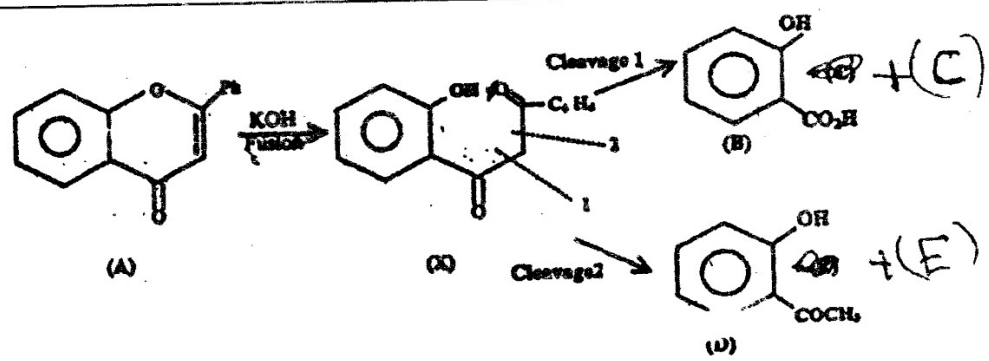
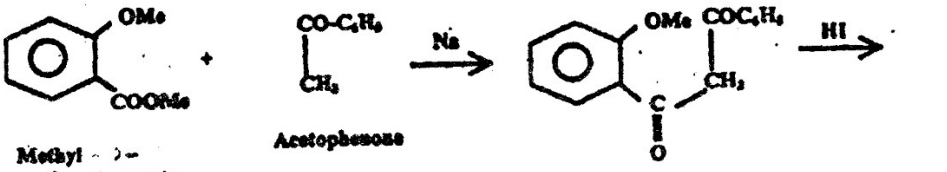
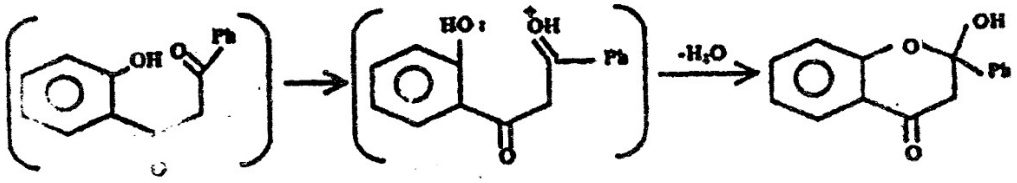
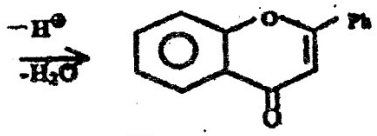


Finally the structure of flavoner is confirmed by its synthesis.

a. Kostaneckis Synthesis :

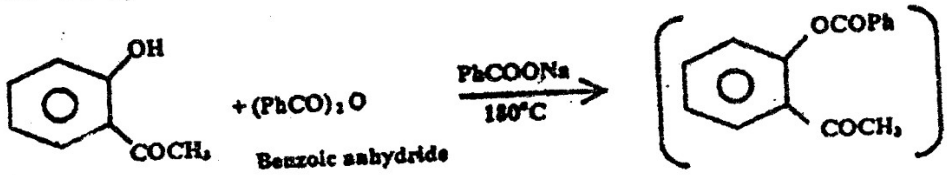




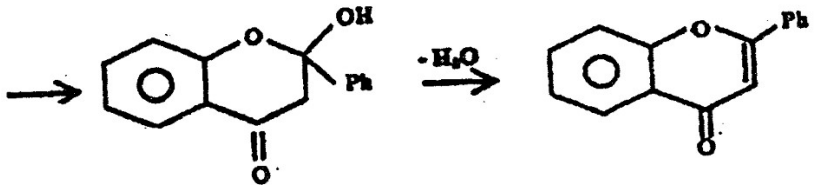


Flavone

b. Robinson's Synthesis :

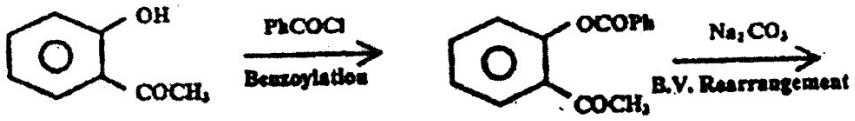


O-Hydroxyacetophenone



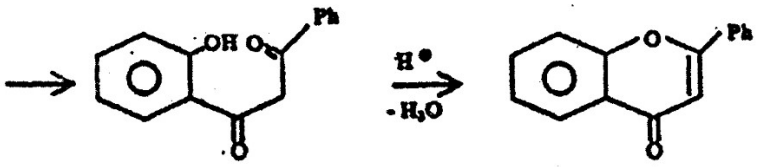
c. Baker - Venkatraman Synthesis :

This synthesis involves the Baker - Venkatraman rearrangement.



2. Hydroxyacetophenone

0-Benzoyloxyacetophenone



O - Hydroxy - β - diketone

Flavone

Quercetin

This is one of the most widely distributed natural pigment. This occurs as the glycoside quercitrin in the bark of quercustinctoria.

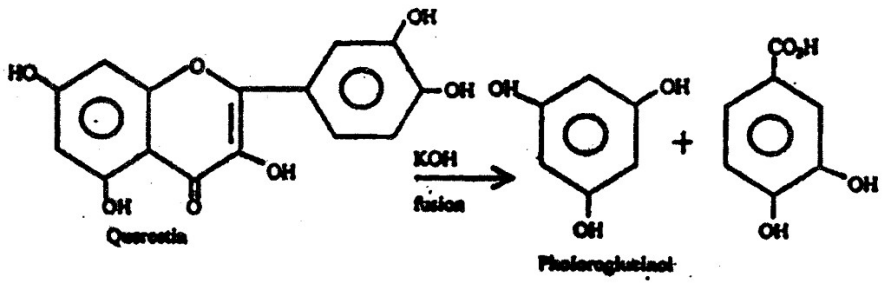
Quercitrin on hydrolysis with hydrochloric acid gives quercetin and a molecule of rhamnose.

$$C_{21}H_{20}O_{11} + H_2O \xrightarrow{HCl} C_{15}H_{10}O_7 + CH_3(CHOH)_4CHO$$

QUERCETIN

Quercetin – Constitution :

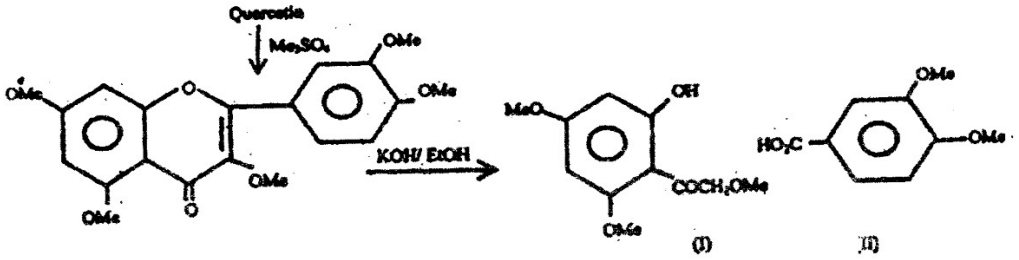
1. From analytical data and molecular weight determination, the molecular formula of quercetin has been found to be $C_{15}H_{10}O_7$.
2. On acetylation it forms a pentaacetyl derivative, suggesting the presence of five hydroxyl groups in quercetin.
3. Negative zeisel determination indicates the absence of methoxy group in quercetin.
4. Postassium hydroxide fusion of quercetin gives phloroglucinol and protoncatechuic acid. This reaction is characteristic of flavylium type nuclei.
5. Pentamethylquercetin, obtained by the methylation of quercetin, on boiling with ethanolic potassium hydroxide gives 6-hydroxy – ω, 2,4 – trimethoxyacetophenone and veratric acid. These reactions suggest that quercetin is 3,3' 4',5,7 – pentahydroxyflavone.



Quercetin

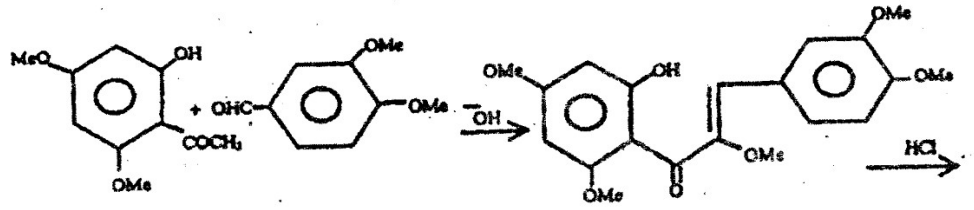
Phloroglucinol

Protocatechuic acid

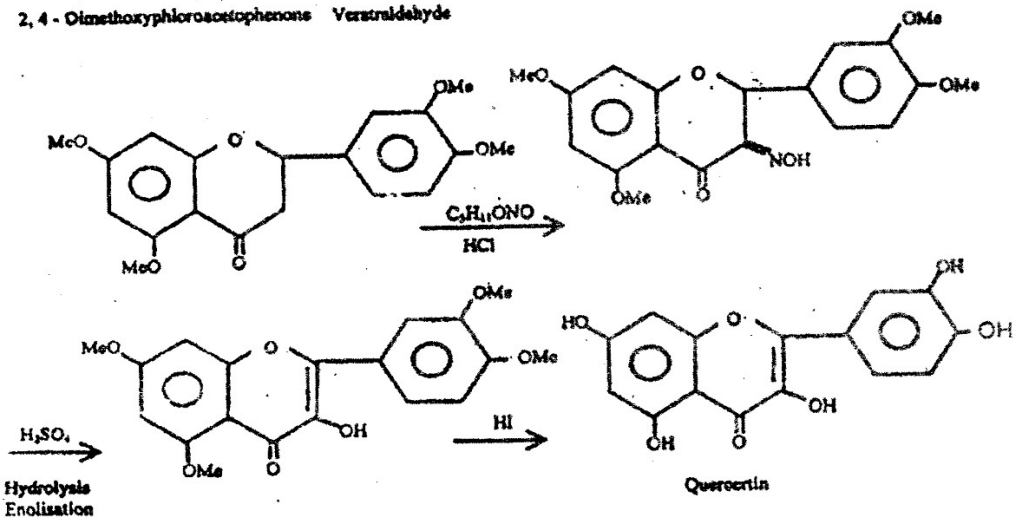


This structure for quercetin is confirmed by its synthesis.

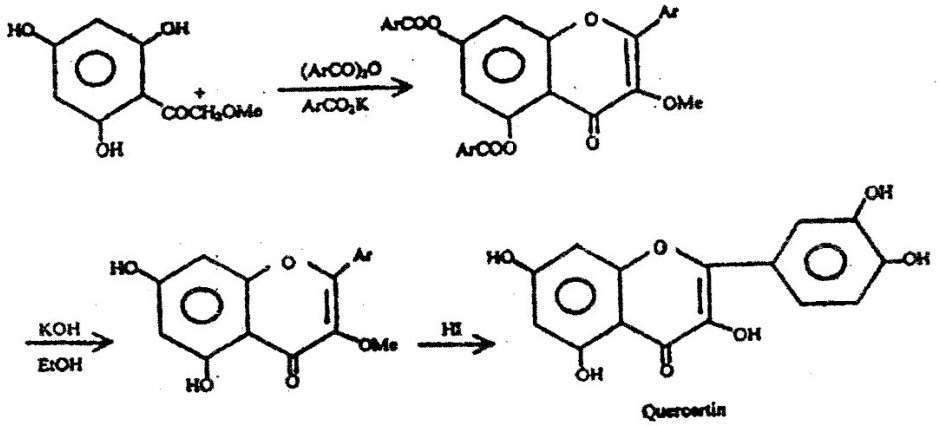
a. Kostanecki's, Synthesis :



2, 4 - Dimethoxyphloroacetophenone Veratraldehyde



b. Robinson's Synthesis :

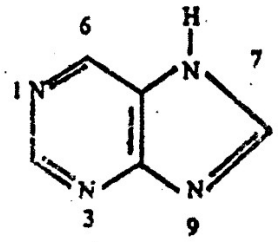


The position of the rhamose residue in quercitrin has been shown to be 3 by Herzing etal.

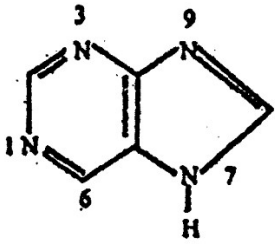
CAFFEINE, THEOBROMINE, THEOPHYLLINE:

Introduction

These three compounds belong to a class of compounds called purines. Purines have two condensed heterocyclic rings. They contain both a pyrimidine ring and an imidazole ring. Two structures can be written for them.



(A)



(B)

The numbering is the same for both the structures. So, whether it is structure (A). or (B) for purine is immaterial. Even among purines, the above three belong to a sub-class called xanthines (2,6 – dihydroxypurine). Thus, caffeine is 1,3,7 – trimethyl xanthine

Theobromine is 3,7 – dimethylxanthine

Theophylline is 1,3 – dimethylxanthine

CAFFEINE

Introduction:

It is present in tea leaves (3%), coffee (1-2%), cocoa beans and some other beverages. Due to its stimulating action on nerves and heart, it is used in medicine. One cup of coffee or tea generally contains 100mg of caffeine. It is used as a diuretic and a heart and nerve stimulant in the form of its citrate and hydrochloride.

Constitution

1. From element analysis and molecular weight determination, the molecular formula of caffeine has been found to be, $C_8H_{10}O_2N_4$
2. Caffeine is found to have three N – methyl groups from Herzing Meyer estimation.

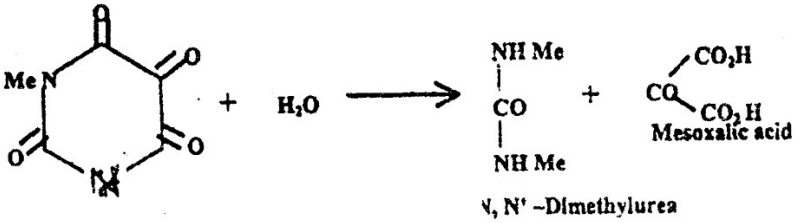
$$C_3HO_2N(N\text{-}CH_3)_3 + 3HI \rightarrow C_5HO_2N(NH_3)_3 + 3CH_3I$$

3. Caffeine is related to uric acid as follows:

a. On oxidation with potassium chlorate and hydrochloric acid, it gives equimolecular amounts of 1,3 dimethylalloxan and monomethylurea.

$$C_8H_{10}O_2N_4 + H_2O + (O) \xrightarrow{KClO_3} \underset{\text{1,3 -Dimethylalloxan}}{C_6H_6O_4N_2} + \underset{\text{monomethylurea.}}{CH_3NHCONH_2}$$

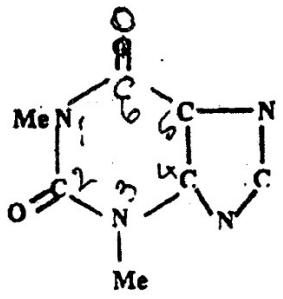
b. Hydrolysis of 1,3 – dimethylalloxan yield N,N' dimethylurea and mesoxalic acid. Thus 1,3 – dimethylalloxan is found to be mesexalyl – sym dimethylurea (structurel).



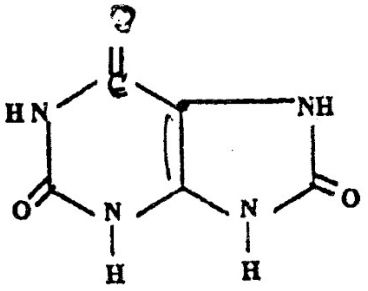
Dimethylalloxan (I)

N, N' -Dimethylurea

c. From the oxidation of caffeine to 1,3 dimethyl alloxan and monomethylurea, if follows that caffeine has the same carbon skeleton as that of uric acid. At the same time it also establishes the position of two methyl groups at 1 and 3 positions and one oxygen atom at position 2 in caffeine. Hence the part structure of carffeine may be written as (II).



Part structure of caffeine
(II)

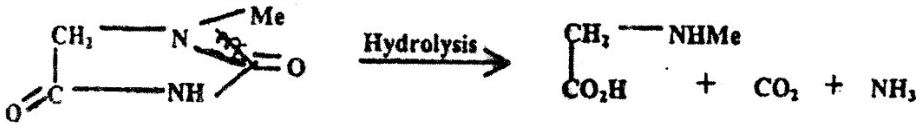


Uric acid

Now the problem is to assign the position of the third N – Me group, which may be at 7 or 9, and the oxygen atom which may be at 6 or 8.

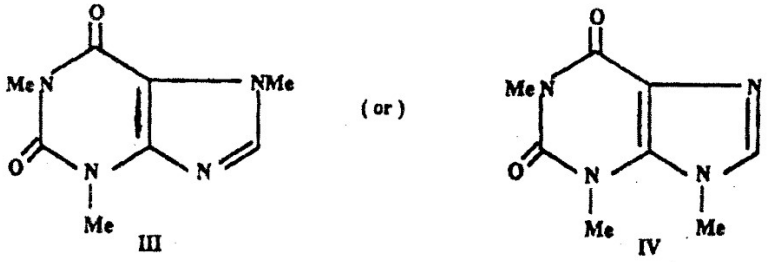
4. POSITION OF THE METHYL GROUP

During the perchlorate oxidation of caffeine, another product is also obtained along with dimethylalloxan and methylurea. The other product is found to be N – methylhydantoin, because it yields N – methyglycine, carbon dioxide and ammonia on hydrolysis.



N-Methylhydantion N-Methylglycine

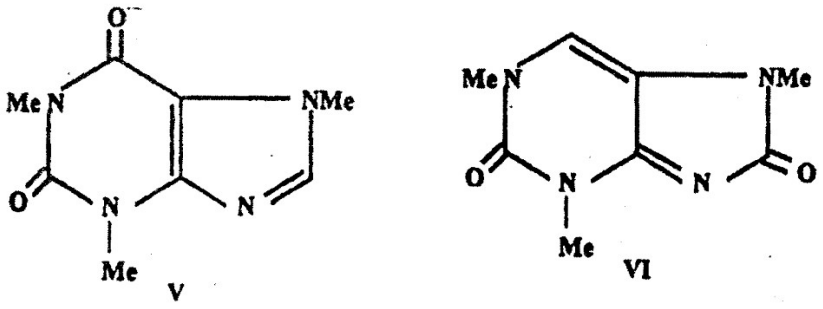
As indicated above the third methyl group may be either at position 7 or 9 and also from the above facts, two structures (III) & (IV) may be written.



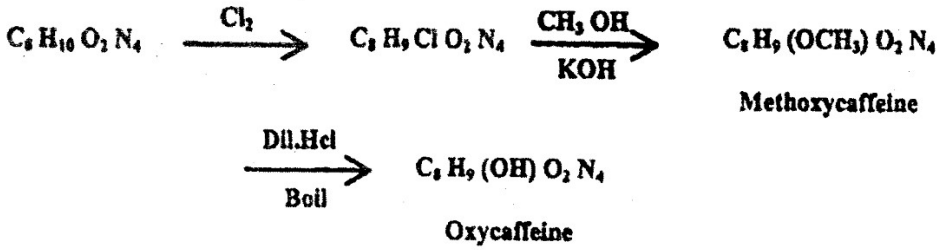
Drastic oxidation of caffeine gives sym-dimethyloxamide (MeNH. CO.CO.NHMe) as one of the oxidation products. Examination of structures (III) & (IV) reveals that the formation of the above product is possible only with structure (III) and not with structure (IV).

POSITION OF THE OXYGEN ATOM:

The second oxygen atom, as stated above, may be at C_6 or C_8. Based on this, two possible structures can be written for caffeine (V & VI).

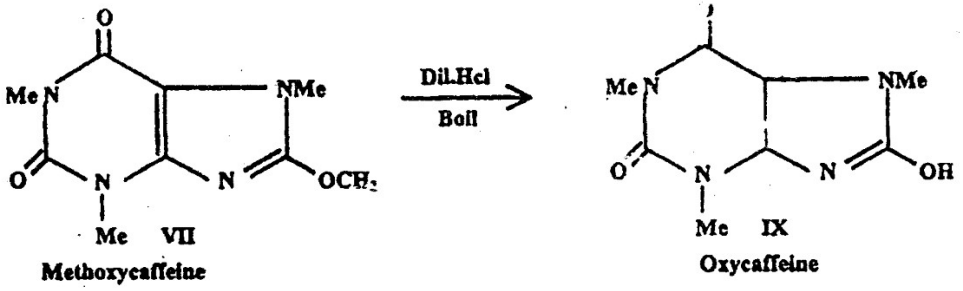


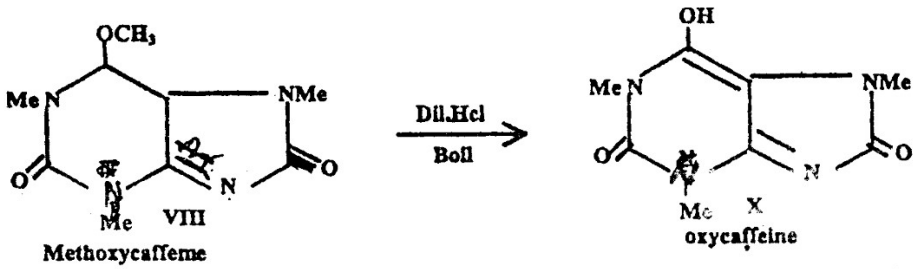
The correct structure for caffeine is identified as follows. (Fischer etal).



Oxycaffeine is also known as hydroxyl caffeine. Structure (V) could explain the above mentioned reactions. Oxycaffeine has been found to be identical with trimethyluric acid because oxycaffeine on methylation with methyliodide and sodium hydroxide gives tetramethyluric acid.

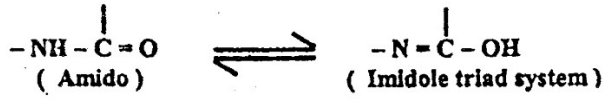
Thus methoxy caffeine may be (VII) or (VIII) and oxycaffeine (IX) or (X)





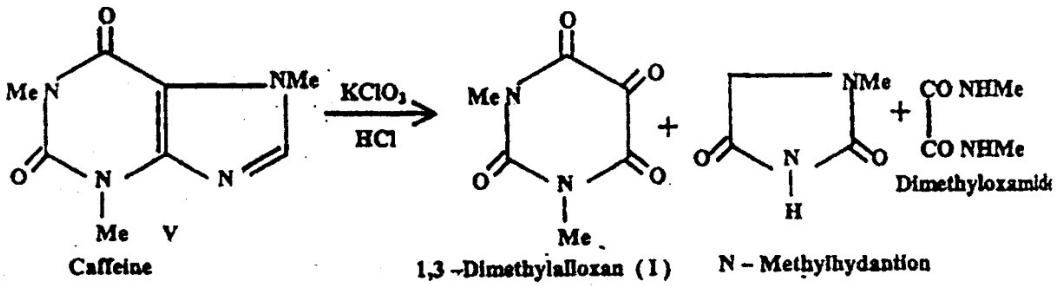
The structure of oxycompound (IX) was found to be correct, which corresponds to structure (VIII) of methoxycaffeine and hence to structure (V) of caffeine. This has been confirmed as follows:

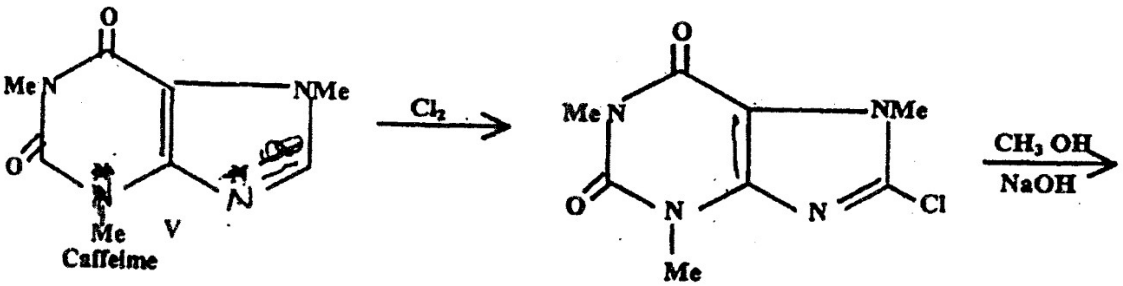
When the silver salt of hydroxyl-caffeine is heated with methyl iodide, it yields a mixture of tetramethyluric acid (having four N – methylgroups) and methoxy caffeine (having three N – methyl groups and one O – methyl group). The formation of these products indicates the presence of an amido – imidole imdole triad tautomeric system in caffeine.

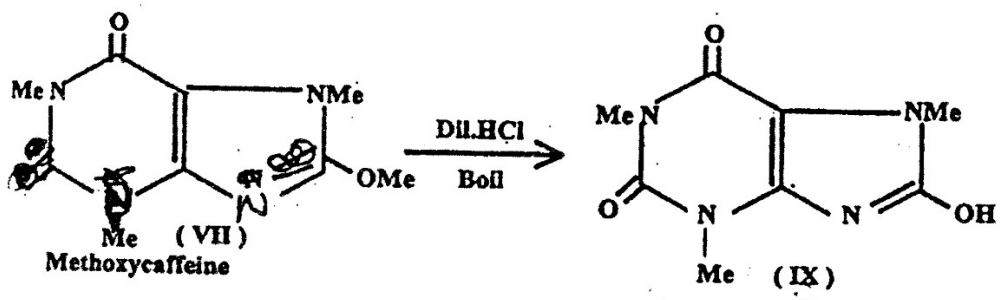


This is possible only with structure (IX) for oxycaffeine and not with structure (X).

Based on the above facts the structure of caffeine may be assigned as structure (V) and all the above reactions can be explained as follows.



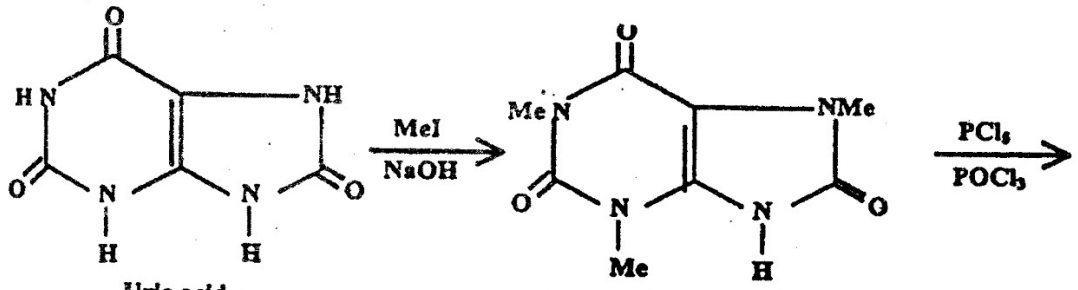


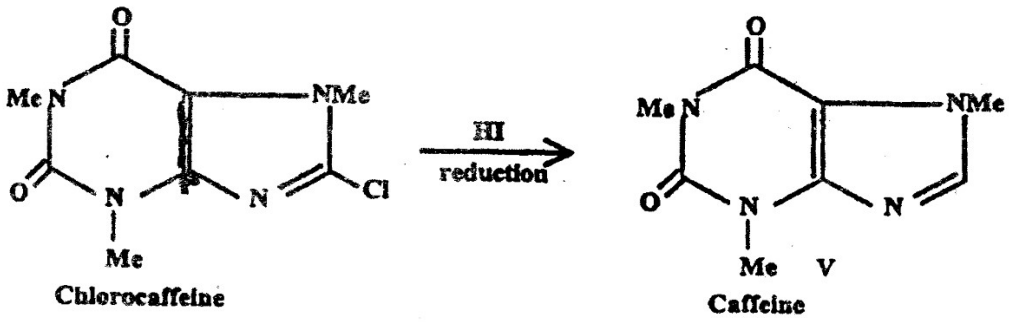


SYNTHESIS:

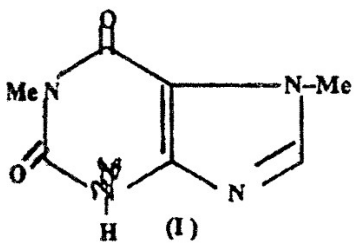
Finally the structure of caffeine has been confirmed by its synthesis.

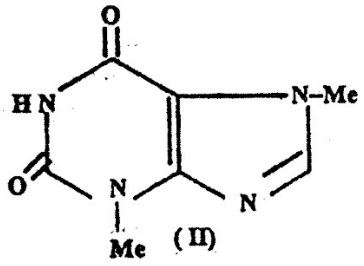
a. FISCHER'S SYNTHESIS:





4. Methylation of the silver salt of theobromine gives caffeine (1,3,7 – trimethlxanthine). That means that one of the methyl group is in position 7, while the other is at 1 or 3 position. This leads to two possible structures for theobromine. (I & II).





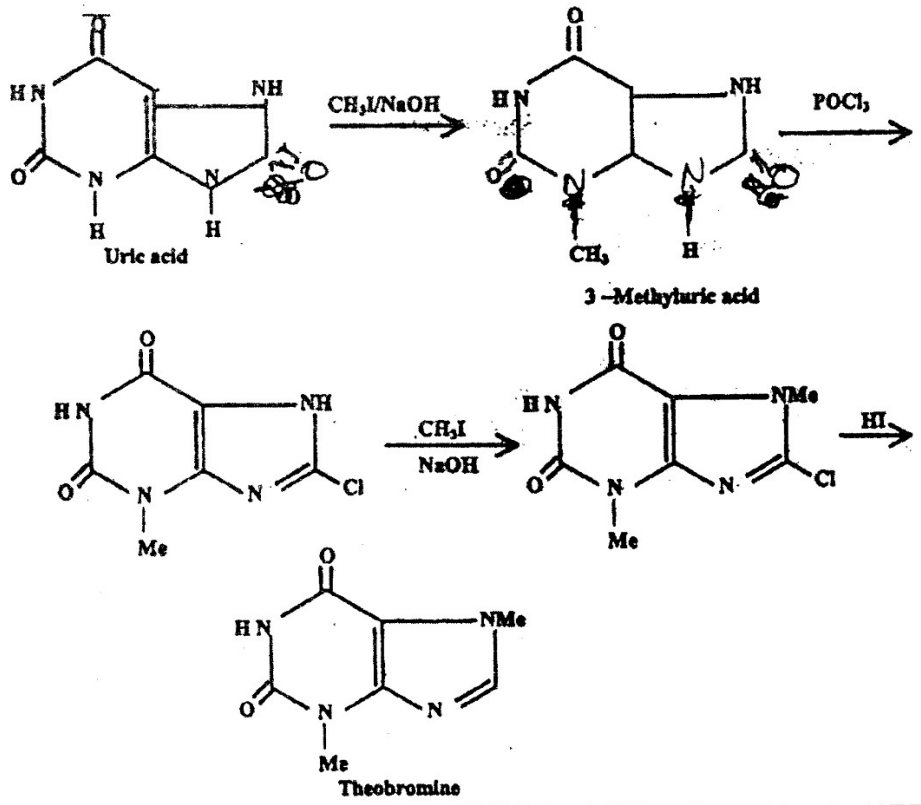
Structure II is found to be correct on the basis of the following.

Theobromine can be synthesized both from 3-methyluric acid as well as 7 – methyluric acid, but not from 1 – methyluric acid.

So, from this it is evident that theobromine is 3,7 – dimethylxanthine.

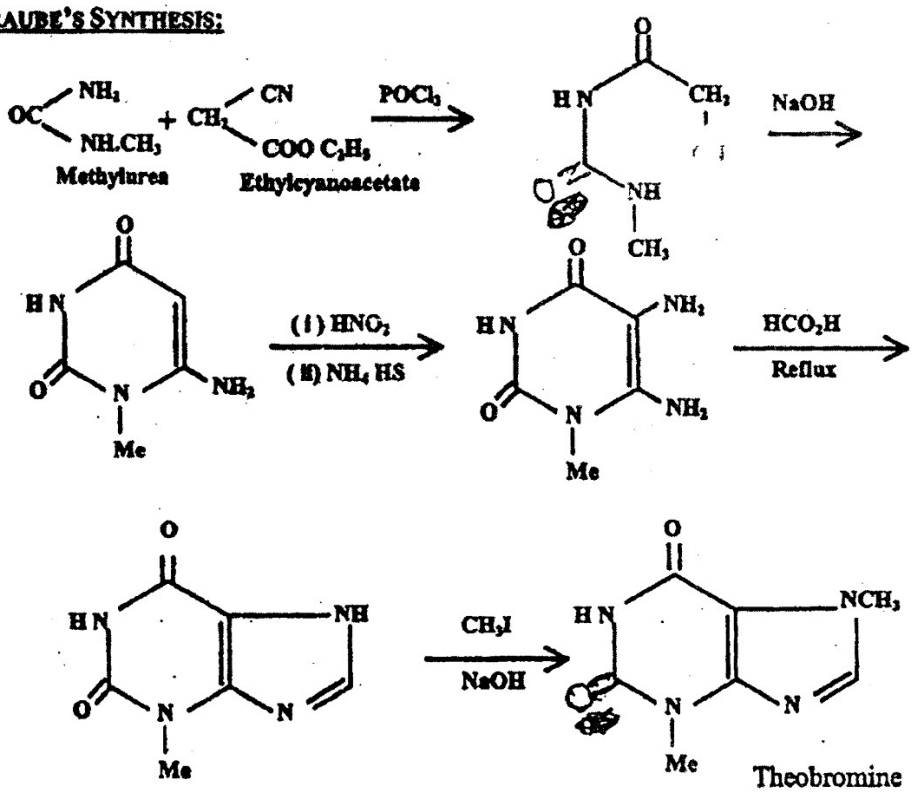
Finally its structure has been confirmed by its synthesis.

SYNTHESIS (FISCHER) :



TRAUBE'S SYNTHESIS :

TRAUBE'S SYNTHESIS:



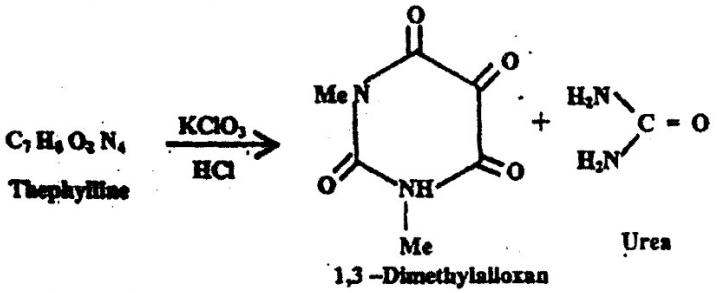
THEOPHYLLINE

INTRODUCTION :

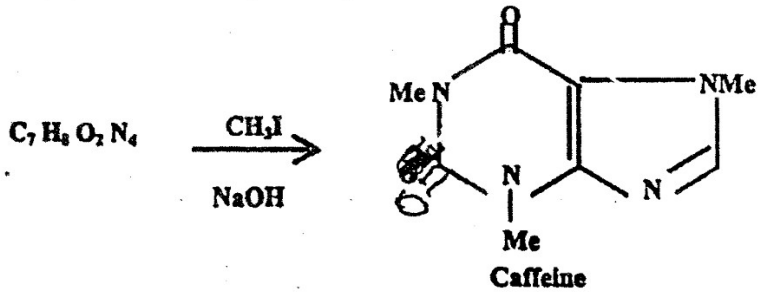
It is isolated from tea leaves. This also is used as a diuretic in medicine. It's diuretic action is superior to that of caffeine.

CONSTITUTION :

1. From analytical data and molecular weight determination, the molecular formula of theophylline has been found to be $C_7H_8O_2N_4$.
2. From Hezig – Meyer method, theophylline is found to have two N – methyl groups.
3. On oxidation with potassium chlorate and hydrochloric acid, theophylline gives dimethylaloxan and urea.

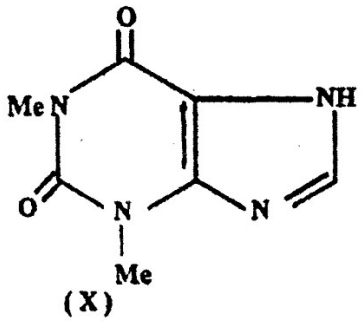


4.Theophylline on methylation yields caffeine.



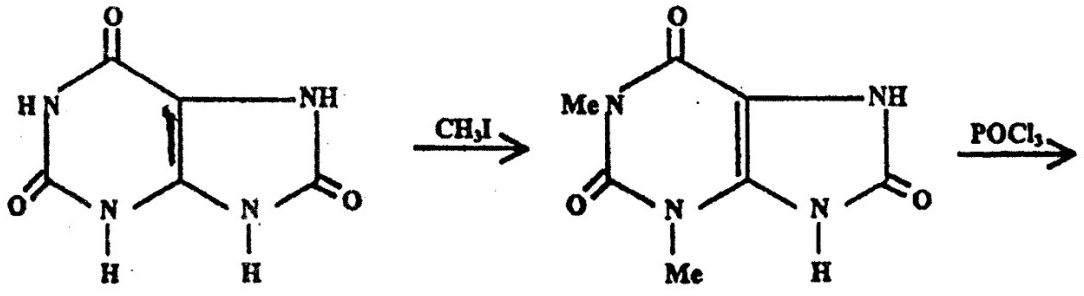
Caffeine

5. From the above facts, it may be inferred that theophylline is 1,3 – dimethylxanthine (X).



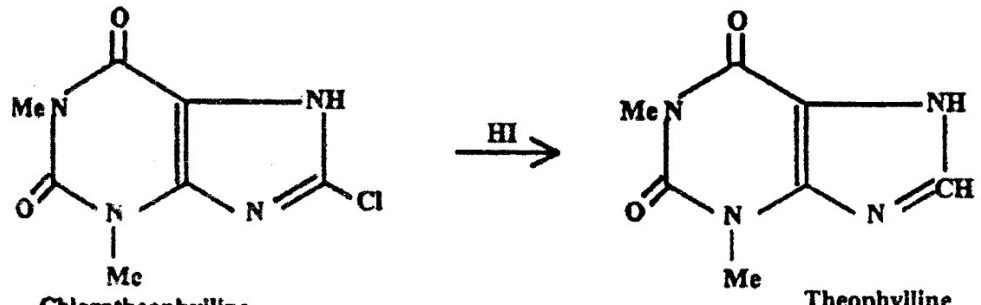
(X)

a.SYNTHESIS (FISCHER):



Uric acid

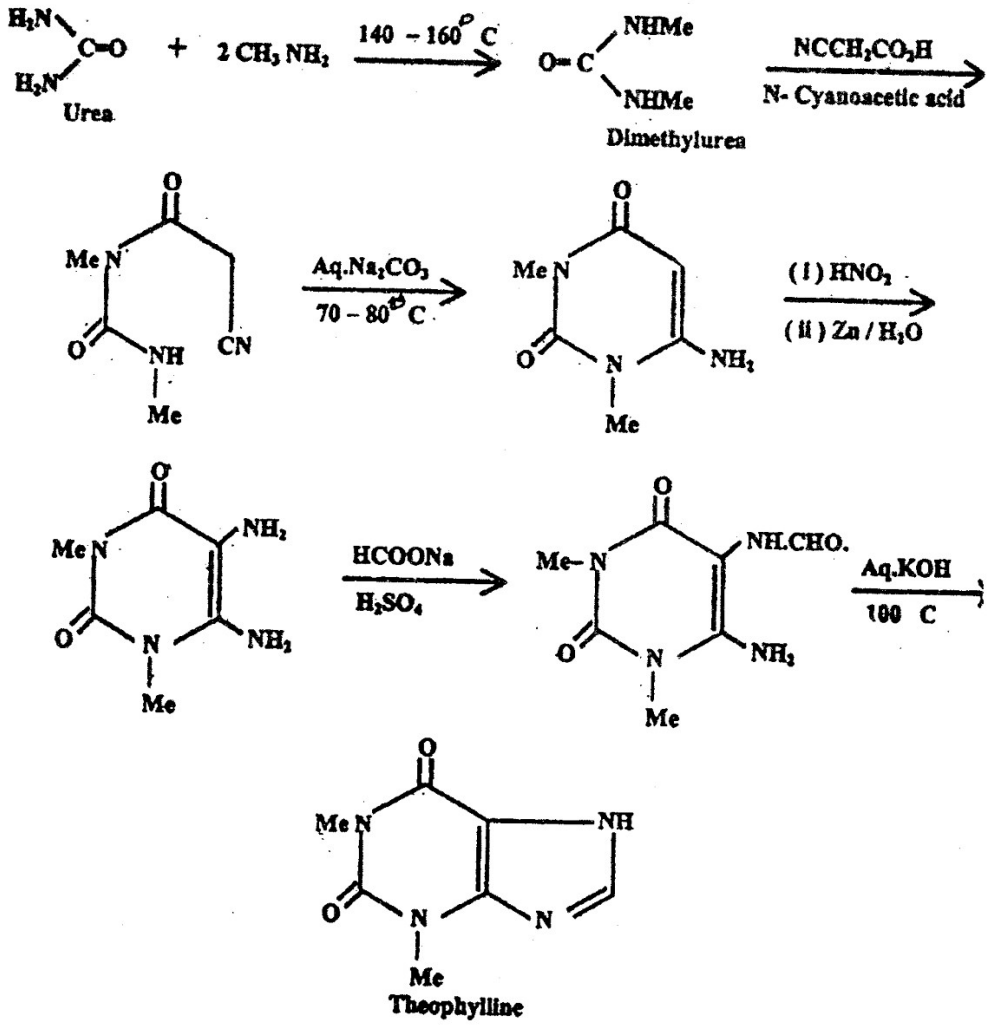
1, 3 –Dimethyluric acid



Chlorotheophylline

Theophylline

b. TRAUBE'S SYNTHESIS (COMMERCIAL):



UNIT – V

ALIPHATIC NUCLEOPHILIC SUBSTITUTION

Substitution of a halogen in an alkyl halide by a nucleophile has been one of the most studied reaction by In gold and others.

$$RX + Z: \rightarrow RZ + X^{\circ}$$

Hydrolysis (Nucleophile) of an alkyl halide, formation of a quarternary halide from a tertiary amine (Menschukin reaction) and hydrolysis of a quartermary salt are to mention a few.

$CH_3Cl + OH^{(-)} \rightarrow CH_3OH + Cl^{(-)}$

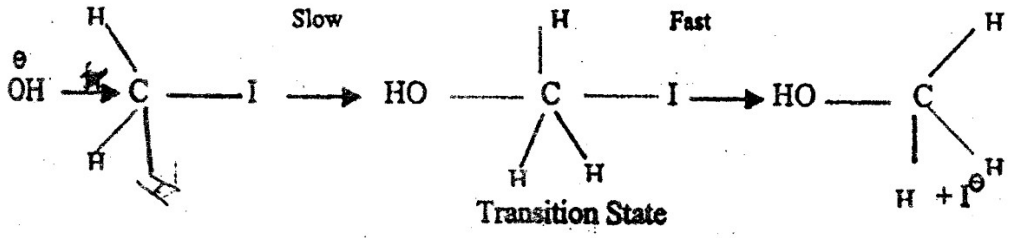
$:NMe_3 + RI \rightarrow RN^{(+)}Me_3 + I^{(-)}$

$RN^{(+)}Me_3OH^{(-)} \rightarrow ROH + NMe_3$

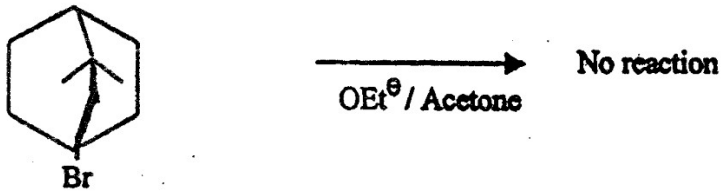
The nucleophiles are normally neutral or negative, and possess unpaired electrons. Kinetic measurements have indicated at least two extreme types of mechanisms.

S_N2 Mechanism

A bimolecular nucleophilic substitution takes place have the attacking nucleophile approaches the reaction molecule (substrate) from the rear position in a one step process.

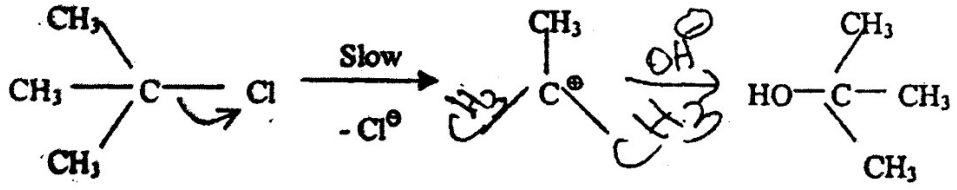


The slow formation of a transition state from the two reacting species indicates that the reaction is bimolecular and second order. During the reaction, the leaving group are 180° to each other and the three non reacting group (hydrogen atoms) nucleophile and the attached to the carbon are on the same plane. The resulting product is normally inverted, and this Walden inversion is a stereochemical evidence for this mechanism. Moreover, lack of reactivity of compounds with halogen at the bridge head, provides another evidence for this mechanism since a bridge head carbon cannot easily become planar and the nucleophilie attack is not possible from the rear position as per the mechanism.

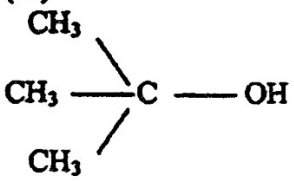


S_N1 Mechanism

The hydrolysis of a tert - butyl halide is found to follow a different mechanism.



(or)



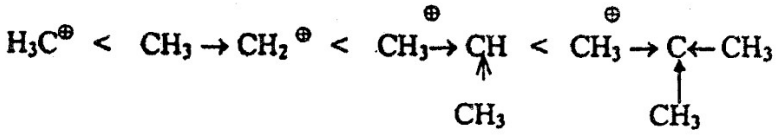
In the slow step during the formation of a planar carbonium ion, only the substrate molecule is involved and hence it follows a first order kinetics. Any factor which stabilized the corbonium ion, will favour the S_N1 mechanism. The attacking hydroxide ion enters the stereochemically same or different alcohols (if the substrate has an asymmetric carbon). Formation of equimolecular quantitites of enantiomers in this reaction is an evidence for this mechanism.

Whether the reaction follows the S_N1 or S_N Mechanism, depends on several factors such as (2) Nature of the substrate, (2) Nature of the nucleophile, (3) Nature of the leaving group and (4) The type of solvent used.

1. Nature of the Substrate (Structure)

a) Polar Effect

It has been generally observed that tertiary alkyl halides undergo hydrolysis at a much faster rate compared to the corresponding secondary and primary halides under normal conditions. This could be due to the stabilization of the terth. Carbonium ion by the polar effects of the alkyl groups attached.



The hyperconjugative effect as well as the electron releasing inductive effect of the methyl groups are found to disperse the positive charge over the carbon, thereby stabilizing the carbonium ion in the give order. Hence SN1 mechanism operates in tert. Halides.

b). Steric Effect

SN2 mechanism is virtually inhibited in tert halides since due to steric overcrowding of the molecule in the transition state with 5 groups attached to the cabron, hence formation of a transition state s not possible. However the steric effect does not affect the stability of the carbonium ion in the SN1 mechanism since formation of a planar intermediate is favoured with only

3 groups attached to the positively charged carbon. Hence, in the primary alkyl halides the mechanism is predominantly SN2 and in tert.alkyl halides it is SNl, whereas it is both SNl and SN2 in other alkyl halides. Accordingly it is found that the isopropyl and ethyl halides resist hydrolysis compared to methyl and t-butyl halides.

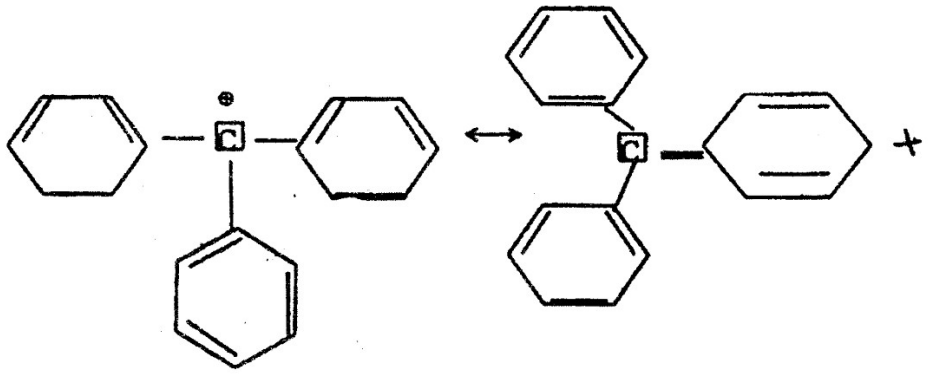
c) Resonance Effect

Comparison of the rate of hydrolysis of methyl, phenyl, methyl, diphenyl methyl and triphenylmethyl chloride shows that SN1 mechanism predominates in the order.

$$Ph_3CCl > Ph_2CH\ Cl > PhCH_2\ Cl > CH_3Cl$$

S_N1

Delocalisation of the positive charge has drastically increased due to a number of phenyl groups attached to the carbon, where resonance operates.



The triphenylmethyl carbonium ion intermediate has been considerably stabilized due to resonance and it hydrolyses 30×10^6 times asfast as that of benzyl chloride.

2) Nature of the Nucleophile

Under S_N2 conditions, nucleophiles with a negative charges are always more efficient than their conjugate acids. Accordingly $\ominus OH$ is more powerful than H_2O and NH2 is better than NH3. Larger atoms are more nucleophilic than smaller ones as observed in the following nucleophiles:

$PhS\ominus >$	$I\ominus >$	$EtO\ominus >$	$Br\ominus >$	$PhO\ominus >$	$Cl\ominus$
(470,000)	(3, 700)	(1000)	(500)	(400)	(80)

The relative rate of their reactivity is given in brackets. However, the order of nucleophilicity depends upon the nature of the solvent used. In aprotic polar solvents,. The smaller negatively charged nuclophiles are more solvated, hence the observed orderi s $Cl\ominus > Br\ominus > I\ominus$.

Since the attack by the nucleophile is not the rate determinng step in a S_N1 reaction, it cannot affect the rate of the reaction. However, when there are several nucleophiles in the reacting medium, the product is decided by their relative nucleophilicity, as in a S_N2 process.

3) Nature of the Leaving Group

Best leaving groups facilitate the nucleophilic attack and they are usually weakest bases. Thus, $I^{\ominus}$ is better than $F^{\ominus}$ and the observed order is $I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$

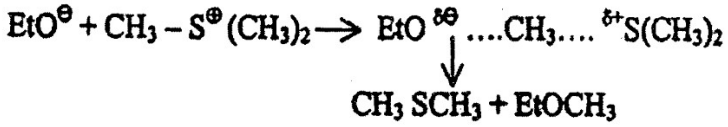
Strong bases such as $^{\ominus}OH$, $^{\ominus}OR$ etc have never been the leaving groups in nucleophilic substitution reactions. Best leaving group such as $I^{\ominus}$ has a high polarizability which makes it a good entering as well as leaving group.

4) Nature of the Medium (Solvent)

Ionization of a neutral molecule to an ion pair is strongly favoured by polar solvents especially in SN1 reactions. t-Butyl Chloride solvolyses 300,000 times faster in water at 25°C compared to that in ethanol. Highly polar solvents with high dielectric constant interact specifically with the reacting molecule in ethanol. Highly polar solvents with high dielectric constant interact specifically with the reacting molecule in separating the ion pair and stabilizing them as well, through salvation. Protic solvents such as water and ethanol also stabilize the carbonium ion through hydrogen bonding, which is not possible in polar aprotic solvents such as Dimethylformamide (DMF), Dimethylslphoxide (DMSO), Acetone etc.

Under SN2 reaction conditions, the solvent polarity has a lesser effect, However it differs from one reaction to the other. In the Menschukin reaction where neutral molecules react, the charge separation state is grater, hence the transition state is solvated effectively, the energy of activation reduced and the reaction rate is enhanced.

On the other hand, displacement of dimethyl sulphide from trimethyl sulphonium ion by ethoxide ion, is retarded by polar solvents, as the starting materials are more charged than the transition state.



This reaction is favoured by less polar solvents.

Change of solvent from polar hydroxylic (methanol) to polar non-hydroxylic (DMF) has a profound effect on the SN2 reaction of methyl Iodide with azide (N_3^-) at 0^0c

$$CH_3I + N_3^{(-)} \rightarrow CH_3N_3 + I^{(-)}$$

The attacking nucleophile $N3^{\ominus}$ is strongly solvated in methanol through hydrogen bonding, but the unsolvated $N3^{\ominus}$ in DMF is a much more powerful nucleophile, raising the reaction rate by 4.5×10^4 times than with methanol. Use of DMSO in this reaction has raised the reaction rate 10^9 times.

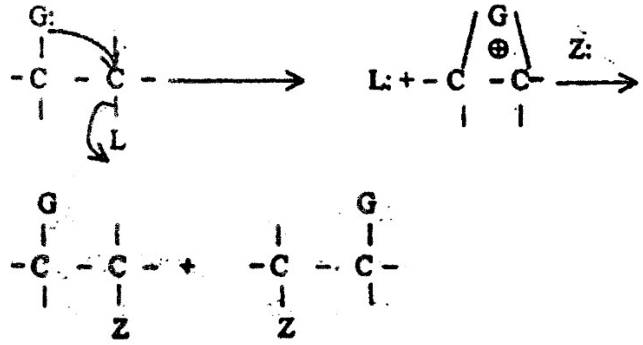
Increase in solvent polarity has also found to change the mechanistic pathway from SN2 to SN1. Similarly, transfer from polar protic to non-protic solvents has resulted in the change of reaction mode from SN1 to SN2, due to singnificant rise in the nucleophilicity of the reagent.

SYMPHORIA

Apart from the above factors such as polar effects, steric effects, solvent effects etc., another structural feature merits consideration. That is, when the reactant and the reagents are brought together and held in exact positions, the proper spatial relationship developed between the molecules, is found to accelerate the reaction at abnormal rates. This factor which makes the process of bringing of reacting molecules together into proper spatial relationship. Is called symphoria. The symphoric factors include the effect of an atom or group adjacent to the reaction center which may temporarily serve as a free to facilitate either the attack by the reacting species or the expulsion of a part of the substrate molecule or both. This may result in the acceleration of reaction rates or enhancement of stereo selectivity, as illustrated under:

The nucleophile Z: attacks the molecule and superficially it appears as

However when the reactant and reagent are taking proper spatial positions, the course of the reaction changes, resulting in a mixture of products.

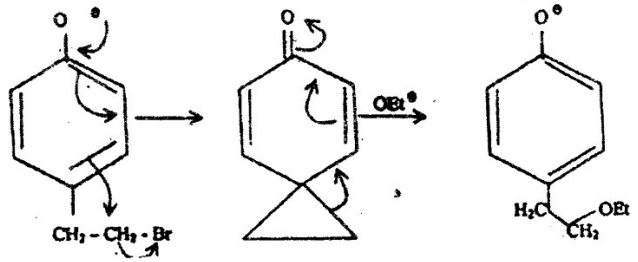


Neighbouring group Participation

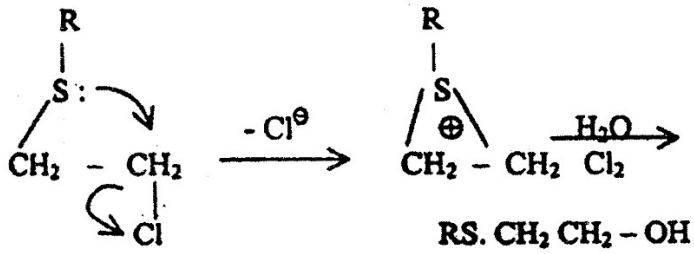
The rates of certain nuclophilic substitution reactions are found to be unusually high without inversion or racemisation, when a neighbouring group, normally β to the leaving group acts as a nucleophile pushing out the leaving group. The participating neighbouring group is found to provide anchimeric assistance. It follows a first order kinetics, since the formation of a bridged of non-classical ion is the slow step. In either case, the non bonding electrons of the neigh boring group or the electrons of a phenyl group are involved in the formation of a symmetrical or non – symmetrical intermediate.

Thus for example Erythro – 3 bromo – 2 butanol an reaction with hydrogen bromide gives meso - 2,3 dibromo butane. This reaction involves the participation by neigh bouring bromine atom in the departure of the leaving group. i.e – OH as H_2O.

Ethanolysis of the following phenolate occurs 10^9 times faster compared to the corresponding aryl bromide, due to the participation of π electrons in the aryl system in the formation of a bridged intermediate.



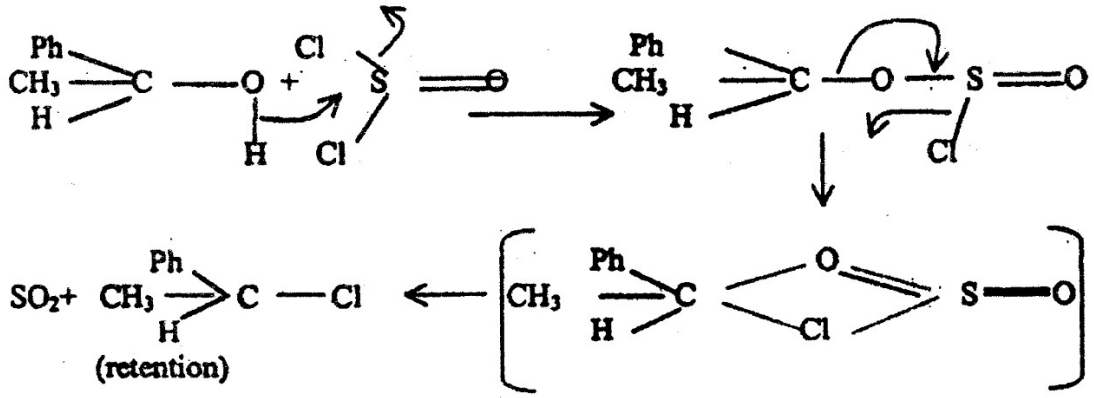
Formation of a cyclic sulphonium ion is found to provide anchimeric assistance to the leaving halogen atom.



The reaction rate is accelerated enormously, compared to the corresponding substrate without the – SR group.

SNI Mechanism (Substitution, Nucleophilic internal)

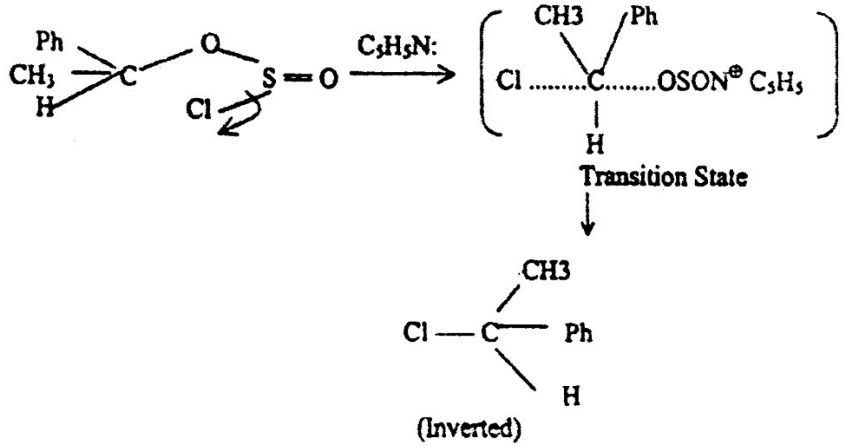
Certain nucleophilic substitution reactions occur with retention in configuration, but do not belong to either SN1 or SN2. The reaction of α - phenylethanol with thionyl chloride proceeds as under:



It is a four centre type of reaction where the nucleophile attacks internally resulting in total retention of configuration.

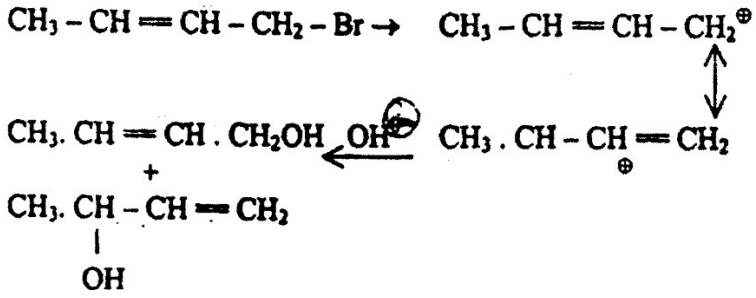
Evidence for this Mechanism

The same reaction when carried out in the presence of pyridine, the product α - Chloroethylbenzene is found to be inverted, since SN2 mechanism is operating, due to the formation of a pyridine complex from the alkylchloriosulphite.



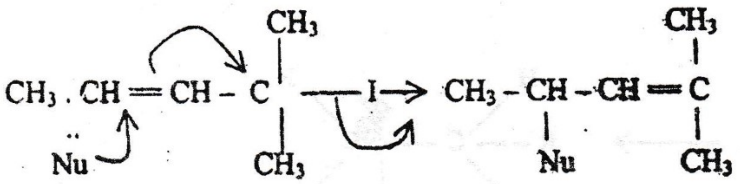
1S'N1', 1S'N2' and 1S'N i' Mechanism

When an allyl halide is acted upon by a nucleophile under SN1 conditions, an allylic shift occurs giving rise to a rearranged product along with the normal product.



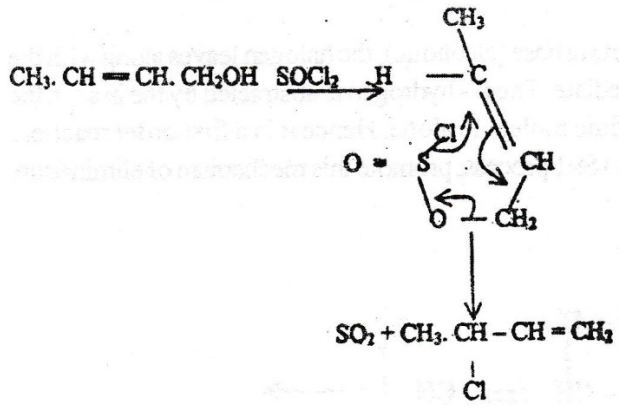
The % of the two products depends on the polarity of the medium. The nature of the products indicates the formation of an ion pair which undergoes some amount of internal return. This mechanism is known as S'N1'.

It is possible that allylic rearrangement can take place under IS'N2' conditions, when the γ - carbon is exclusively attacked by the nucleophile. The reaction is perfectly second order. It occurs when the α - carbon is sterically crowded which does not allow α - substitution under IS'N2' conditions as shown:

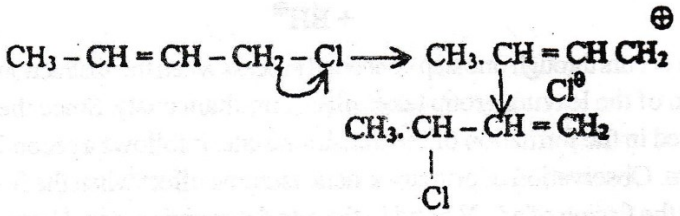


This mechanistic condition is under IS'N2'

A leaving group in a molecule (like thionyl chloride) attacks the γ - position of an allylic system, the raction resembles an internal nucleophilic substitution and this mechanism has come to be known as SNI' e.g: Reaction between 2- buten-1 -01 and thionyl chloride in either.

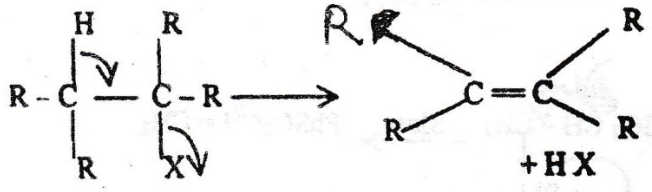


Reactions in which a leaving group gets detached from the allylic system to from an ion pair and reattacking the molecule not at the same position but at the allylic system, are also known.



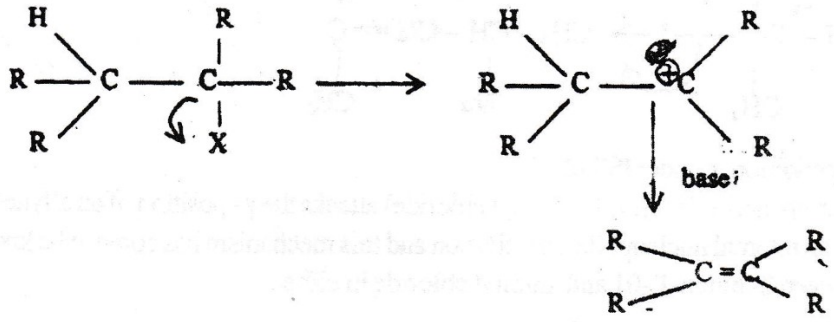
ELIMINATION REACTIONS

Reations in which two groups are eliminated from neighbouring atoms, result in the formation of a double bond. In most of such reactions, an atom of hydrogen is eliminated from the β - position to the leaving group.



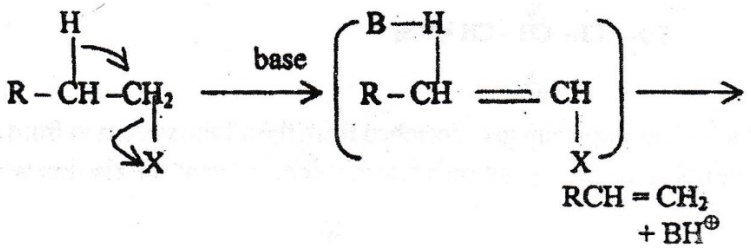
The elimination is accomplished by at least three different mechanisms.

E1 Mechanism



When an alkyl halide is acted upon with a strong base (alcoholic), the halogen leaves along with the bonded electrons to form a carbonium ion intermediate. The β - hydrogen is abstracted by the base in the second step resulting in the formation of an olefinic molecule alone. Hence it is a first order reaction. Factors which stabilize the carbonium ion as in an 1SN1 process, promote this mechanism of elimination.

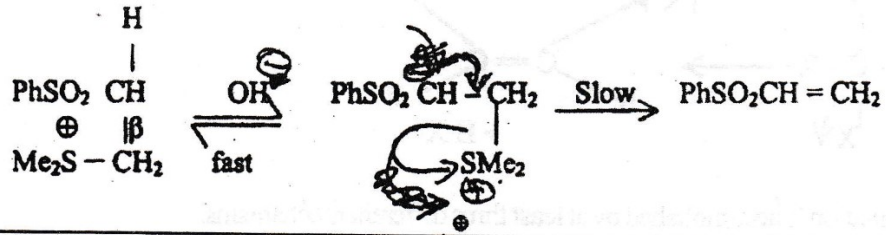
E2 Mechanism



The most common type of elimination occurs through one step concerted process when the abstraction of the proton by the base and the expulsion of the leaving group takes place simultaneously. Since the substrate molecule and the base are involved in the formation of the transition state, it follows a second order kinetics, and known as E2 mechanism. Observation of primary kinetic isotopic effect when the β - hydrogen is replaced by deuterium, proves the fission of a C-H bond in the rate determining step. Hence the solvent which normally acts as the medium for the base, as well as the strength of the base plays a leading role in the mechanism.

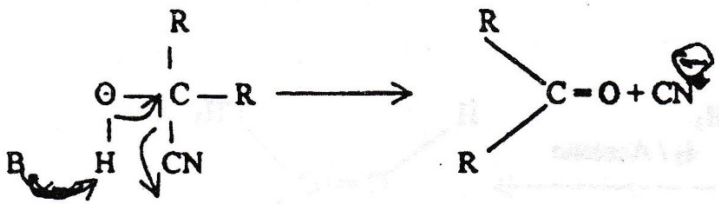
E1CB Mechanism

Anothermechanism consistent with the second order kinetics involves rupture of the β-H to form an intermediate carbanion with the subsequent loss of the leaving group.



Such reactions are rare as the substrate molecule must have the following requirements: 1) Electronegative atoms or groups on the β carbon to make the β-hydrogen acidic 2) Stabilization of carbanion through electron withdrawal. 3) Poor leaving group, preferably a positively charged substituent at the α - carbon.

Another example is the hydrolysis of a cyanohydrin to ketone.



In such reactions, elimination from the intermediate conjugate base occurs, hence the mechanism is known as E1CB.

Factors Affecting E1 and E2 Mechanism

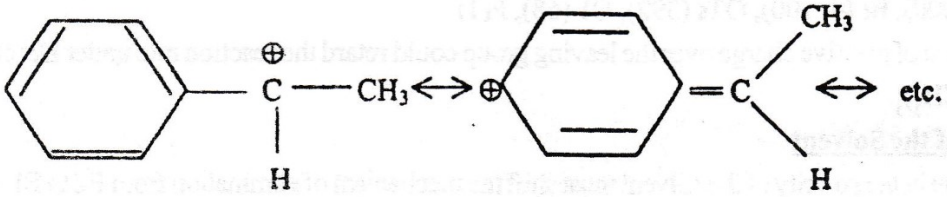
1. Nature of the Substrate

The yield of olefin decreases steadily from the t-butyl to methyl halide under E_1 conditions.

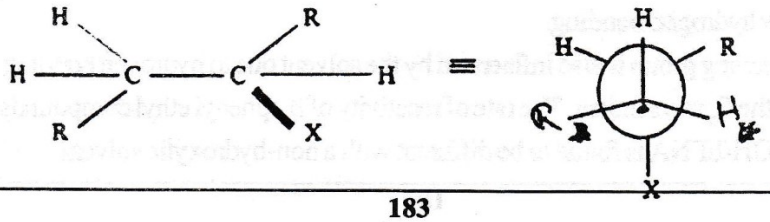
$(CH_3)_3$ C> $(CH_3)_2$ CH>CH_3CH_2>CH_3.

Since the respective carbonium ion stability falls in the given order. The hyperconjugative stabilization is maximum in t-butyl group. Moreover, the formation of an SP^2 carbon (bond angle 120) from an Sp^3 carbon (bone angle 109.5) in the rate determining stage, relieves the steric strain in the substrate molecule and favours elimination. The steric strain is further relieved when a proton is lost from the carbonium ion.

Resonance stabilization of the carbonium ion could also favour the E1 mechanism, as observed in the elimination of phenylmethylcarbinuyl chloride compared to isopropyl chloride.

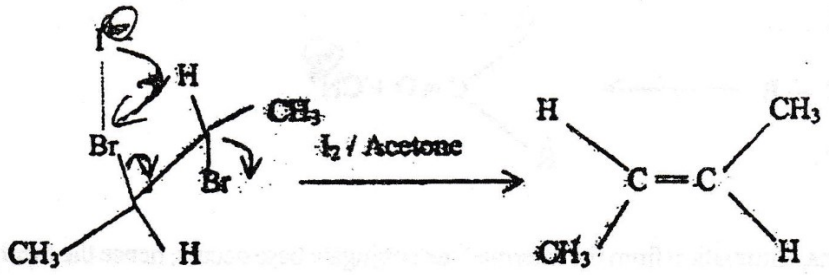


Stereochemical orientation of the leaving group as well as the β - hydrogen in the substrate decides the course of E2 eliminations. The two groups are found oriented in trans position (anti) in fast elimination since an anti periplanar geometry is a favourable prerequisite in the transition state attained under E2 conditions.



However cis orientation will lead to ecolipsing of the two group which will not allow a smooth elimination. Accordingly, the threo form of 1-chloro 2-methyl-1, 2 diphenylethane undergoes elimination rapidly, compound to the erythro form.

The debronination of meso dibromobutane in the presence of I_2 in acetone occurs twice as fast as the d, 1-dibromide for the same reason.



2. Strength of the Base (Basicity)

Stronger bases are found to favour E2 processes as expected from the mechanism, as proton abstraction is effective with such bases as $Nh_2^{\ominus}$, $OR^{\ominus}$ etc compared to $OH^{\ominus}$, $X^{\ominus}$ etc. the rate of E2 reaction falls sharply as under.

$NH\Theta_2$>t-BuOΘ>EtO>ΘOACΘ>BrΘ.

The decrease in concentration of the base will also tilt the mode of elimination from E2 to E1.

3. Effect of Leaving Group

The rate at which leaving groups depart, depends on their anionic stability. Best leaving groups are anions of strong acids. Accordingly the following rate has been observed in the elimination reactions of β - phenyl ethyl compounds in EtONG, EtOH, under E2 conditions.

1 (26,000), Br (4, 100), OTs (392), C1 (68), F(1).

Presence of positive charge over the leaving group could retard the reaction rate under E2 process e.g. – $N\Theta(CH_3)_3$.

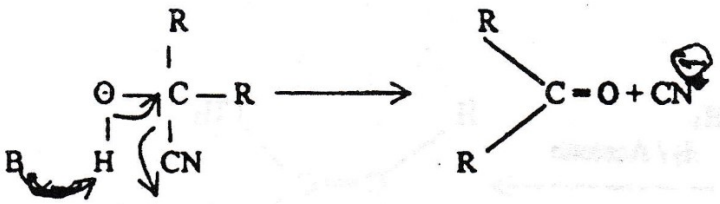
4. Polarity of the Solvent

Increase in the polarity of the solvent must shift the mechanism of elimination from E2 to E1, as the carbonium ions are more stabilized in the polar medium. However non-polar solvents facilitate spreading of charges in the transition state and better suited for E2 reactions. depending on the nature of the solvent, the nature of the solvent, the strength of the base can alter and thereby tilt the mechanism. For instance, use of bipolar aprotic solvent such as DMF and DMSO in the place of H_2O or EtOH, is found to shift the mechanism from E1 to E2, since the strength of the base (OH or OR) is profoundly enhanced and the base in no longer bound by hydrogen bonding.

The ability of leaving group is also influenced by the solvent due to hydrogen bonding or salvation in the transition state in the E_2 mechanism. The rate of reactivity of β - phenyl ethyl compounds (Ref. effect of leaving group) in ETOH/EPNA is found to be different with a non-hydroxylic solvent.

Such reactions are rare as the substrate molecule must have the following requirements: 1) Electronegative atoms or groups on the β carbon to make the β-hydrogen acidic 2) Stabilization of carbanion through electron withdrawal. 3) Poor leaving group, preferably a positively charged substituent at the α - carbon.

Another example is the hydrolysis of a cyanohydrin to ketone.



In such reactions, elimination from the intermediate conjugate base occurs, hence the mechanism is known as E1CB.

Factors Affecting E1 and E2 Mechanism

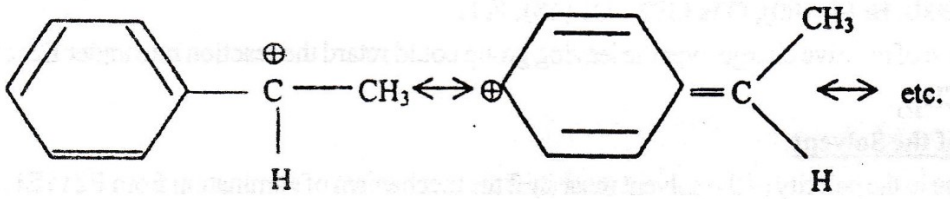
1. Nature of the Substrate

The yield of olefin decreases steadily from the t-butyl to methyl halide under E_1 conditions.

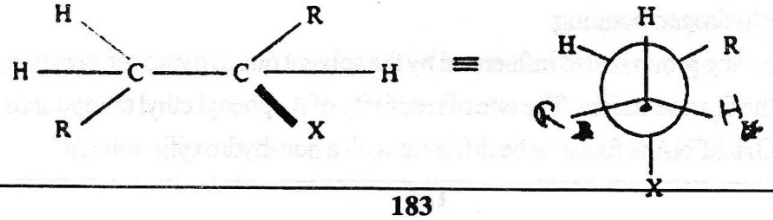
$(CH_3)_3$ C> $(CH_3)_2$ CH>CH_3CH_2>CH_3.

Since the respective carbonium ion stability falls in the given order. The hyperconjugative stabilization is maximum in t-butyl group. Moreover, the formation of an SP^2 carbon (bond angle 120) from an Sp^3 carbon (bone angle 109.5) in the rate determining stage, relieves the steric strain in the substrate molecule and favours elimination. The steric strain is further relieved when a proton is lost from the carbonium ion.

Resonance stabilization of the carbonium ion could also favour the E1 mechanism, as observed in the elimination of phenylmethylcarbinuyl chloride compared to isopropyl chloride.

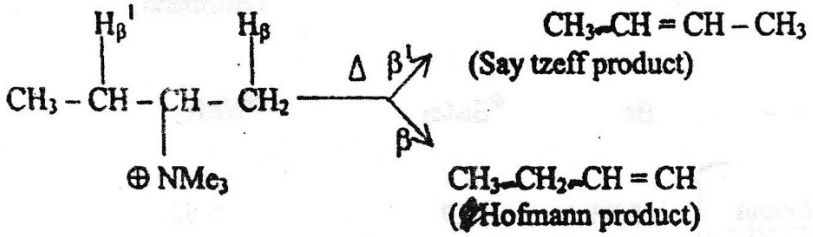


Stereochemical orientation of the leaving group as well as the β - hydrogen in the substrate decides the course of E2 eliminations. The two groups are found oriented in trans position (anti) in fast elimination since an anti periplanar geometry is a favourable prerequisite in the transition state attained under E2 conditions.



Hofmann Rule

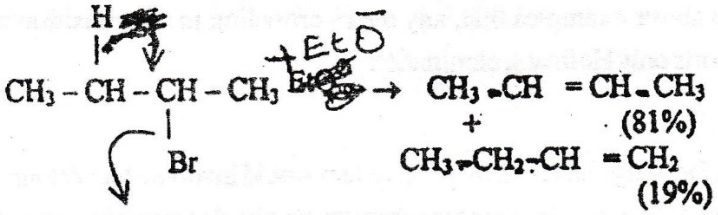
Similar to alkyl halides, quartarmary ammonium salts, sulphonium salts and tosylates undergo elimination reaction, when heated with a base, under E2 conditions.



In the given example, two β- Hydrogen atoms are present, but the more acidic β- hydrogen is eliminated by the base, to form butene-1 as the major product. The acidity of the β- hydrogen partially neutralized by the electron releasing methyl group. Hence, according to Hofmann to Hofmann rule, 'when more than one olefin is possible from an onium salt, the olefin bearing less number of Alkyl substituents predominates in bimolecular/eliminations'. However, in such reactions, the Hofmann product is not formed exclusively but minor quantities of the other olefin are also formed.

Savtzeff Rule

It states that, in the dehydrohalogenation of alkyl halides where more than one olefin is possible, the olefin with more number of alkyl substituents predominates.



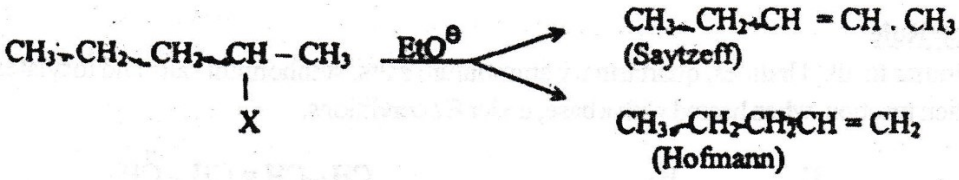
The product is more decided by the stability of the resulting alkene. When there is more number of methyl groups across the double bond, there is greater stability due to hyperconjugation. Hence butane-2 predominated in the given example.

Saytzeff Vs Hofmann Product

In the given example under Hofmann rule and Sattzeff rule, the substrate is same, only the leaving group differs. Still, the products are strikingly different and this apparent contradiction is explained by the acidity factor of the β-hydrogen, under Hofmann rule and the hyperconjugative stability of the olefin under Saytzeff rule. However, other factors also play vital role in deciding the percentage of the two products.

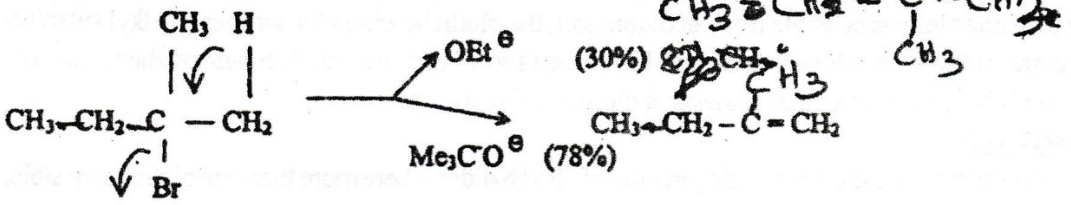
Steric Effect

The steric factor is more pronounced in E2 mechanism and accordingly the % of the Hofmann product progressively increases with increase in the bulkyness of the leaving group in the following reaction.



X	Br	$^{\oplus}SMe_2$	$^{\oplus}NMe_3$
Hofmann / Saytzeff	0.45	6.7	> 50

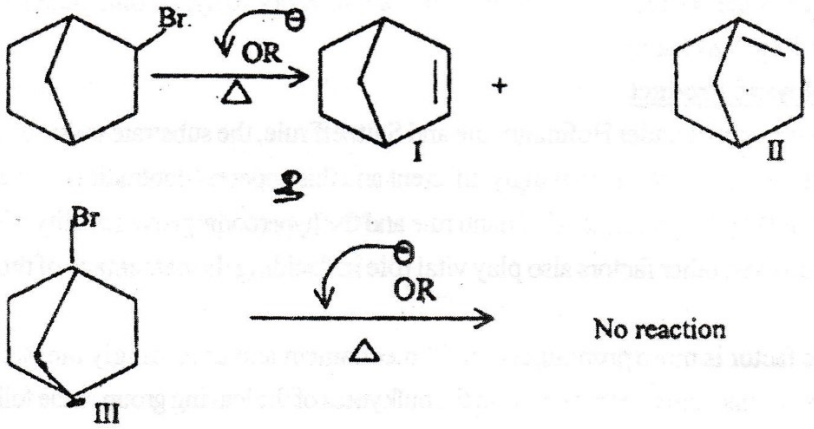
Increasing size of the substrate as well as the base molecule also promotes Hofmann elimination over Saytzeff.



It is clear from the above examples that, any over –crowding in the transition state due to the substrate or the base supports only Hofmann elimination.

Bredt's Rule

The double bond at the bridge head of a bicyclic system would involve a lot of strain in the molecule and according to Bredt's rule, 'Irrespective of the mechanism involved in a elimination reaction, a double bond is not formed at the bridge head carbon atom'. Hence the following bicyclic bromide gives only product I not II. Compound III, does not undergo any reaction at all.

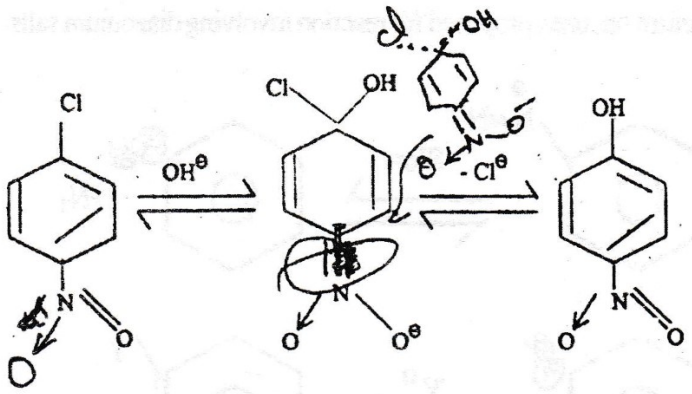


Aromatic Nucleophilic Substitution

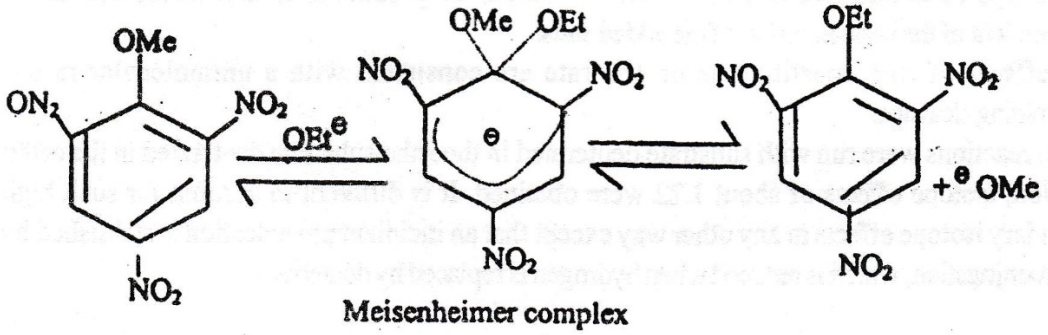
Direct substitution at a H-in aromatic nucleus by a nucleophile seldom occurs, since H – is not a good leaving group. However, whenever a good leaving group is attached to the ring, substitution takes place.

SN2Ar Mechanism

It has been often observed that presence of an electron - withdrawing group in the aromatic nucleus facilitates nucleophilic substitution even under mild conditions. (e.g.) p-Nitrochlrobenzene, where the halogen is replaced by hydroxyl group.



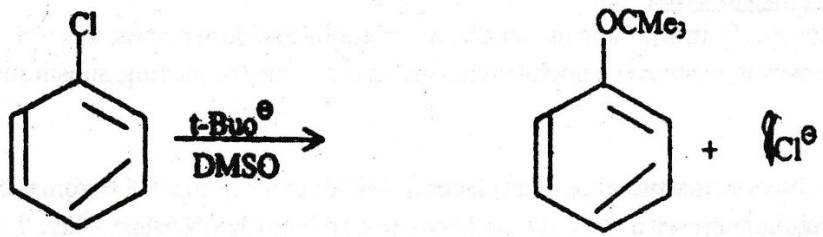
The reaction proceeds through an Addition – Elimination mechanism. The reaction is clearly second order, as the formation of the intermediate σ - complex has been proved through isolation in similar cases. (e.g) The intermediate also known as Meisenheimer complex has been isolated as a red crystalline solid, when 2,4,6 – trinitroanisole is acted upon by E.E.O



Meisenheimer complex

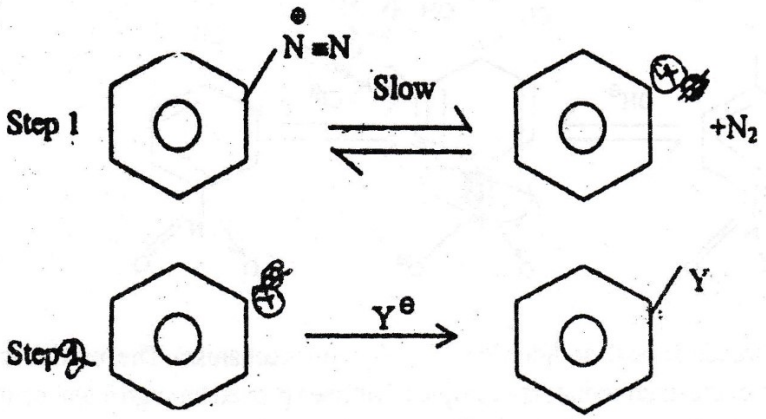
The 3 nitro groups present in the nucleus stabilize the σ complex through electron withdrawal.

But a number of unactivated halides could be made to proceed at a faster rate using aprotic bipolar solvents such as DMSO. Since there is no hydrogen bonded envelope around the nucleophile, the latter can function more effectively in DMSO and the energy of activation for such reactions are much lower. (e.g).



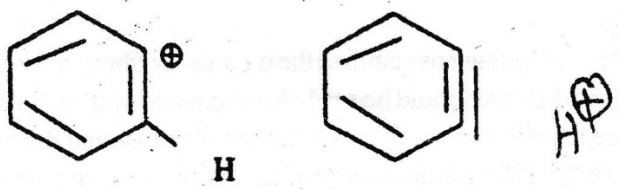
The SN1 Mechanism

Unmolecular mechanism has been proposed for reaction involving diazonium salts.



Among the evidence for the IS'N1 mechanism with aryl catious as intermediates is the following.

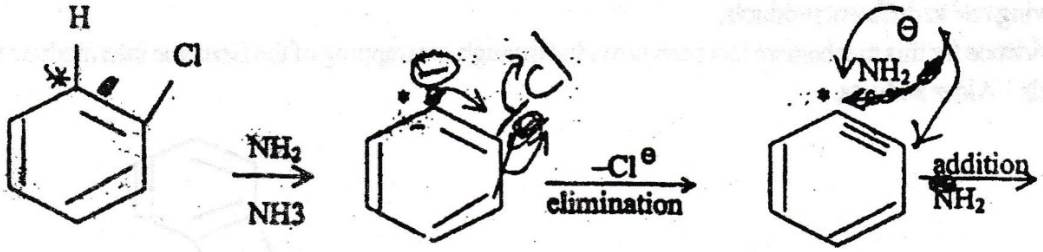
1. The reaction rate is first order in diazonium salt and independent in of the concentration of Y.
2. When high concentrations of halide salts are added, the product is an aryl halide but rate is independent of the concentration of the added satls.
3. The effects of ring substitutents on the rate are consistent with a unimolecular rate – determining cleavage.
4. When reactions were run with substrate deuterated in theortho substrate deuterated in the ortho position, isotope effects of about 1.22 were obtained. It is different to account for such high secondary isotope effects in any other way except that an incipient phenylcation is stablished by hyperconjugation, which is reduced when hydrogen is replaced by deuterium.

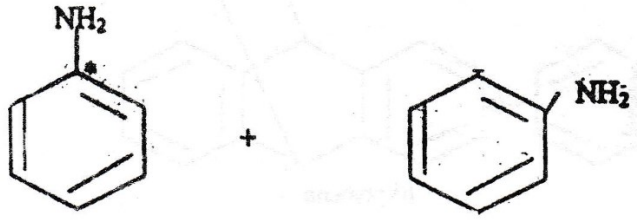


5. That the first step is a reversible cleavage was demonstrated by the observation that when $ArN\equiv\overset{15}{N}^{\oplus}$ was the reacting species, recovered starting material contained not only $ArN\equiv\overset{15}{N}^{\oplus}$, but also ArN, but also $ArN\equiv\overset{15}{N}^{\oplus}$. This could arise only if only if the nitrogen breaks away from the ring and then returns.

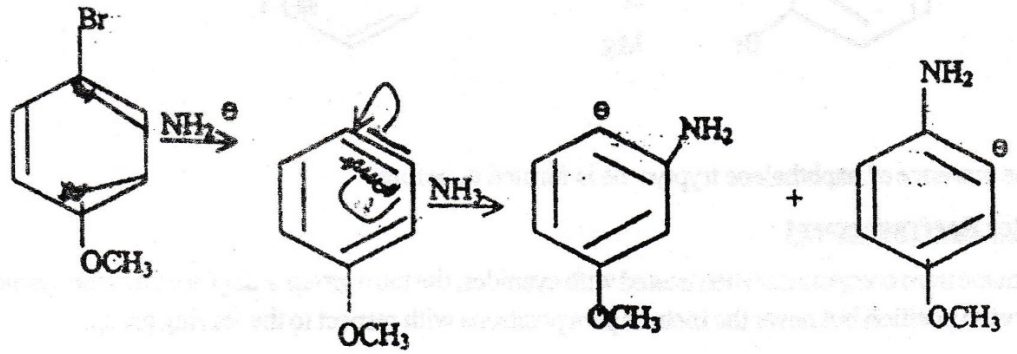
Benzyne Mechanism (Aryne Mechanism)

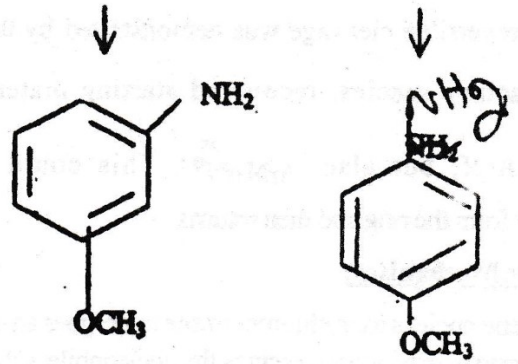
When unactivated benzene nucleus as in chlorobenzene undergoes an elimination addition type of reaction in the presence of a strong base which also acts as the nucleophile, substitution occurs through the formation of a symmetrical intermediate.





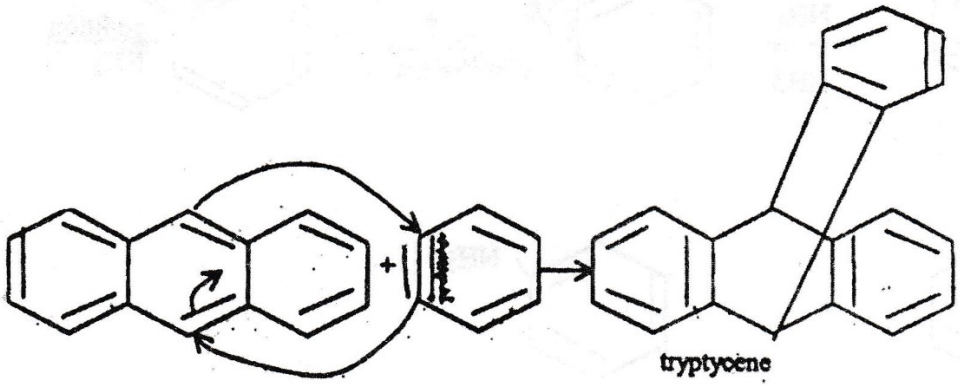
Chlorobenzene labeled with C^{14} is found to give aniline where C^{14} is equally distributed between the ortho carbon atom and the carbon attached to chlorine. Moreover, p-bromoanisole under similar conditions give p – anisidine an m-anisidine. Formation of the NH^2 group at the ortho position of the leaving group is surprising. These results could be rationalized by postulating the formation of an aryne intermediate in these reactions.



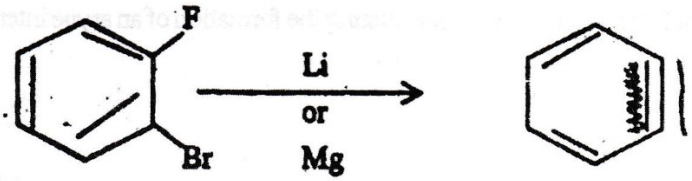


The unsymmetrical intermediate could be acted upon by the nucleophile at either of the two carbon atoms giving rise to different products.

Evidence for this mechanism has been provided through the trapping of the Benzyne intermediate to form Diels – Alder adducts.



Aryne intermediate is also formed when o – bromofluorobenzene is treated with Li or Mg.



In the presence of naphthalene tryptycene is formed as before.

Von Richter Rearrangement

Aromatic nitro compounds when treated with cyanides, the nitro group is displaced and the cyanide enters the ortho position but never the meta or para positions with respect to the leaving group.