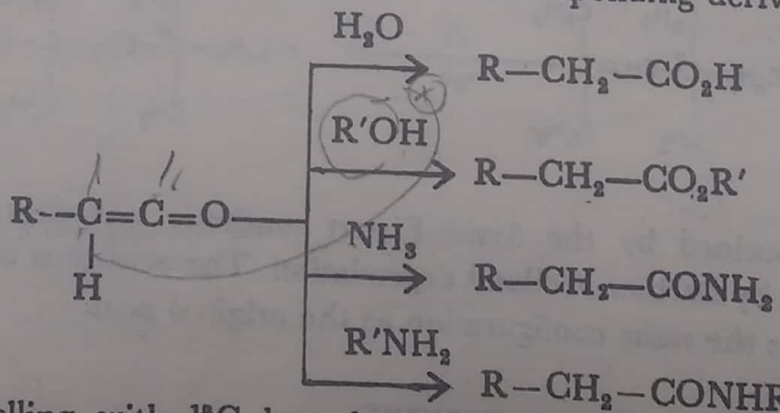
A number of rearrangements are known in which not a carbonium ion but a related species is involved. In all these processes there is 1, 2-shift of a group together with its pair of bonding electrons. The requirement for these rearrangements to occur is that the initial bond fission must produce an atom with an incomplete octet, normally a sextet. The most common rearrangements of this type involve carbene, nitrene, positive nitrogen and positive oxygen as intermediates.

10.2.1 The Wolff Rearrangement

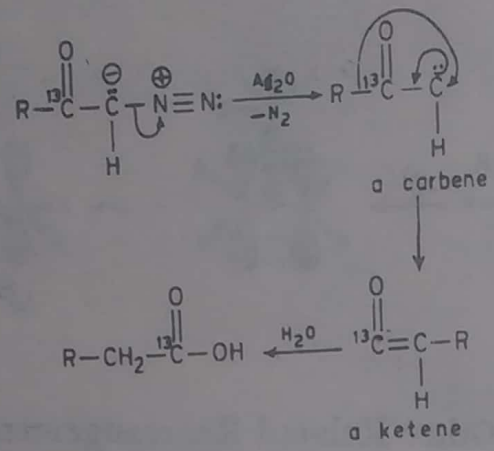
The Wolff rearrangement consists in the conversion of an α-diazoketone into a ketene and nitrogen.

$$R-\underset{\underset{O}{\|}}{C}-CHN_2 \longrightarrow R-CH=C=O+N_2$$

The rearrangement is carried out either by heating in solvents or with catalysts like silver oxide. In presence of water, alcohols, ammonia or amines, the ketenes are converted into the corresponding derivatives.



Isotopic labelling with ^{13}C has shown that the carbonyl carbon of α-diazoketone is converted into the carboxyl carbon of the resulting acid. On this basis the mechanism of the rearrangement can be written in the following steps:

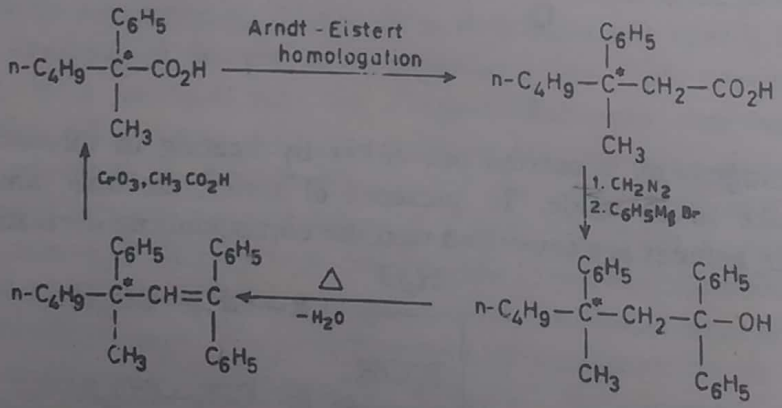


The Wolff rearrangement has practical utility in Arndt-Eistert homologation in which an acid is converted into its higher homologue by the following steps:

$$RCO_2H \xrightarrow{SOCl_2} R{-}COCl \xrightarrow{CH_2N_2} R{-}COCHN_2$$

$$\xrightarrow{Ag_2O} R{-}CH{=}CO \xrightarrow{H_2O} R{-}CH_2{-}CO_2H$$

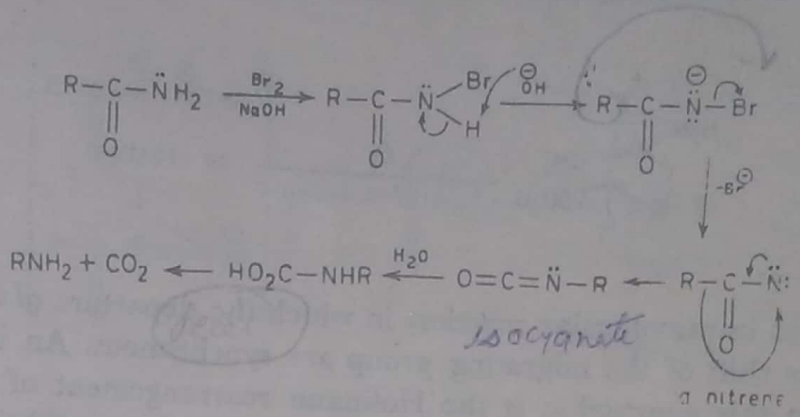
That the group R migrates with *retention of configuration* has been confirmed by the following transformations involving an optically active acid.



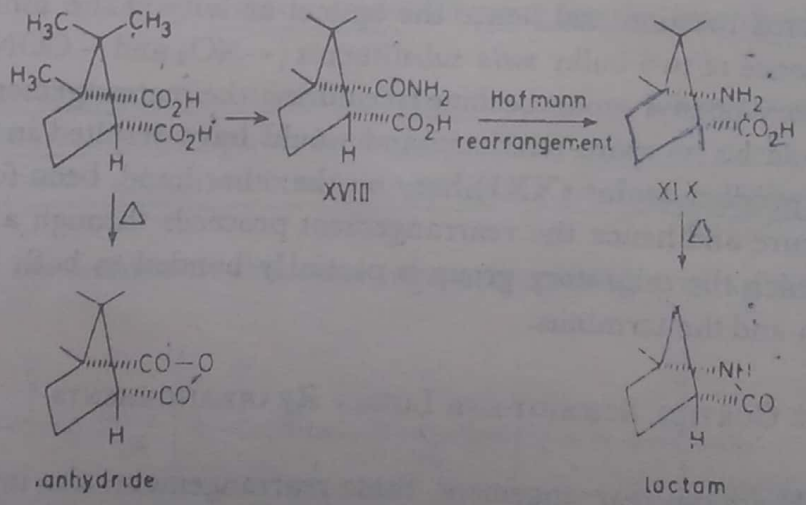
The acid obtained by the Arndt-Eistert synthesis was degraded to the original acid by Barbier-Weiland degradation. The acid thus obtained was found to have the same configuration as the original acid.

10.2.2 The Hofmann Rearrangement

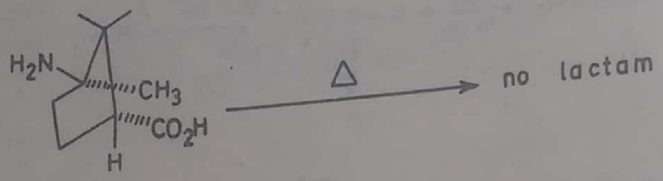
The Hofmann rearrangement consists in converting an amide to a primary amine by the action of halogens and base. The mechanism of the reaction may be depicted as follows:



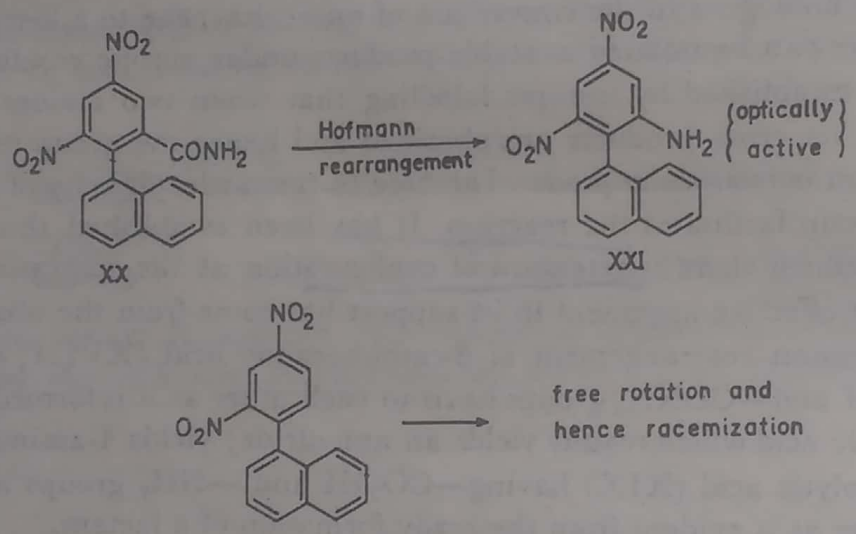
The intermediate nitrene contains a nitrogen atom having a sextet of electrons and so it is electron-deficient. The rearrangement of nitrene to isocyanate is analogous to the conversion of an acylcarbene to a ketene. The isocyanates can be isolated as stable products under aprotic conditions. It has been established by isotopic labelling that when two amides are rearranged no cross products are obtained and hence the group migration must be an *intramolecular process*. Increase in the nucleophilicity of the migrating group facilitates the reaction. It has been established that in this rearrangement there is retention of configuration at the migrating atom. The most effective argument in its support has come from the observation that Hofmann rearrangement of β-camphoramic acid (XVIII; in which —COOH and—$CONH_2$ groups lie *cis* to each other as it is formed from *cis* camphoric acid which readily yields an anhydride) yields 1-aminodihydro-α-campholytic acid (XIX) having—COOH and —NH_2 groups also *cis* to each other as is evident from the ready formation of a lactam.



Had there been an inversion of configuration at the migrating carbon, a *trans* amino acid would have been the product and this is incapable of forming such a lactam.



Thus it is an intramolecular reaction in which the departure of the halide ion and the shift of the migrating group are synchronous. An interesting example in this connection is the Hofmann rearrangement of an amide (XX) which is optically active due to restricted rotation around single bond joining the phenyl and the naphthyl groups.

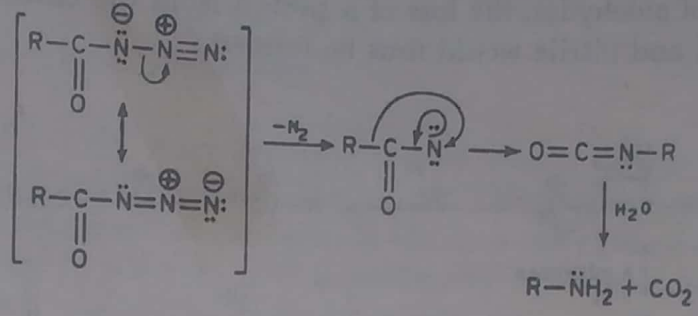


The restricted rotation and hence the optical activity of the amide is due to the presence of two bulky *meta* substituents ($-NO_2$ and $-CONH_2$). Had the migratory phenyl group become free during the rearrangement, the rotation would be no more restricted and would have resulted in racemization. The product, amine (XXI) has, on the other hand, been found to be optically pure and hence the rearrangement proceeds through a transition state in which the migratory group is partially bonded to both the migration origin and the terminus.

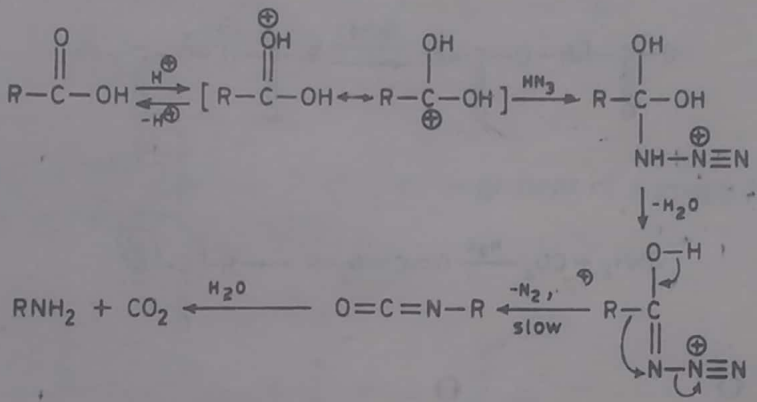
10.2.3 The Curtius, Schmidt and Lossen Rearrangements

As in the Hofmann rearrangement, these rearrangements also involve shifting of a group from carbon to nitrogen. The intermediate nitrenes rearrange to isocyanates which are finally converted into primary amines in the presence of water.

Curtius rearrangement consists in heating an acyl azide which loses nitrogen and then rearranges to an isocyanate.



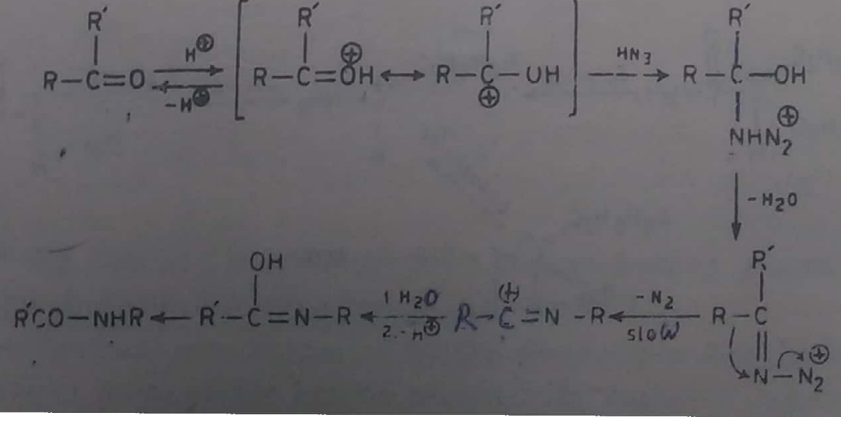
In the Schmidt modification of this reaction, the acyl azide is prepared by condensing a carboxylic acid and hydrazoic acid (HN_3) in the presence of sulphuric acid. The acyl azide is normally not isolated but allowed to decompose and rearrange in the reaction mixture itself. The following mechanism is consistent with the experimental observations.



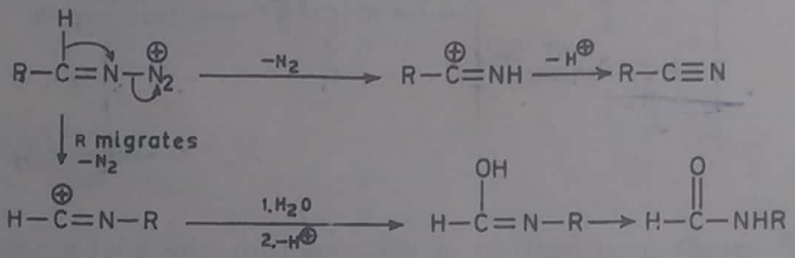
Since N-alkylated cations derived from the condensation of alkyl azides (RN_3) and carboxylic acids do not undergo Schmidt rearrangement, it appears that the removal of water molecule precedes the rate-determining step.

Carbonyl compounds also undergo Schmidt reaction when treated with hydrazoic acid in sulphuric acid. Ketones produce *amides* whereas aldehydes generally yield a mixture of the corresponding *nitrile* and *N-formyl* derivative.

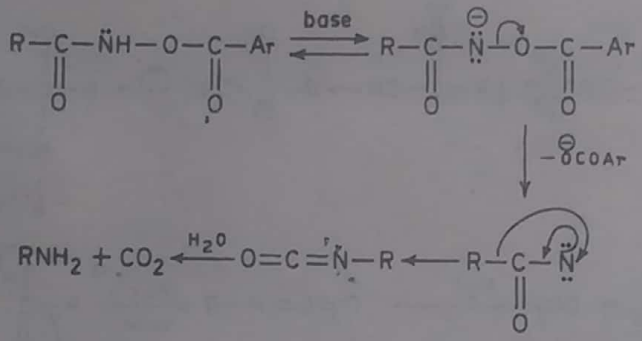
A probable mechanism of this rearrangement may be written as follows:



In the case of aldehydes, the loss of a proton from the carbonium ion may be preferred and nitrile would thus be formed.

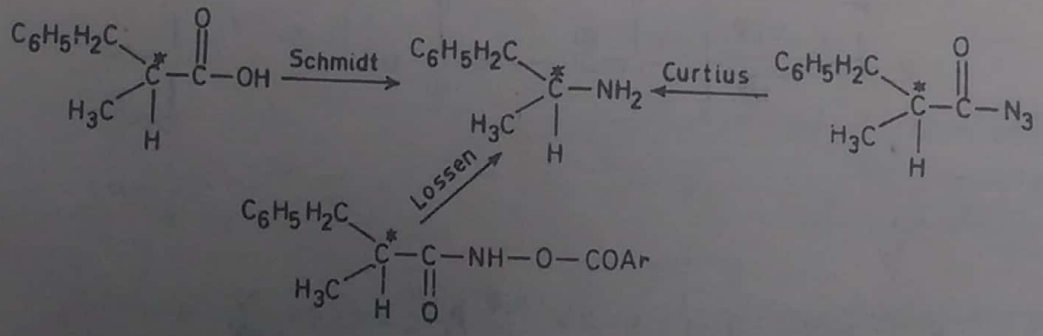


In the Lossen rearrangement a derivative of hydroxamic acid (RCONHOH) is decomposed in presence of base. The mechanism of the reaction is as follows:



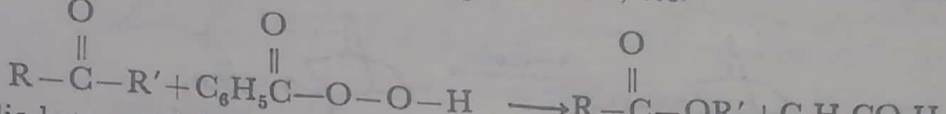
Since $\overset{O}{\overset{\|}{OC}}-Ar$ leaves as $\overset{O}{\overset{\|}{OC}}-Ar^-$ its separation and hence the rearrangement is facilitated by the presence of electron-withdrawing substituents in *meta*- or *para*-positions.

All these reactions—Curtius, Schmidt and Lossen—are *intramolecular rearrangements* in which the migrating group never becomes free. Also, the migrating group shifts from carbon to nitrogen with *retention of configuration*. These conclusions have been proved in a most elegant way by rearranging the appropriate derivatives of α-benzylpropionic acid, which yielded α-benzylethylamine having the same configuration as the starting materials.

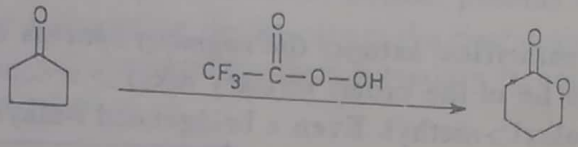


10.2.4 Baeyer-Villiger Oxidation

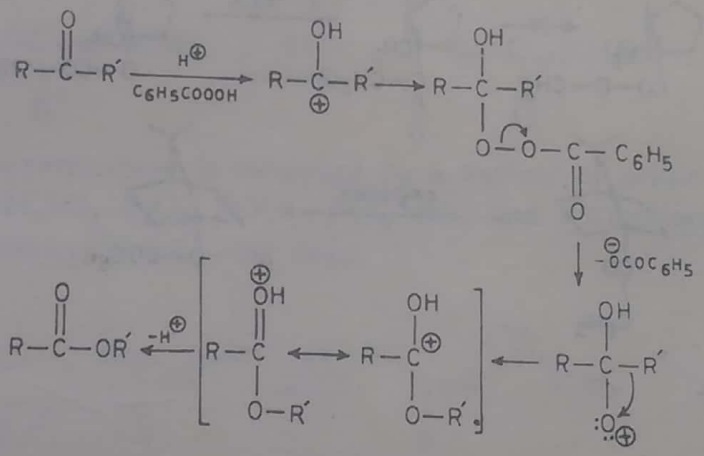
Several examples of the rearrangement of groups from carbon to electron-deficient oxygen atom are known. The Baeyer-Villiger reaction is the most interesting rearrangement of this type. It involves the oxidation of ketones to esters by means of peracids such as perbenzoic acid, peracetic acid, peroxytrifluoroacetic acid, permonosulphuric acid, etc.



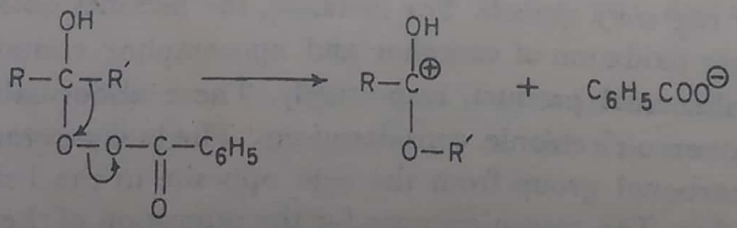
Cyclic ketones yield lactones.



The key step in this reaction is the rearrangement of a group from carbon to the electron-deficient oxygen.

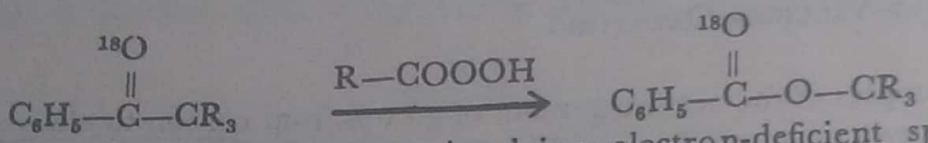


Most probably the loss of the carboxylate anion and the rearrangement are concerted.

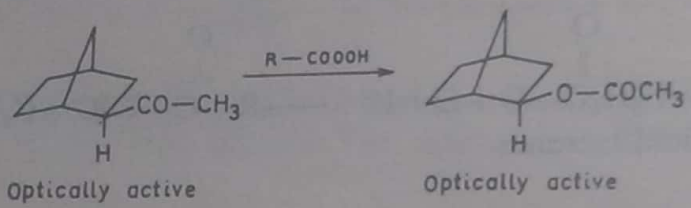


The rate of the reaction is accelerated by *electron-donating* groups in the ketone and by *electron-withdrawing* groups in the peracid.

The above mechanism is supported by the observation that the labelled carbonyl oxygen atom of the ketone becomes the carbonyl oxygen atom of the ester.

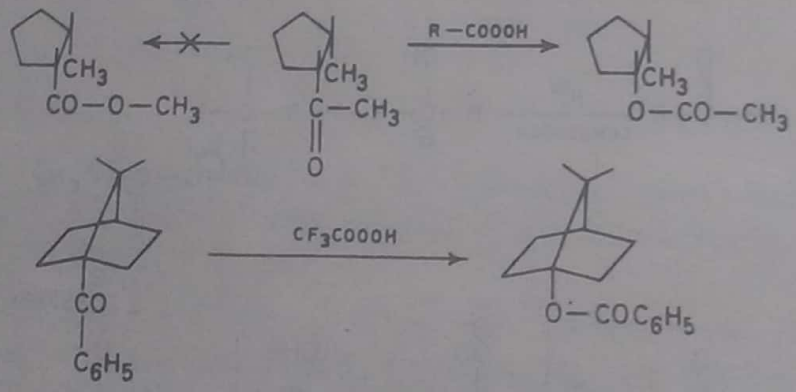


Like other rearrangements involving electron-deficient species, the Baeyer-Villiger reaction also takes place with the *retention of configuration* in the migrating group.

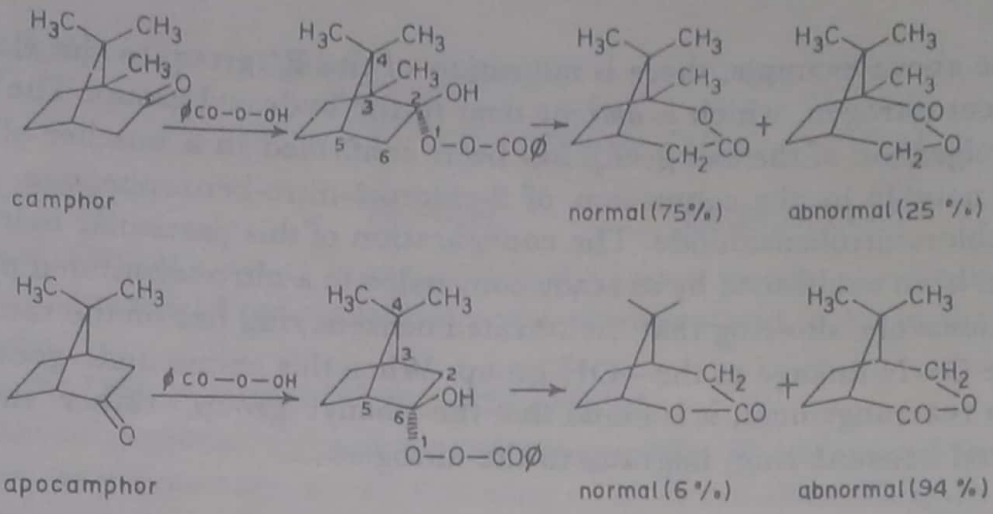


Optically active — Optically active

Finally, in unsymmetrical ketones the *migratory aptitude* of various groups has been found to be of the order: tertiary alkyl > secondary alkyl, aryl, benzyl > primary alkyl > methyl. Even a bridgehead *t*-alkyl group migrates in preference to the phenyl group.



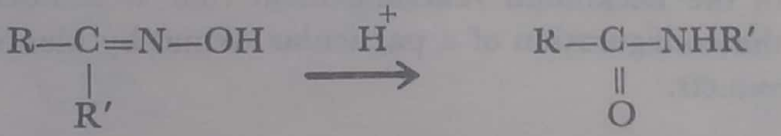
In condensed carbocyclic ketonic compounds, however, abnormal lactones are often formed in varying proportions by migration of the carbons having lesser *migratory aptitude*. For instance, the lactones obtained by the Baeyer-Villiger oxidation of camphor and apocamphor contain 25% and 94% of the abnormal product, respectively. These abnormalities can be explained on stereo-electronic considerations. The bulky peracid molecule attacks the carbonyl group from the side opposite to the bridge due to steric interaction. The transition state for the migration of the bridge-head carbon in either case would be the unfavourable twisted boat (atoms 1,2,3, 4,5,6,) whereas that for the migration of the primary carbon it would be the favourable chair shape.



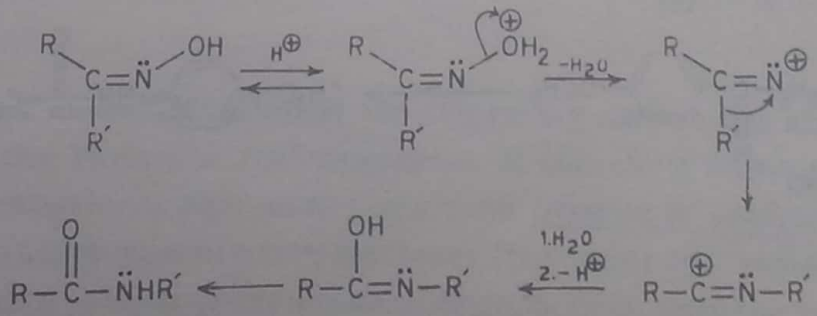
The much larger proportion of the normal product from camphor may be explained by the relative dominance of the electronic factor, i.e., the migrating carbon for the normal product is tertiary in camphor as against secondary in apocamphor.

10.2.5 The Beckmann Rearrangement

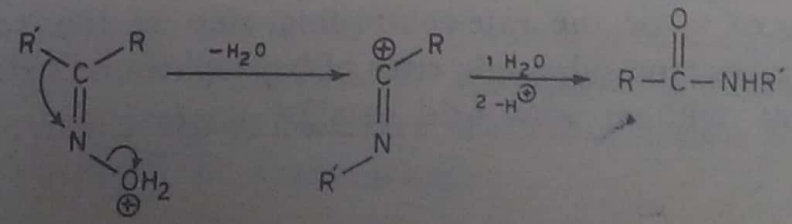
The acid-catalyzed transformation of a ketoxime to an N-substituted amide is known as the Beckmann rearrangement.



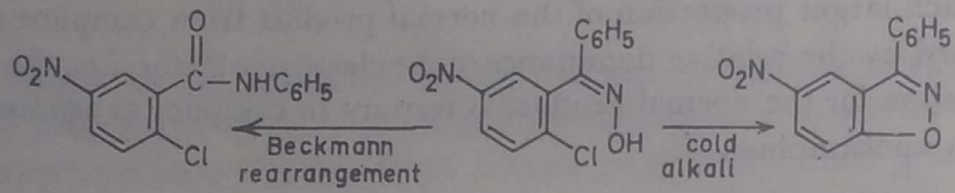
This rearrangement is catalyzed by a variety of acidic reagents such as H_3PO_2, H_2SO_4, P_2O_5, $SOCl_2$, PCl_5, etc., and a simplified mechanism can be written in the following steps.



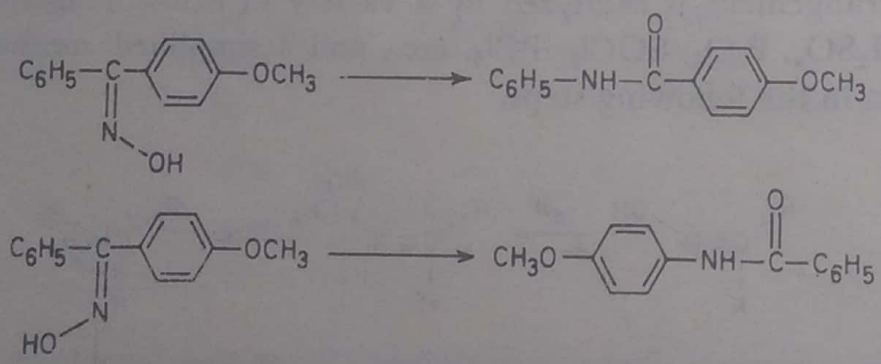
The rearrangement is highly *stereospecific* in that the migrating group always approaches the nitrogen atom on the side opposite to the oxygen atom.



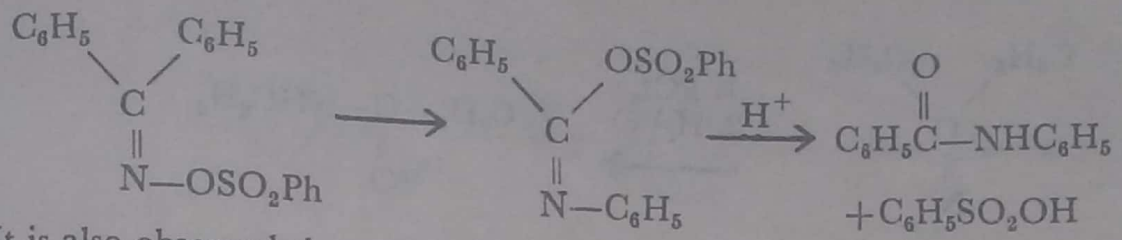
In the above example, there is migration of the R′ group to the electron-deficient nitrogen, which is *anti* or *trans* to the hydroxyl group. The exclusive migration of the *anti* group has been confirmed in a number of cases, most notably in the conversion of 2-chloro-5-nitro-benzophenone oxime to a chloronitrobenzanilide. The configuration of this particular oxime has earlier been established by its ready conversion to a nitro-substituted phenylbenzisoxazole, showing that the nitrated benzene ring lies on the same side of the C=N linkage as the—OH group. When this oxime undergoes Beckmann rearrangement, it is found that the phenyl group, rather than the nitrated benzene ring, migrates to the nitrogen.



Since it is always the *anti* group that migrates, it appears that either the breakage of the N—O bond and the group migration are synchronous or these two steps follow each other quickly. The migration of the *anti* group is so much certain in the Beckmann rearrangement that it is normally possible to establish the configuration of a particular oxime by identifying its rearrangement products.



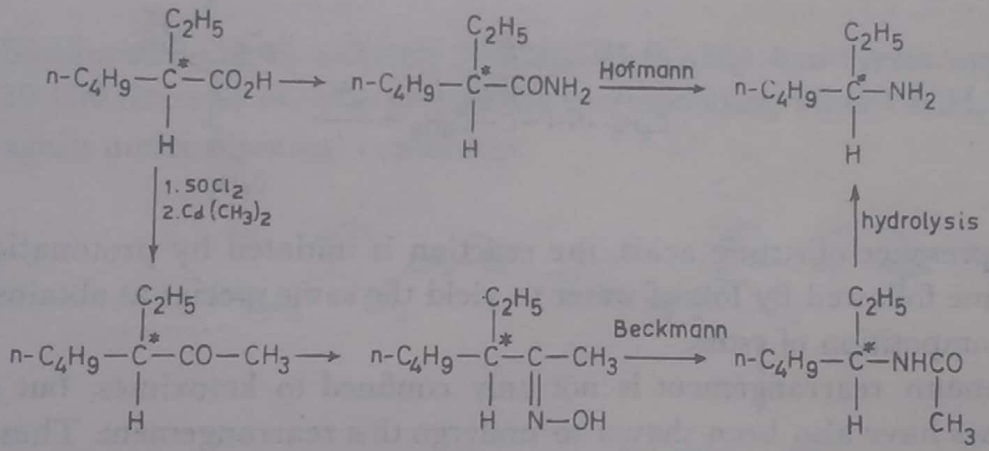
Another mechanistic feature of the rearrangement has been worked out by Kuhara and later by Chapman who established that the rearrangement does not take place in the oxime itself, but in its acyl derivative which ionizes and subsequently rearranges. The ionization of the acyl derivative has been shown to be the rate-controlling step of the rearrangement. Typically, the benzene sulphonic ester of benzophenone oxime undergoes rearrangement without any acid catalyst.



It is also observed that rates of isomerization of various oxime esters ran parallel to the strength of the esterifying acids which is found to be in the following order.

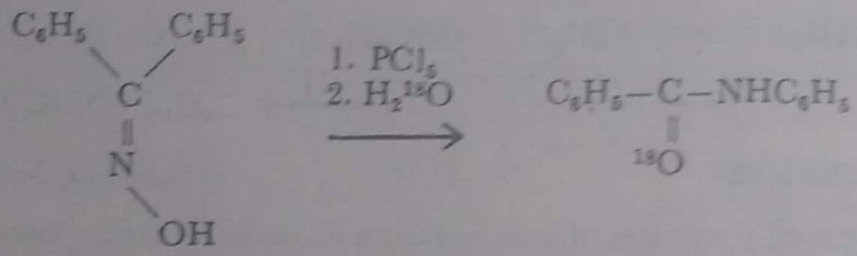
$$C_6H_5SO_2OH > C_6H_5COOH > CH_3COOH$$

Finally, the carbon atom of the migrating group *retains its configuration* in the Beckmann rearrangement. By the following series of reactions, Kenyon and Young not only proved retention of configuration but also correlated Beckmann and Hofmann rearrangements. Optically active 3-heptylcarboxylic acid was converted to its amide and subjected to Hofmann rearrangement. In another set of experiment the same acid was converted into 3-heptylmethyl ketone and then the oxime of this ketone was rearranged by the Beckmann method. Both these rearrangements yielded the same optical isomer of 3-heptylamine.

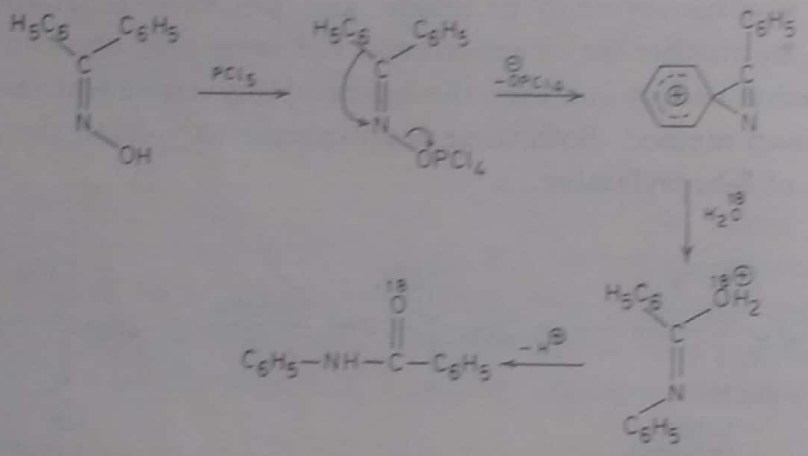


Since the retention of configuration at the migrating carbon has already been confirmed in the Hofmann rearrangement, it therefore follows that the Beckmann rearrangement also takes place with *retention of configuration*. Apparently the migrating group never becomes free from the remainder of the molecule and it also appears reasonable to believe that the breakage of C—C bond and the formation of the new C—N bond take place *synchronously*.

However, Beckmann rearrangement as a whole is not an intramolecular process since the carbonium ion, once formed, may combine with a hydroxyl ion present in solution. The rearrangement of benzophenone oxime into benzanilide was studied in presence of water containing heavy oxygen (^{18}O) The product incorporated the heavy isotope.

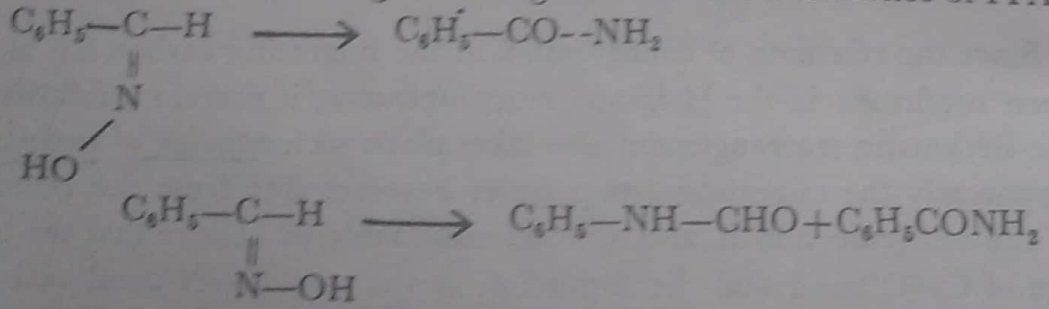


It is therefore evident that the Beckmann rearrangement does not proceed by an intramolecular exchange of the hydroxyl and the phenyl group; rather it passes through a carbonium ion which accepts hydroxyl ion or a water molecule from the solvent. Thus there is complete loss of the original oxime oxygen from the molecule during the reaction. A reasonable mechanism for the Beckmann rearrangement may be summed up as under:



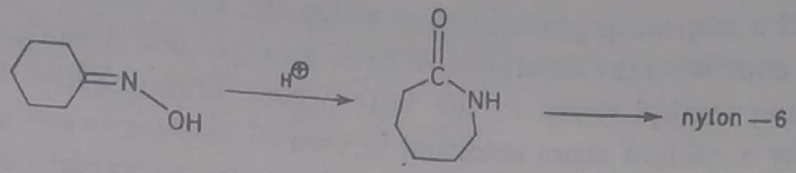
In the presence of strong acids, the reaction is initiated by protonation of the oxime followed by loss of water to yield the same species as obtained by the decomposition of ester.

Beckmann rearrangement is not only confined to ketoximes, but some aldoximes have also been shown to undergo this rearrangement. Thus, *syn*- and *anti*-benzaldoximes undergo rearrangement under the influence of PPA.



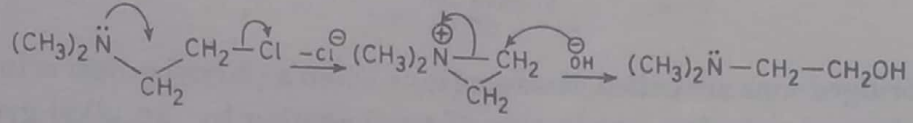
The formation of benzamide in the rearrangement of the *syn*-isomer has been explained by the ready conversion of some of the *syn*-form into the *anti* which then rearranges with a hydrogen migration.

Beckmann rearrangement has also been used for the enlargement of rings. An example of considerable industrial importance involves the rearrangement of cyclohexanone oxime to ω- caprolactam used for the manufacture of nylon-6.

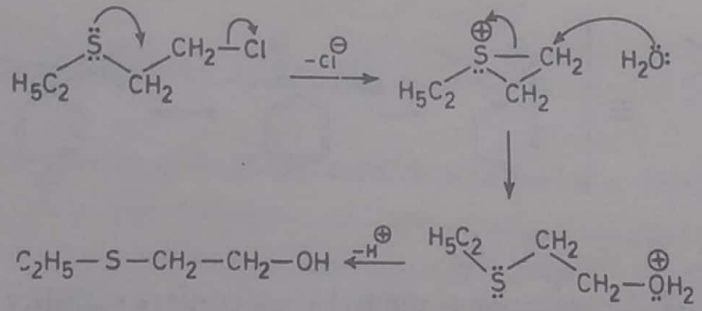


10.3 Bridged or Non-Classical Carbonium Ions

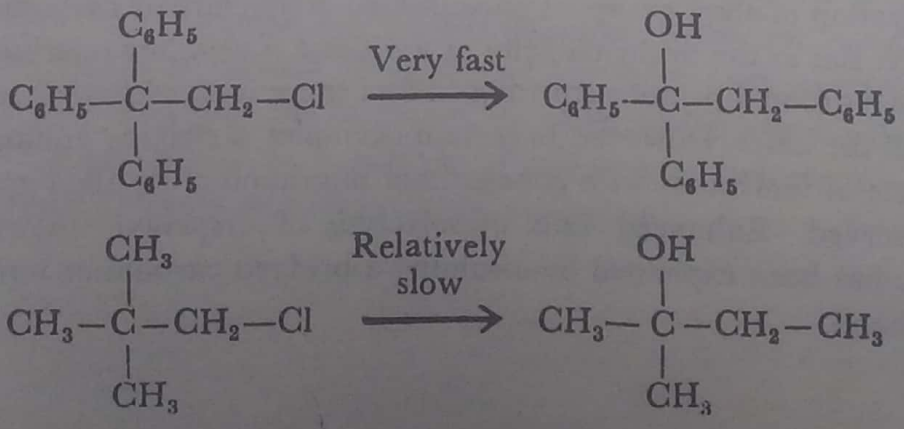
In many cases it has been found that phenyl or even alkyl group migration assists the formation of carbonium ions. This rate enhancement may be compared with the neighbouring group effects which result in rate-acceleration due to the nitrogen atom in the first order hydrolysis of substances such as $ClCH_2CH_2N(CH_3)_2$. This reaction is found to be thousands of times faster than the hydrolysis of nonaminated alkyl chlorides.



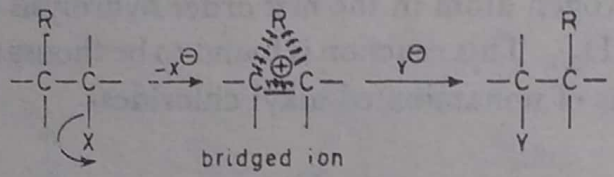
Similarly, β-chloro sulphide ($ClCH_2CH_2SC_2H_5$) hydrolyzes approximately 10,000 times as rapidly as does the corresponding ether $ClCH_2CH_2OC_2H_5$, again under identical conditions.



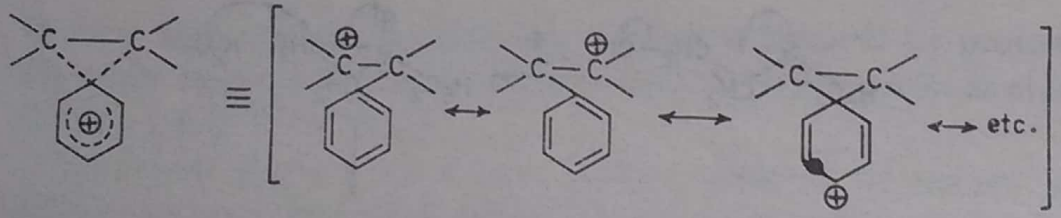
A typical example of the participation of the phenyl group is the solvolysis of βββ-triphenylethyl chloride, which has been found to be 60,000 times faster than the corresponding reaction of neopentyl chloride under identical conditions.



Evidently, the migrating phenyl group assists the separation of chloride in the former case whereas assistance of such a magnitude is not provided by the migrating methyl group in the latter case. This neighbouring group assistance by a carbon atom resulting in overall rate-acceleration has been termed *anchimeric assistance* by Winstein. In order to explain anchimeric assistance, the concept of bridged ion was proposed. Broadly speaking, the only requirement for such neighbouring group participation is that a substituent possessing a lone pair of electrons should be situated in the molecule in such a position as to become partially bonded to the carbonium ion. Since the carbonium ion gets stabilized due to the dispersal of positive charge, an increased reaction rate *(anchimeric assistance)* is observed.



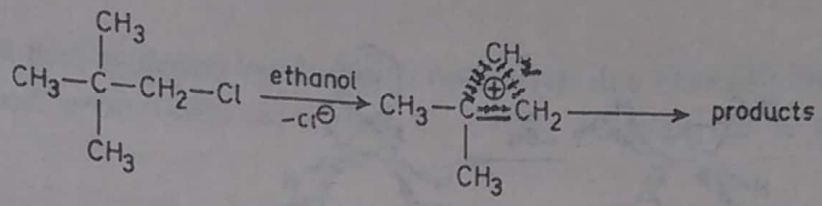
These bridged ions are called *phenonium* ions when a phenyl group is involved or *non-classical carbonium ions* in case of participation by an alkyl group. It may be noted that phenonium ions closely resemble the intermediates of electrophilic aromatic substitution and can be represented by the following resonating structures.



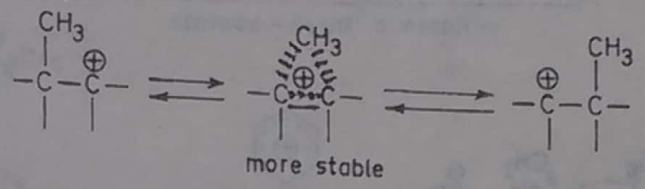
Delocalization of charge over a phenyl ring confers stability to a phenonium ion.

10.3.10 Bond Participation

The migration of alkyl groups is encountered frequently in carbonium ion chemistry. But as the nucleophilicity of a σ bond is very low relative to that of a phenyl group, it is not surprising to find there is no *anchimeric assistance* in most of the cases. However, in certain examples a striking enhancement of the rate of ionization with concomitant migration of an alkyl group has been observed. Enhanced rate of solvolysis of *neo*pentyl chloride, for instance, has been explained by assuming a bridged carbonium ion involving a σ bond.



The driving force behind the migration of an alkyl group has been explained by assuming that a bridged ion is more stable than any of the two alternate structures due to the delocalization of the migrating σ-electrons over the two carbon atoms with the positive charge divided between them.

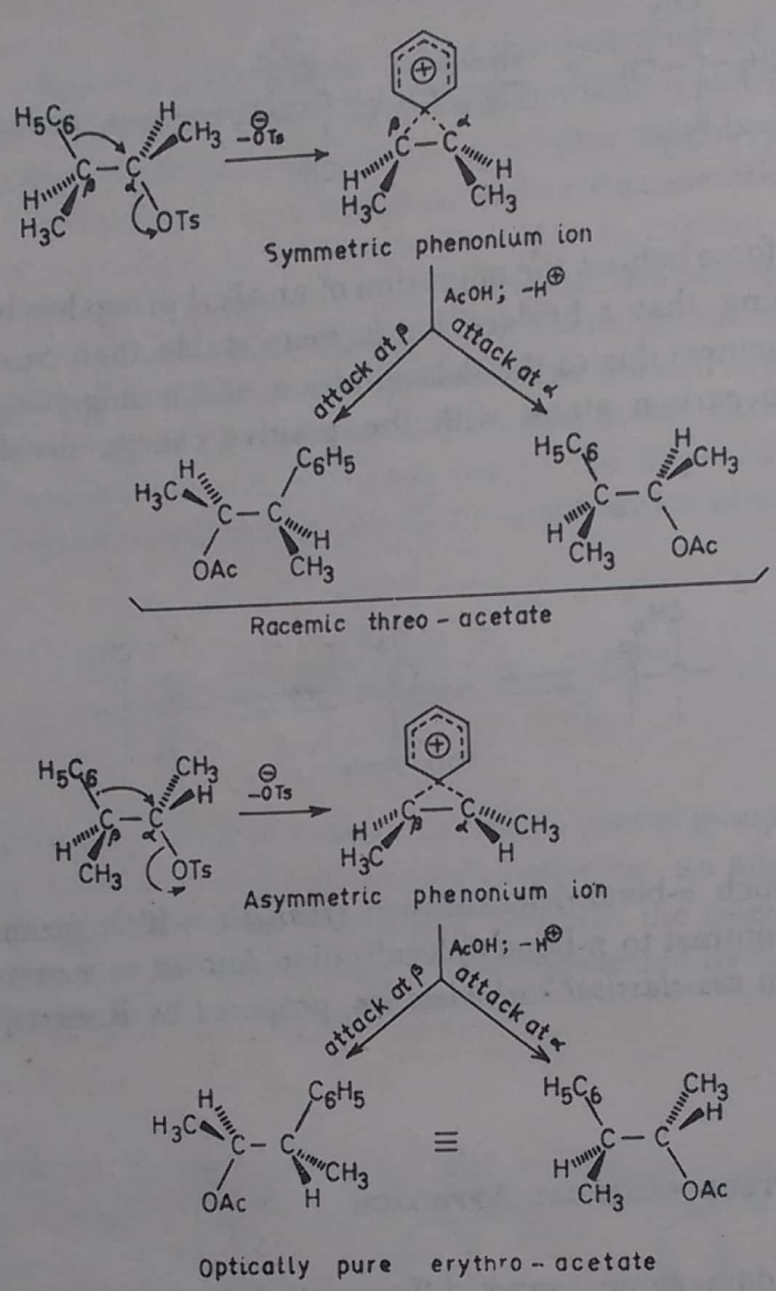


Ingold calls such σ-bond delocalization *synartesis*, which means fastening together, in contrast to π-bond delocalization known as *mesomerism*. However, the term *non-classical carbonium ion*, proposed by Roberts, is more in use.

10.3.2 The Stereochemical Approach

Since kinetic data alone cannot differentiate between a *bridged ion* and a *bridged transition state*, the existence of non-classical carbonium ions is a subject of great controversy. But at least in some cases, when the stereochemical course of 1,2-shift is coupled with the kinetic data, there is definite evidence for the existence of bridged carbocyclic cations as discrete reaction intermediates.

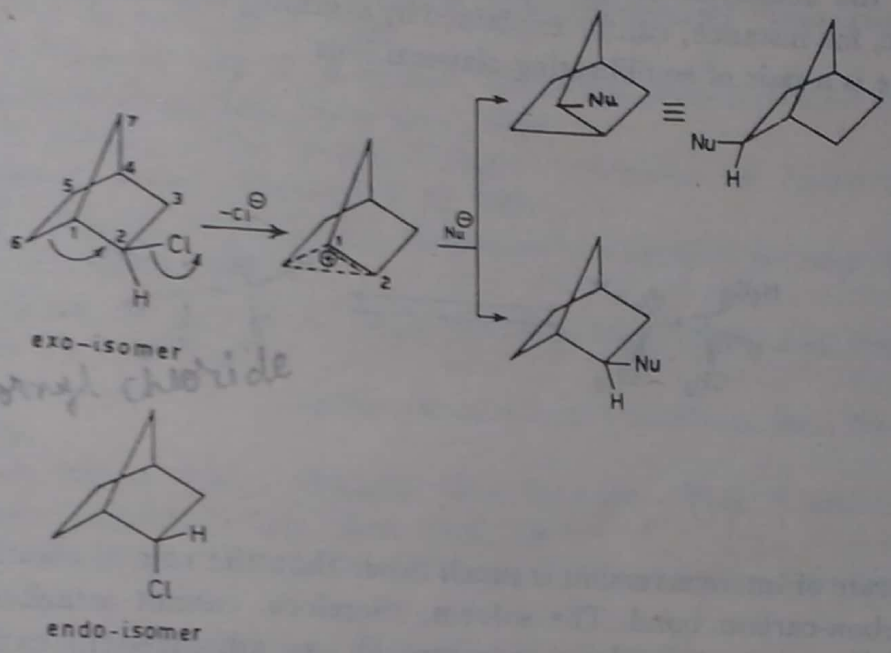
The stereochemical evidence for the existence of phenonium ion is provided by the remarkable stereospecificity observed in the acetolysis of optically active *erythro*- and *threo*-3-phenyl-2-butyl tosylates. Cram has conclusively demonstrated that the product acetates have the same configuration as the tosylates from which they are produced. In other words, the tosyl group is replaced by acetyl group with *retention of configuration*, which is a characteristic feature of neighbouring group participation.



It is clear *that rotation of the intermediates about the C—C—bonds is restricted because of the formation of phenonium ions* and the nucleophile attacks the positively charged species from the side away from phenyl. It is to be noted that in the formation of a bridged ion, phenyl group proceeds by a rearward attack resulting in the inversion of configuration, whereas a second inversion occurs during the attack by a nucleophile, resulting in overall retention of configuration.

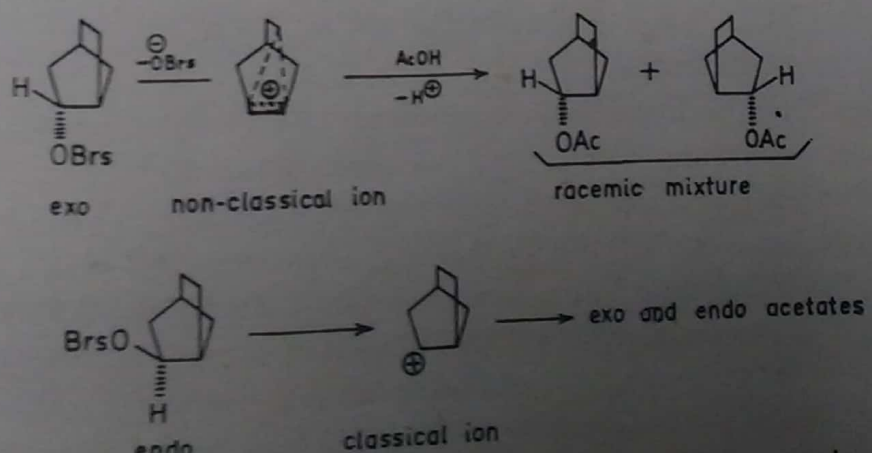
The solvolysis of norbornyl compounds is also believed to proceed through the intermediacy of non-classical ions. Solvolysis of 2-*endo*-norbornyl chloride takes place at the same rate as that of the corresponding cyclopentyl and cyclohexyl derivatives. But the *exo*-isomer undergoes solvolysis 80 times faster than the *endo*-isomer indicating anchimeric assistance during the solvolysis of the *exo* compound. The $C_6—C_1$ bond is situated at the rearside of the ionizable group and the σ-electrons attack the carbon bearing the ionizable group thus facilitating the ionization. The intermediate non-classi-

cal carbonium ion is attacked by the nucleophile (in this case solvent molecules) with equal probability at either C_1 or C_2 resulting in a racemic product.

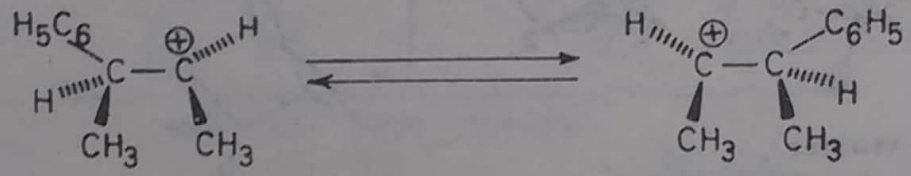


The *endo* isomer does not get such anchimeric assistance since the C_6-C_1 bond is situated on the same side of the ionizable group and consequently its rate of solvolysis is normal.

Another interesting example is the acetolysis of *exo*-2,2,1-bicycloheptyl bromobenzene-*p*-sulphonate which is 350 times as fast as acetolysis of its *endo* epimer. This has again been explained by a rearside attack of σ-electrons on the back of the carbon precisely at the same time as the ionizable group starts leaving the carbon. This leads to a non-classical carbonium ion which reacts with acetic acid to yield the racemic mixture of acetates. No such anchimeric assistance is available to the *endo* isomer which undergoes slow acetolysis through classical carbonium ions.



Brown has taken a different view regarding bridged ions as intermediates in solvolysis reactions and has explained the kinetic and stereochemical results on the basis of classical carbonium ions. The observed stereospecificity in the acetolysis of optically active *erythro-* and *threo*-3-phenyl-2-butyl tosylate, for instance, can be explained by assuming that the solvolysis intermediate is a pair of equilibrating classical ions,



whose rate of interconversion is much faster than the rate of rotation about the carbon-carbon bond. The solvent, therefore, cannot attack from the phenyl side of the ions. Another argument was advanced to explain fast solvolysis of the above-mentioned *exo* isomers by presuming that the solvolysis of *exo* derivative is normal and that of *endo* compounds is unusually slow because of steric factors.

Thus bridged ions are a subject matter of great controversy. It is reasonable to believe that cases in which ionization of a compound leads directly to a stable classical carbonium ion, there is no neighbouring group participation by carbon.